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Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.01/F5

Topic: A.01. Neurogenesis and Gliogenesis

Support: This research was supported by National Institutes of Health Grants P20GM113131, R15MH126317, and R15MH125305; and Cole Neuroscience and Behavioral Faculty Research Awards, and a COLSA Community of Teaching and Research Scholar Award (to X.C.)
Grants-in-aid for Scientific Research of Japan Society for Promotion of Science JP23H02491 (to Y.H.), JP24KJ1889 (to Y.T.), JP20H03384 and JP23K27324 (to M.H), JP20H05688 and JP25K02437 (to K.N.)
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Title: Reelin-Dab1 Signaling Impacts the Directional Orientation, Intracellular Positioning and Length of Primary Cilia in Pyramidal Neurons of the Cerebral Cortex

Authors: *S. AKTER[1], X. CHEN[2], M. HATTORI[5], L. QIU[3], Y. HIROTA[7], Y. TAKEKOSHI[6], M. LYON[4], K. NAKAJIMA[8];
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Abstract: The primary cilia of pyramidal neurons in inside-out laminated brain regions orient predominantlytoward the pial direction, indicating reverse movement during early postnatal development. Wepreviously reported that Reelin modulates the apical localization and directional orientation ofprimary cilia in pyramidal neurons likely by influencing radial migration and subsequent reversesoma movement. Reelin exerts its effects through binding to the lipoprotein receptors ApoER2 andVLDLR, triggering a signaling cascade that involves phosphorylation of the adaptor proteinDisabled-1 (Dab1). However, it remains unknown if Dab1 mediates Reelin-dependent regulationof cilia orientation, positioning and morphology. Here, we show that in wild-type mice, primarycilia of pyramidal neurons are preferentially localized near the base of the apical dendrite andpositioned on the nuclear side opposite the axon initial segment (AIS). In *Dab1* mutant mice(*yotari*), the directional orientation and apical localization of primary cilia in pyramidal neuronsare disrupted, resulting in randomly oriented cilia and abnormal intracellular positioning.Furthermore, *Dab1* deficiency elongates cilia in principal neurons throughout the cerebral cortexat developmental stages when cilia length has stabilized in wildtypes. *Dab1* mutants largelyphenocopy Reelin mutants in terms of effects on cilia. Together, these findings demonstrate thatDab1 is required for the Reelin-mediated regulation of cilia positioning and likely the reversemovement of pyramidal neurons.

Disclosures: S. Akter: None. **X. Chen:** None. **M. Hattori:** None. **L. Qiu:** None. **Y. Hirota:** None. **Y. Takekoshi:** None. **M. Lyon:** None. **K. Nakajima:** None.

Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.02/F6

Topic: A.01. Neurogenesis and Gliogenesis

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Title: Lamin B1 physically regulates neuronal migration by modulating nuclear deformability in the developing cortex

Authors: *M. SHIN[1], S. ISHIDA[3], J. YU[4], G. RAMAZZOTTI[5], J.-C. RAH[2], Y. IMAI[3]; [1]Korea Brain Res. Inst., Deagu, Korea, Republic of; [2]Korea Brain Res. Inst., Daegu, Korea, Republic of; [3]Kobe Univ., Kobe, Japan; [4]Advanced Neurosci. Inst., Deagu, Korea, Republic of; [5]Univ. of Bologna, BOLOGNA, Italy

Abstract: During cortical development, newborn excitatory neurons must traverse dense tissue to reach their final laminar position, requiring repeated nuclear deformation to navigate confined intercellular spaces. Although nuclear mechanical properties have been linked to migration in non-neuronal contexts, whether they play a functional role in radial neuronal migration remains unknown. We investigated the role of Lamin B1 (LB1), a nuclear lamina component encoded by LMNB1, as a physical regulator of cortical neuronal migration. Using in utero electroporation in mice, we show that overexpression of human LB1 (hLB1-OE) markedly arrests radial migration: neurons accumulate in the intermediate zone and fail to reach the cortical plate. This migratory defect occurs without altering laminar identity or disrupting pre-migratory transcriptional programs, as confirmed by RNA-seq of FACS-sorted EGFP-positive neurons. Patch-clamp electrophysiology revealed that ectopically positioned neurons exhibit electrophysiological immaturity compared to normally positioned controls, linking migration failure to functional impairment. To determine how LB1 regulates migration mechanically, we performed atomic force microscopy on isolated nuclei and found that LB1 overexpression significantly increases nuclear stiffness, whereas LB1 knockdown decreases it. Microfluidic confinement assays demonstrated that LB1-overexpressing neurons show severely reduced motility under physical confinement, while LB1 knockdown enhances it. Live imaging revealed that control neurons undergo saltatory migration (~27 μm/h) with nuclear aspect ratio fluctuations that precede and

correlate with velocity peaks, a pattern ablated in hLB1-OE neurons (~4 μm/h). Three-dimensional computational modeling of a migrating cell with a nucleus navigating immobile obstacles confirmed that nuclear stiffness is a rate-limiting parameter: increasing stiffness beyond a critical threshold causes migration arrest, reproducing the in vivo phenotype. Finally, to address disease relevance, we generated human cerebral organoids (hCOs) from iPSCs derived from autosomal dominant leukodystrophy (ADLD) patients, who harbor genomic duplications of LMNB1. ADLD patient-derived hCOs recapitulate neuronal migration defects, establishing a direct link between pathological LB1 elevation and cortical organization. Together, these findings identify nuclear deformability as a biophysical determinant of radial neuronal migration and implicate aberrant nuclear stiffness as a cellular mechanism underlying ADLD-associated cortical pathology.

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Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.03/F7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01AA029114

Title: Nuclear calcium transients during cortical migration, a potential mechanism for location-dependent maturation

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Abstract: During cortical development, migrating cortical projection neurons (mCPNs) traverse distinct microenvironments before undergoing the critical transition from locomotion to post-migratory differentiation and apical dendritogenesis within the marginal zone (MZ). Multiphoton imaging of E15 whole hemisphere explants expressing nuclear-localized GCaMP8s for up to 6 hours provided novel insights into nuclear calcium dynamics in migrating and immediate postmigratory neurons. Comprehensive quantification using an automated image analysis pipeline identified robust nuclear calcium transients ($F/F_0 > 2$) occurring at a relatively consistent basal frequency of approximately one event per cell-hour regardless of cell position. Strikingly, the amplitude of these large nuclear transients peaked at two distinct anatomical landmarks: just beneath the subplate (SP) and just beneath the MZ, precisely where neurons are initiating axons and dendrites respectively.Mechanistically, deprivation of extracellular calcium rapidly prevented these transients, demonstrating a dependence on calcium influx rather than internal store release. Pharmacological blockade of NMDA receptors lowered steady state nuclear

calcium levels and reduced both the frequency and amplitude of the nuclear transients but did not abolish transients entirely. Collectively, these data outline a model in which developing mCPNs possess an intrinsic, baseline depolarization frequency. As migrating neurons enter specialized cortical microenvironments, characterized by volumetric glutamatergic transmission—namely, the SP and the MZ—baseline depolarizations sufficient to relieve Mg2+ blockade of the NMDA receptors are amplified by increased calcium influx through glutamate activation of these receptors. This mechanism provides a direct coupling between a neuron's physical position within the developing cortex and elevated nuclear calcium signaling, potentially coordinating location-appropriate cellular responses. Given the specific signaling molecules involved, disruption of this microenvironment-to-nuclear signaling pathway may contribute to the pathophysiology of both syndromic intellectual disability and toxic insults like ethanol exposure

Disclosures: J. Enck: None. **E.C. Olson:** None.

Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

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Program #/Poster #: PSTR001.04/F8

Topic: A.01. Neurogenesis and Gliogenesis

Support: ZIA NS002824-35

Title: The influence of AMPA signaling on GnRH cell migration

Authors: *S. JACOBS[1], J. FLANNERY[2], M. AKRAM[3], S. WRAY[3];
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Abstract: During prenatal development, Gonadotropin-Releasing Hormone-1 (GnRH) neurons originate in the nasal placode and migrate along olfactory sensory axons into the forebrain. Once within the forebrain, GnRH cells become an essential component of the Hypothalamic-Pituitary-Gonadal Axis, and as such reproductive maturation and function. Improper migration of GnRH cells during prenatal development can result in various reproductive disorders such as Kallman's Syndrome.GluA1 is one of the four AMPA receptor (AMPAR) subunits that form ionotropic glutamate receptors and is well known for its role in mediating fast excitatory neurotransmission and synaptic plasticity in the adult central nervous system. GluA1-containing AMPARs are often calcium permeable and contribute to activity-dependent cellular signaling through dynamic receptor trafficking and regulation of receptor composition at the cell surface. While the functions of GluA1 in mature neural circuits have been extensively characterized, its role during prenatal development, prior to the establishment of mature synaptic connections, remains poorly understood. In this study, the AMPAR subunit GluA1 was investigated as a potential regulator of GnRH cell migration, which emerged as a candidate protein from expression analyses of embryonic GnRH neurons.GnRH cell specific GluA1 subunit knockout mice were examined at

three different stages; embryos (E12.5 and 13.5), postnatal 10 (PN10) brains, and adult brains. Immunocytochemistry was used to visualize the GnRH cells and perform cell counts per anatomical area. Preliminary results show that, prenatally, GRIA KOs had more GnRH cells in nasal areas and fewer in the brain compared to WT controls. In PN10 brains, the total number of GnRH cells is comparable between genotypes, but location is presently being evaluated. Concurrently, we are performing migration assays of GnRH cells treated with either GRIA1 agonist or antagonists using an explant model. These findings may help better understand the migration of GnRH cells and the development of the reproductive system.

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Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.05/G1

Topic: A.01. Neurogenesis and Gliogenesis

Support: P50MH136297
RS-2025-02633344

Title: ALS/FTD-associated TANK-Binding Kinase 1 (TBK1)as a novel regulator of cortical development via DISC1

Authors: *B. GOO[1], A. SAITO[2], H. JAARO-PELED[2], K. ISHII[7,8], Y. WOO[9], Q. CHEN[10], C. TRISTAN[11], S. PARK[9], G. URSINI[12], K. ISHIZUKA[1], A. SAWA[3,4,1,5,6];
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Abstract: Prenatal brain development is known as precisely a coordinated process, underlying young adult-onset psychiatric conditions, such as schizophrenia. The delayed onset of the disease many years after the initial perturbation is actively studied in psychiatric research. Meanwhile, it remains elusive whether and how such early developmental processes also underlie adult or geriatric neurodegenerative disorders. Through our long-term investigation of DISC1, we identified that a specific phosphorylation of DISC1 [Serine-710 (S710) in mice] has a pivotal role in the neurodevelopmental switch from progenitor proliferation to neuronal migration in the developing cortex. The next question was to identify the responsible kinase. Accordingly, we conducted an unbiased CRISPR-based screening. Here we report TANK-Binding Kinase 1 (TBK1) as a kinase that directly phosphorylates DISC1 at S710. We observed that TBK1 is expressed not only in non-neuronal cells but also in radially migrating neurons in the developing

cortex, and the overlapped expression with S710-phosphorylated DISC1 (pDISC1) occurred in the neurons. Selective knockdown (KD) of neuronal TBK1 reduced pDISC1 levels, resulting in delayed neuronal migration in wild-type (WT) mice. To address the relationship between TBK1 and DISC1, we generated DISC1 knock-in mouse lines: phospho-deficient (S710A) and phospho-mimic (S710E), respectively. As expected, we observed a delayed neuronal migration in S710A mice, whereas the phenotype is intact in S710E mice. Notably, TBK1 KD-elicited neuronal migraton in WT mice did not occur in S710E mice. These data a pivotal role of DISC-S710 phosphorylation by TBK1 in proper neuronal migration in the developing cortex. Loss-of-function mutations in *TBK1* are genetically associated with frontotemporal dementia (FTD) / amyotrophic lateral sclerosis (ALS) and the genetic association with *DISC1* in the disease condition has also been suggested. Thus, we tested the gene-gene interaction of *TBK1* and *DISC1* and obtained a significant interaction in a dataset of 2,242 ALS/FTD cases and 1,920 controls. Collectively, these data imply that TBK1-DISC1 interaction plays a pivotal role in proper cortical development and underlies the genetic risk of FTD/ALS. Accordingly, we further tested whether and how the TBK1 KD, leading to the loss of pDISC1, in the developing cortex had an impact on neuropsychiatric behaviors. At 7-9 weeks of age, the mice with TBK1 KD displayed anxiety-like behaviors and social interaction deficits.

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Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.07/G2

Topic: A.01. Neurogenesis and Gliogenesis

Title: Contribution of rare coding variants to microcephaly in individuals with neurodevelopmental disorders

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Abstract: Microcephaly, characterized by an abnormally small head size, frequently co-occurs with neurodevelopmental disorders (NDDs). While the genetic basis of NDDs has been widely investigated, the contribution of rare coding variants to microcephaly remains poorly understood. Here, we investigated the relationships between head circumference and rare coding variants in 418 individuals with microcephaly, analyzing data from 1050 exomes. Participants were classified into primary microcephaly (PM) and secondary microcephaly (SM) groups, and their clinical and genetic characteristics were systematically assessed. Exome sequencing revealed 142 causative and 12 candidate genes associated with microcephaly. Pathway analyses indicated

that PM genes are linked to early phases of brain development, whereas SM genes are more associated with later stages of neuronal maturation. In addition, the PM group had a significantly higher proportion of autosomal recessive disorders and exhibited more severe microcephaly than the SM group. Notably, females displayed greater microcephaly severity than males, primarily attributable to differences in the origin of the allele and inheritance patterns on the X chromosome. The functional impact of high-priority candidate genes, *RTF1* and *ASAP2*, was further validated using neural progenitor cells (NPCs) and human forebrain organoid models. Functional experiments using CRISPR-Cas9 knockout in NPCs and brain organoids demonstrated reduced NPC proliferation, supporting the essential role of *RTF1* and *ASAP2* in brain development. This study sheds light on the complex genetic architecture of microcephaly, emphasizing the impact of rare coding variants on brain development and delineating distinct clinical and molecular profiles underlying PM and SM.

Disclosures: H. Jang: None. **K. Yoon:** None.

Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.08/G3

Topic: A.01. Neurogenesis and Gliogenesis

Support: DOST Grants-in-Aid

Title: Brain region, not environmental endocrine-disruptor exposure, governs neurogenic and glial marker expression in caged Nile tilapia (Oreochromis niloticus)

Authors: C. GERON[1,2], **S. KANG**[3], Z. PEREZ[4,2], L. AGUIRRE[2], S. JEONG[5], J. LEE[5], S. ARREOLA[2], M. ESPINO[6], C. MOON[5], M. PARASO[2], *M. C. ANG[2];
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Abstract: Untreated sewage discharges are suspected sources of estrogenic endocrine-disrupting compounds (EDCs) detected in several lakes in San Pablo City, Philippines. Previous studies on caged Nile tilapia (*Oreochromis niloticus*) in the lakes of San Pablo City revealed gill, liver, and testicular histopathological alterations, with some responses showing lake-specific patterns, but whether this peripheral damage reaches the brain is unknown. The teleost brain is a plausible EDC target: it sustains lifelong, brain-wide neurogenesis from estrogen-responsive radial glia. In fish from four sewage-exposed lakes and a laboratory reference (3-4 fish/site), we measured four immunomarkers in four brain subdivisions: the telencephalon, mesencephalon, diencephalon, and rhombencephalon. The markers were doublecortin (DCX; neurogenesis), glial fibrillary acidic protein (GFAP) and vimentin (astroglia and radial glia), and ionized calcium-binding

adaptor molecule 1 (Iba-1; microglia), each quantified as 3,3'-diaminobenzidine optical density (H-DAB color deconvolution, Fiji). This exploratory study modeled effects of site (lake) and brain region using linear mixed models (fish as a random effect), Friedman tests, and per-region Kruskal-Wallis tests with false-discovery-rate (FDR) correction. Marker levels were related to lake estrogenic burden (estradiol equivalents, EEQ) by Spearman correlation. Expression was organized by brain region, not by lake. DCX and vimentin formed significant forebrain-dominant gradients (highest in the telencephalon and diencephalon, lowest in the rhombencephalon; mixed-model brain-region effect $p<0.0001$; Friedman $p<=0.001$), whereas GFAP and Iba-1 were uniform across subdivisions. EDC exposure, by contrast, left no detectable signature. No marker differed among the lakes and the reference for the whole brain (mixed model, all $p>0.14$), and this absence of a lake effect held within every subdivision (per-region Kruskal-Wallis all $p>0.09$; FDR $q>0.5$), with no lake-by-region interaction (all $p>0.7$). The only exposure-linked signal was exploratory and limited to the four lakes: glial markers rose with estrogenic burden (GFAP rho=1.0; vimentin rho=0.8) while neurogenesis fell (DCX rho=-0.8), converging on the highest-EEQ lake. Thus, unlike its peripheral organs, the tilapia brain preserved an intact, regionally patterned neurogenic and glial program, buffered against the lake EDC gradient over sub-chronic exposure. It behaves as a conservative, late-stage indicator in which the estrogen-responsive radial-glia compartment is the most promising read-out for powered, cell-resolved follow-up.

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Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.09/G4

Topic: A.01. Neurogenesis and Gliogenesis

Title: Blood exposure disrupts the cytoarchitecture of human cortical organoids

Authors: *E. NOEL[1], M. CASTELLANOS[1], D. JGAMADZE[2], H. SONG[3], G.-L. MING[3], H.-C. I. CHEN[2];
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Abstract: Human cortical organoids (hCOs) are 3D stem cell-derived structures that recapitulate basic aspects of cortical organization, including the formation of ventricular zones (termed rosettes) and rudimentary laminar structure. Due to their cellular architecture, hCOs have been used for a variety of neurobiological applications, including modeling disease and development. Given the broad importance of structure for function in the nervous system, we set out to understand how molecular factors may disrupt hCO structure, and therefore function. Other labs have suggested that exposure to blood impairs neurogenesis in neural organoids (Seah et al., 2025). Therefore, we sought to determine whether blood exposure disrupts the structural

organization of hCOs, including rosette integrity and laminar architecture, critical for cortical development and function. This study uses immunohistochemistry (IHC) to determine if whole blood and blood fractions can drive changes in hCO rosette structure *in vitro*. Blood was collected from rat tail vein and centrifuged to obtain plasma, buffy coat, and red blood cells. Whole blood and fractions were diluted in culture media at low and high concentrations and applied to day 50 hCOs (n = 8/condition). hCOs were incubated on a shaker at 37°C for 7 days and processed using IHC for Pax6 (neural progenitor cells), TBR2 (intermediate progenitor cells), cortical laminar markers, including CTIP2 (layer V), RorBeta & Necab1 (layer IV), Satb2 & CUX1 (layer II/III), and RELN (layer I), and apoptosis via cleaved caspase-3 (CC3). Results suggest that all blood conditions reduce rosette number, with no broad changes in the percentage of Pax6 progenitors for any blood condition. All blood conditions show an increase in apoptosis. Most apoptotic cells are progenitors, indicated by CC3 colocalization. In high concentrations of whole blood condition, lower-layer cell type percentages were decreased. In the low concentrations of plasma, red blood cell and high concentration of whole blood conditions, upper-layer cell type percentages were *increased*. There were no significant changes in upper- or lower-layer cells after exposure to any other fraction of blood. These observations suggest that all fractions of blood reduce the number of rosettes. The number of neural progenitors remains stable, with these cells dispersed throughout the hCO. Rosettes recapitulate ventricular zones in the developing cortex, and their disruption may impact the organization of the cortical plate, relevant to neonatal models of intraventricular hemorrhage. Future experiments will use apoptotic inhibitors with the hope of reversing blood-induced rosette loss.

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Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.10/H1

Topic: A.01. Neurogenesis and Gliogenesis

Title: Comparison of NGN2 gene syntax for optimizing neuronal differentiation

Authors: *K. R. MERCADO ROSADO, M. E. WARD;
Natl. Inst. of Neurolog. Disorders and Stroke, Natl. Inst. of Hlth., Bethesda, MD

Abstract: Neuronal differentiation is characterized by the transition of cells through neurogenesis toward a neuronal fate. Human induced pluripotent stem cells (iPSCs) are useful for modeling this process because they can be directed toward neuronal lineages in a controlled and reproducible manner. One widely used approach to induce rapid neuronal differentiation in iPSCs involves doxycycline (DOX)-inducible expression of the transcription factor neurogenin 2 (NGN2). While existing protocols yield high differentiation efficiency, they often rely on antimitotic agents such as 5-fluoro-2′-deoxyuridine (FUDR) to limit proliferative cells, which

causes cellular stress. Recent work has demonstrated that gene syntax influences transcriptional activity through supercoiling-mediated feedback, where promoter orientation modulates DNA topology and gene expression dynamics. Divergent promoter configurations enhance transcriptional activation while convergent arrangements can introduce transcriptional interference. Considering this, we investigated whether promoter orientation impacts NGN2-driven neuronal differentiation efficiency and reliance on antimitotic selection. Human iPSCs carrying inducible NGN2 cassettes arranged in divergent or convergent promoter configurations were differentiated using multiple DOX concentrations with or without FUDR. Residual proliferative cells were quantified using 5-ethynyl-2′-deoxyuridine (EdU) incorporation, while neuronal differentiation was assessed by TUJ1 immunofluorescence. Preliminary analyses from three technical replicate wells showed that FUDR treatment reduced proliferative cells across conditions. Notably, this effect seems stronger in the convergent configuration, suggesting increased progenitor persistence in the divergent configuration. These findings indicate that promoter architecture influences NGN2-driven differentiation and suggest that optimizing promoter configuration and differentiation parameters may improve DOX-inducible NGN2-based neuronal differentiation while reducing reliance on antimitotic selection.

Disclosures: K.R. Mercado Rosado: None. **M.E. Ward:** None.

Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

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Topic: A.01. Neurogenesis and Gliogenesis

Support: The Zvi and Ofra Meitar Family Fund
Knowledge Foundation
Arsenov Foundation
NIH

Title: The first migratory neurons of the emerging human forebrain

Authors: *I. BYSTRON;
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Abstract: The hierarchy of early human neurogenesis remains unexplored. Here we identify previously unrecognized stem-cell niches that generate the first migratory neurons of the human forebrain and adjacent cephalic ectoderm. These neuronal populations use distinct migratory strategies before the onset of local neurogenesis within their target regions. Human embryos from Carnegie stages (CS) 10-18 (29-43 days post-conception) were obtained from the Human Developmental Biology Resource UK. Neuronal, proliferative and regional markers were combined with confocal microscopy and three-dimensional reconstruction to define the origin and trajectories of early neuronal populations. During neural fold closure, phalloidin and laminin

delineate the ventricular and pial neuroepithelial surfaces, respectively. While predecessor neurons of the dorsal diencephalon migrate along the pial surface towards the prospective cortical wall, Meitar neurons arising in the chiasmatic plate undergo translocation along the ventricular surface and enter the developing optic vesicle before retinal neurogenesis begins. This distinctive migration may reflect transient use of the ventricular surface during morphogenetic transitions underlying bilateral eye separation and optic vesicle formation. Their leading processes terminate among retinal progenitor endfeet at the vitreal surface shortly before the onset of local retinal neurogenesis. In parallel, bipolar TU20-positive neurons migrate through the cephalic ectoderm, exit into periocular mesenchyme and extend non-axonal processes towards the developing eye and rostral telencephalon. These migratory neurons are molecularly distinct from neural crest populations. Additional migratory neurons emerge from the oral ectoderm of Rathke's pouch, a previously unrecognized neurogenic domain. Calbindin immunoreactivity identifies early progenitor domains in the dorsal diencephalon, olfactory placode and ciliary margin of the developing retina, marking neurogenic niches that contribute to the formation of the epithalamus, olfactory bulb and retina. Our results suggest that the first neurons of the forebrain arise from multiple neurogenic niches and use distinct migratory strategies to establish the earliest neural architecture of the developing human brain and eye. These previously unrecognized neuronal populations highlight an unexpected divergence in early neurogenesis between experimental models and humans.

Disclosures: I. Bystron: None.

Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.12/H3

Topic: A.01. Neurogenesis and Gliogenesis

Support: JP20H05688
JP16H06482

Title: Why do excitatory neurons in the cerebral neocortex and the hippocampus migrate differently—in locomotion mode versus climbing mode?

Authors: *H. HASEGAWA[1], A. KITAZAWA[2,1], S. YOSHINAGA[2,1], K.-I. KUBO[2,1], K. NAKAJIMA[1];
[1]Dept. of Anat., Keio Univ. Sch. of Med., Tokyo, Japan; [2]Dept. of Anat., The Jikei Univ. Sch. of Med., Tokyo, Japan

Abstract: Neurons use diverse migration modes during brain development. In the developing neocortex, for example, superficial-layer neurons migrate toward the pial surface along radial glial fibers using the “locomotion mode”, whereas hippocampal pyramidal neurons migrate in a zigzag manner with multiple processes, a behavior termed the “climbing mode” (Kitazawa et al.,

2014). Previous analyses showed that neocortical locomotion is faster than hippocampal climbing mode migration (20.5 and 7.1 μm/h, respectively), suggesting that these two populations use distinct cellular mechanisms to move through their respective cortical structures. However, the molecular basis underlying these different migration modes remains poorly understood.
To investigate what distinguishes neocortical locomotion from hippocampal climbing mode migration, we performed transplantation experiments and found that cell-intrinsic mechanisms contribute to the region-specific migration modes. We next compared migrating neurons from the two regions and found several differences in gene expression. Functional analyses showed that manipulating some of these genes altered migratory behavior, suggesting that they contribute to the region-specific migration modes.
We also performed additional molecular and functional analyses to examine the relationship among these candidates. These experiments suggested functional interactions among neocortex-enriched candidates, providing a framework for understanding how region-specific migration modes are regulated.

Disclosures: H. Hasegawa: None. **A. Kitazawa:** None. **S. Yoshinaga:** None. **K. Kubo:** None. **K. Nakajima:** None.

Poster

PSTR001: Mechanisms of Neuronal Migration and Cortical Development

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.13/H4

Topic: A.01. Neurogenesis and Gliogenesis

Title: Transcriptome-Resolved Precision Neuropathology of Focal Cortical Dysplasia

Authors: *X. QIAN[1,2];
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Abstract: Focal cortical dysplasia type 2 (FCD2) is a major cause of childhood drug-resistant epilepsy and is defined by focal cortical dyslamination, dysmorphic neurons, and, in FCD2b, balloon cells. Although somatic mutations in the PI3K-AKT-mTOR pathway are established drivers of FCD2, these variants are often present in only a small fraction of cells within the resected lesion. This creates a central paradox: how do rare mutant cells generate broad architectural disorganization involving surrounding cells that are likely genetically normal? To address this question, we developed a spatial single-cell transcriptomic framework for transcriptome-resolved precision neuropathology in FCD2 surgical specimens. Using MERFISH, we profiled large tissue areas across FCD2 resections and control cortex, resolving neuronal, glial, vascular, and immune populations in preserved cytoarchitecture. This approach revealed subtype-selective disruption of cortical organization, including broadened and ectopic distributions of neuron subtypes, abnormal localization of astrocyte and oligodendrocyte

populations, and lesion compartments spanning transitions from relatively preserved to severely dysplastic cortex. Targeted sequencing enabled integration of spatial phenotypes with mutation status and mosaic burden. PS6-positive cells were absent from control cortex but formed lesion-specific transcriptomic clusters in FCD2. These pS6-positive populations included dysmorphic neuron-like cells with aberrant glial marker expression and astrocyte-like populations expressing neuronal markers, suggesting mixed or unstable cellular identity. Immunostaining confirmed pS6-positive cells co-expressing NeuN and VIM. Anchor-centered neighborhood analysis further suggested that dysmorphic neuron- and balloon cell-associated microdomains are accompanied by local changes in cell composition and transcriptional state. Finally, mosaic human brain organoids provide a complementary experimental system to test how sparse mTOR-pathway perturbations generate dysmorphic cell states and alter neighboring cells. Defined-ratio mosaic organoids with inducible mTOR-pathway activation produced enlarged pS6-positive, NeuN-positive DN-like cells, non-cell-autonomous pS6 activation in surrounding unlabeled cells, and rapamycin-sensitive dysmorphic phenotypes. Together, these data establish a spatial single-cell framework for defining FCD2 lesion architecture, linking mTOR hyperactivation to mixed dysmorphic cell states, and nominating non-cell-autonomous mechanisms by which rare mutant cells may remodel surrounding cortical tissue.

Disclosures: X. Qian: None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.01/H5

Topic: A.06. Developmental Disorders

Support: IBRO

Title: The Intrinsic Nature of Inanimate Object Preference over Faces in Children with ADHD

Authors: *K. SHARMA;
Physiol., AIIMS, New Delhi, Delhi, India

Abstract: The Intrinsic Nature of Inanimate Object Preference over Faces in Children with ADHD Kajal Sharma[1,3], Ujjwal Chandela[1,2], Deepak Joshi[2], Rita Sharma[3], Bichitra Patra[1], Suman Das[1] [1]All India Institute of Medical Sciences, New Delhi; [2]Indian Institute of Technology, [3]Delhi; ITM University, GwaliorAttention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder affecting 4-12% of school-aged children and about 4-5% of college students and adults worldwide. It is characterized by developmentally inappropriate inattention, hyperactivity, and impulsivity, often beginning in childhood and manifesting as poor concentration, disorganization, forgetfulness, and difficulty completing tasks. A significant amount of attention has been paid to the characteristics of eye movement and their neurobiological roles in ADHD. Eye-tracking represents a non-invasive approach for assessing

specific cognitive domains, particularly visual attention, by quantifying the duration and pattern of gaze fixation on defined areas of interest. In the present study, we aim to investigate whether children with ADHD exhibit intrinsic visual preferences toward biologically salient animate stimuli (human faces and birds) compared with non-biological inanimate objects (mobile phones and bikes) when presented simultaneously within a shared visual field. Our hypothesis was that children with ADHD would demonstrate altered visual preference patterns relative to healthy controls and children with other psychiatric conditions.

Disclosures: K. sharma: None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.02/H6

Topic: A.06. Developmental Disorders

Title: Characterizing Transcriptome Alterations in Williams Syndrome Induced Pluripotent Stem Cell (iPSC)-Derived Neural Cells

Authors: C. DA SILVA CAMARGO[1], *S. D. DETERA-WADLEIGH[2], N. AKULA[3], A. SCHULMANN[4], K. JOHNSON[2], M. D. GREGORY[5], D. P. EISENBERG[6], M. H. GARVEY[7], J. S. KIPPENHAN[2], A. ELKAHLOUN[2], K. F. BERMAN[8], F. J. MCMAHON[9]; [1]NIH/NIMH, Bethesda, MD; [3]Mood and Anxiety disorders, [2]NIH, Bethesda, MD; [4]Mol. Imaging and Neuropathology Div., Columbia Univ. & NYSPI, Bronx, NY; [5]NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD; [6]Clin. and Translational Neurosci. Br., CTNB, NIMH IRP, Bethesda, MD; [7]NIMH/University of Cambridge, Washington, DC; [8]Clin. and Translational Neurosci. Br., NIH/National Inst. of Mental Hlth., Bethesda, MD; [9]NIMH, Bethesda, MD

Abstract: Background: Williams Syndrome (WS) is a rare neurodevelopmental disorder caused by a large hemizygous deletion on chromosome 7q11.23. It is characterized by mild intellectual disability, distinctive cognitive and behavioral traits, unique facial features, overly social behavior, and other nervous system abnormalities. Although WS has a well-defined cognitive and behavioral profile, its cellular and molecular mechanisms remain incompletely understood. **Methods:** To investigate neurobiological mechanisms disrupted in WS, we performed single-cell RNA sequencing (scRNA-seq) and compared the transcriptome profiles of iPSC-derived neural progenitor cells (NPCs) and cortical neurons from WS participants and their non-carrier siblings. **Results:** scRNA-seq analysis identified clusters corresponding to distinct stages of neural differentiation. Cells captured at the early developmental stage, expressed NPC markers such as *nestin* and *PAX6*. A subset of cells showed progression toward neuronal maturation, with expression of genes associated with GABAergic and glutamatergic neurons. As expected, genes located within the 7q11.23 hemizygous deletion region, including *GTF2I* and *LIMK1*, were significantly downregulated. Differentially expressed genes (DEGs) at the NPC stage were enriched for cell cycle and mitotic processes, while DEGs detected at the postmitotic neuron

phase were enriched for nervous system development and synaptic signaling pathways. **Conclusion:** These findings provide insight into stage-specific molecular alterations in WS neural development. Future studies will incorporate multi-omics analyses and integrate molecular data with available neuroimaging and clinical phenotypes of study participants, potentially identifying pathways relevant for therapeutic development.

Disclosures: C. da Silva Camargo: None. **S.D. Detera-Wadleigh:** None. **N. Akula:** None. **A. Schulmann:** None. **K. Johnson:** None. **M.D. Gregory:** None. **D.P. Eisenberg:** None. **M.H. Garvey:** None. **J.S. Kippenhan:** None. **A. Elkahloun:** None. **K.F. Berman:** None. **F.J. McMahon:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.03/Web Only

Topic: A.06. Developmental Disorders

Support: National Science and Technology Council, Taiwan, (114-2813-C-002-127-B and 112-2314-B-002-119-MY3)

Title: Acute high intensity interval training speeds up motor execution and decreases variability in adults with Attention-Deficit Hyperactivity Disorder (ADHD): A preliminary study

Authors: *Y.-R. HSU[1], H.-I. KUO[1,2];
[1]Natl. Taiwan Univ., Taipei, Taiwan; [2]Dept. of rehabilitation, Natl. Taiwan Univ. Hosp., Taipei, Taiwan

Abstract: Background: Adults with ADHD show deficits in implicit motor sequence learning and increased trial-to-trial variability. While aerobic exercise modulates motor learning performance, the efficacy of high-intensity interval training (HIIT) remains underexplored. This study investigated whether acute HIIT modulates implicit learning and response stability in adults with ADHD.**Methods:** Thirteen young adults with ADHD (age: 25.58 ± 3.82 years; male/female: 7/6) completed a randomized crossover study (HIIT vs. Rest). The HIIT protocol involved 20 minutes of interval cycling. Performance on the Serial Reaction Time Task (SRTT) was assessed Pre, Post, and at 24h-Retention. We analyzed implicit sequence learning scores, reaction time, and the intra-individual coefficient of variation (ICV) to assess response stability.**Results:** Data from twelve participants were analyzed through linear mixed model (LMM). Implicit learning scores did not differ between conditions. However, HIIT significantly reduced ICV immediately post-exercise compared to baseline, whereas the control condition showed no improvement, indicating stabilized performance in HIIT group. Additionally, standardized RT decreased significantly post-HIIT, though this difference did not persist at 24 hours retention.**Conclusions**: Acute HIIT did not enhance implicit learning magnitude but significantly reduced variability and transiently sped responses. This suggests HIIT acts as a state

modulator, stabilizing neural resources to facilitate motor skill expression immediately after exercise.**Clinical Implications:** HIIT may serve as a preparatory strategy to transiently stabilize performance and reduce reaction-time variability in adults with ADHD.**Keywords:** attention-deficit/hyperactivity disorder, implicit sequence learning, high-intensity interval training, aerobic exercise

Disclosures: Y. Hsu: None. **H. Kuo:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.04/H7

Topic: A.06. Developmental Disorders

Title: Drug-Specific Treatment Persistence in Pediatric Attention-Deficit/Hyperactivity Disorder: A Nationwide Japanese Cohort Study

Authors: *R. SUZUKI[1,2], H. MURAOKA[1], M. AKAZAWA[2], K. INADA[1];
[1]Dept. of Psychiatry, Kitasato Univ. Sch. of Med., Sagamihara, Japan; [2]Dept. of Publ. Hlth. and Epidemiology, Meiji Pharmaceut. Univ., Kiyose / Tokyo, Japan

Abstract: Treatment persistence is critical for sustained benefit of attention-deficit/hyperactivity disorder (ADHD) pharmacotherapy, yet contributing factors may differ across medications. This exploratory retrospective cohort study used the JMDC nationwide claims database (January 2018-August 2024) in Japan to identify drug-specific determinants of switching versus discontinuation among three ADHD medications. We identified 29,257 children aged 6-17 years (74.5% male; mean age 10.3±3.3 years) initiating osmotic controlled-release oral delivery system methylphenidate (OROS-MPH, n=9,846), atomoxetine (ATX, n=8,135), or guanfacine extended-release (GXR, n=11,276), followed up to 730 days. The composite endpoint was the earlier of switching (Event 1) or discontinuation defined as a prescription gap ≥60 days (Event 2); persistence was the time to this endpoint. Persistence was compared using Kaplan-Meier and log-rank tests; drug-group-specific Cox models were fitted within each cohort, adjusting for age, sex, prescribing specialty, and concomitant melatonin, risperidone, and aripiprazole. Persistence differed significantly (χ^2=338, $p<2\times10^{-16}$), ranking GXR>ATX>OROS-MPH. At 730 days, persistence was 62.2% (GXR), 59.8% (ATX), and 50.4% (OROS-MPH), driven predominantly by discontinuation (χ^2=375) rather than switching (χ^2=64.2). Kaplan-Meier curves showed a biphasic pattern: steep decline within 180 days, then gradual attrition. Drug-specific models revealed heterogeneous determinants. Older age was associated with reduced switching in all groups (all $p<0.001$) but not discontinuation. In OROS-MPH recipients, males showed lower switching (HR=0.91, p=0.039) but higher discontinuation risk (HR=1.14, p=0.014). Melatonin was associated with higher persistence in ATX (HR=0.67, p=0.001) and GXR (HR=0.63, $p<0.001$), but not OROS-MPH. In GXR recipients, aripiprazole showed divergent associations: lower switching (HR=0.80, $p<0.001$) but higher discontinuation (HR=1.36, $p<0.001$), likely

reflecting comorbid autism spectrum disorder. Determinants of treatment persistence in ADHD pharmacotherapy are not uniform across agents, supporting drug-specific persistence strategies. This study was approved by the Research Ethics Review Committee of Meiji Pharmaceutical University (registration number: 202408).

Disclosures: R. Suzuki: None. **H. Muraoka:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); EA Pharma Co., Ltd., Viatris Pharmaceuticals Japan Inc., Eisai Co., Ltd., MSD K.K., Otsuka Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., Sumitomo Pharma Co., Ltd., Daiichi Sankyo Company, Limited., Takeda Pharmaceutical Company Limited., Meiji Seika Pharma Co., Ltd., Mochida Pharmaceutical Co., Ltd., Lundbeck Japan K.K.. **M. Akazawa:** None. **K. Inada:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); EA Pharma Co., Ltd., Viatris Pharmaceuticals Japan Inc., Eisai Co., Ltd., MSD K.K., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Kowa Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., Sumitomo Pharma Co., Ltd., Daiichi Sankyo Company, Limited., Takeda Pharmaceutical Company Limited, Mitsubishi Tanabe Pharma Corporation., Nipro Corporation, Nippon Chemiphar Co., Ltd., Eli Lilly Japan K.K., Boehringer Ingelheim Japan, Inc., Nexera Pharma K.K., Novartis Pharma K.K., Nobelpharma Co., Ltd., Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd., Mochida Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Lundbeck Japan K.K., Yoshitomi Pharmaceutical Industries, Ltd..

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.05/H8

Topic: A.06. Developmental Disorders

Support: NIH grants R01NS97846, R01NS097846-02S1, R01NS092876 and NIAAA of NIH grant R01AA031319 to MS

Title: Neuronal and Microglial Injury: Biomarkers in Fetal Brain-derived Exosomes Isolated from Mothers' Blood to Predict Fetal Alcohol Spectrum Disorders

Authors: *M. E. SELZER[1], U. BHARAI[6], L. DRAK[7], T. SA NGUANPHO[8], M. HAMPE[6], J. HAMZE[10], J. HU[2], S. HASSAN[3], E. OLIVER[4], R. MOSSABEB[5], M. MORRISON[11], L. HART[12], N. DARBINIAN[9];
[1]Neural Sci., Lewis Katz Sch. of Med. At Temple Univ., Philadelphia, PA; [2]Neural Sci., Lewis Katz Sch. of Med. At Temple Univ., Ambler, PA; [3]Obstetrics and Gynecology, Lewis Katz Sch. of Med. At Temple Univ., Philadelphia, NJ; [4]Obstetrics and Gynecology, Lewis Katz Sch. of Med. At Temple Univ., Philadelphia, PA; [5]Pediatrics, Lewis Katz Sch. of Med. At Temple Univ., White Non-Hispanic, PA; [6]Temple Univ., Philadelphia, PA; [7]Temple Univ., Feasterville-Trevose, PA; [8]Temple Univ., Mechanicsburg, PA; [9]Dept. of Neural Sci., Temple Univ., Philadelphia, PA; [10]Lewis Katz Sch. of Med. at Temple Univ., Philadelphia, PA; [11]Psychiatry,

Lewis Katz Sch. of Med. at Temple Univ., Wynnewood, PA; [12]Obstetrics & Gynecology, Lewis Katz Sch. of Med. at Temple Univ., Philadelphia, PA

Abstract: Introduction. Fetal alcohol spectrum disorders (FASD) are associated with early neuroinflammatory changes, but non-invasive biomarkers capable of detecting these alterations during pregnancy are limited. This study examines neuron-microglia interaction biomarkers carried within fetal brain-derived exosomes (FB-Es) isolated from maternal blood as potential early indicators of FASD. **Methods**. FB-Es were collected by immunoprecipitation targeting fetal neural markers, using maternal blood from our two human Biobanks, and exosomal cargo was analyzed for proteins and microRNAs involved in neuroinflammatory signaling, synaptic pruning, and neuron-microglia communication. **Results**. Preliminary findings reveal differential expression of key neuron-microglia interaction markers in alcohol-exposed pregnancies compared to controls, suggesting early perturbations in microglial activation and neuronal support. Shifts in levels of BDNF, synaptophysin, neurotoxicity markers (including caspase-3), and the neurotoxic cytokine TNFα, as well as the neuroprotective cytokine IGF1, were detected non-invasively from FB-Es in maternal blood. The shifts were generally in the direction of neurotoxicity and provided insight into early neuroimmune dysregulation associated with prenatal alcohol exposure. **Conclusions**. The results support the feasibility of using FB-E biomarkers of neuron-microglia interactions as tools for early prediction of FASD.

Disclosures: M.E. Selzer: None. **U. Bharai:** None. **L. Drak:** None. **T. Sa Nguanpho:** None. **M. Hampe:** None. **J. Hamze:** None. **J. Hu:** None. **S. Hassan:** None. **E. Oliver:** None. **R. mossabeb:** None. **M. Morrison:** None. **L. Hart:** None. **N. Darbinian:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.06/I1

Topic: A.06. Developmental Disorders

Support: NIH NICHD R15HD087937
Alan & Wendy Pesky Research Grant

Title: Contrastive learning reveals specific maze learning parameters associated with dyslexia

Authors: *L. A. GABEL[1], P. KAUSHIK[2], A. BELEJ[1], R. BURKE[1], K. PERETZ[3], V. BROWN[3], L. DOWSETT[1], L. BOYLE[4], A. NAM[5], Y.-C. YU[2];
[1]Neurosci., [2]Electrical and Computer Engin., [3]Biol., [4]Neurosci. and Computer Sci., [5]Psychology, Lafayette Col., Easton, PA

Abstract: Reading disabilities (RDs) are the most prevalent form of learning disabilities and are characterized by deficits in phonological processing, working memory, planning and attention. Recently we have demonstrated that maze learning and reading may rely on partially overlapping neural systems, resulting in measurable associations between maze learning strategies and

reading ability. While converging evidence from behavioral, genetic, and neurobiological studies supports this relationship, the mechanisms linking navigation and reading remain poorly understood. We therefore examined whether latent patterns of maze learning behavior, identified using deep contrastive learning, were associated with dyslexia. A total of 342 children between 5 and 12 years of age completed a virtual Hebb-Williams maze task consisting of repeated trials across multiple maze configurations. Maze performance was quantified using completion time, path distance, deviation from the true path, and a learning efficiency score capturing performance changes across repeated trials. Deviation scores incorporated both route inefficiency and navigation errors to provide a comprehensive measure of learning. These behavioral features were used as input to a deep neural network containing a 32-dimensional embedding layer trained using a contrastive learning framework. Rather than relying on individual performance measures, the network learned a latent representation that maximized similarity among behaviorally related samples while increasing separation between dissimilar samples. Learned embeddings were visualized using Uniform Manifold Approximation and Projection (UMAP). Visualization of the original behavioral feature space demonstrated substantial overlap between reading groups. In contrast, the learned embeddings revealed distinct clustering according to reading status, indicating that maze learning behavior contains distributed information associated with dyslexia that is not readily apparent in individual performance metrics. The observed separation emerged from multivariate patterns spanning navigation efficiency, route selection, and error rate rather than any single behavioral measure. These findings suggest that children with dyslexia may exhibit distinct learning strategies during the completion of this task. These results highlight the potential of combining non-reading behavioral measures with machine learning approaches to identify novel behavioral markers of dyslexia and to advance understanding of the neurocognitive systems that support reading development.

Disclosures: L.A. Gabel: None. **P. Kaushik:** None. **A. Belej:** None. **R. Burke:** None. **K. Peretz:** None. **V. Brown:** None. **L. Dowsett:** None. **L. Boyle:** None. **A. Nam:** None. **Y. Yu:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.07/I2

Topic: A.06. Developmental Disorders

Support: BlinkLab Ltd
NL Mental Care Group B.V.

Title: Characterizing Sensory Processing in Children with ADHD Using Smartphone-Based Measurements of Acoustic Startle and Prepulse Inhibition

Authors: *L. E. M. ROGGEVEEN[1], S. LINDEMAN[1], M. DETTINGMEIJER[1], V. KUHNKE[1], A. MUNTEANU[1], H.-J. BOELE[2,1,3];
[1]BlinkLab, Leiden, Netherlands; [2]Neurosci., Princeton Neurosci. Inst., Princeton, NJ; [3]Erasmus MC, Rotterdam, Netherlands

Abstract: Atypical sensory processing is increasingly recognized as a common feature of attention-deficit/hyperactivity disorder (ADHD), with auditory hypersensitivity as the most frequently reported sensory symptom. Here we investigated sensory processing of auditory stimuli in ADHD by assessing the acoustically evoked startle response (ASR) and prepulse inhibition (PPI), and compared these measures between children with ADHD and typically developing children. Participants included 22 children with ADHD (6-18 years) undergoing diagnostic evaluation at a specialized ADHD clinic in the Netherlands and a large neurotypical reference cohort of 152 typically developing children. All participants completed a 12-minute smartphone-based assessment of the ASR and PPI using headphones. ASR and PPI were quantified through eyelid closure detected via facial landmark tracking. Auditory stimuli were presented at 65 dB (soft), 75 dB (moderate), 83 dB (medium), and 105 dB (loud). Group differences were analyzed using linear mixed-effects models. Children with ADHD exhibited significantly greater ASR amplitudes than typically developing controls at moderate ($t(172)=3.00$, $p=0.0062$) and medium ($t(172)=4.54$, $p=0.0003$) sound intensities, indicating enhanced auditory sensitivity. No significant group differences were observed in PPI ($F(2,248)=0.97$, $p=0.3823$), suggesting intact sensorimotor gating in ADHD. These findings demonstrate heightened auditory sensitivity, but preserved sensorimotor gating, in children with ADHD. The results further support the feasibility of smartphone-based neurobehavioral testing for quantifying sensory processing phenotypes in pediatric populations. Future studies should evaluate the diagnostic utility of these measures and their potential contribution to objective ADHD assessment.

Disclosures: L.E.M. Roggeveen: A. Employment/Salary (full or part-time):; BlinkLab. **S. Lindeman:** A. Employment/Salary (full or part-time):; BlinkLab. **M. Dettingmeijer:** A. Employment/Salary (full or part-time):; BlinkLab. **V. Kuhnke:** A. Employment/Salary (full or part-time):; BlinkLab. **A. Munteanu:** A. Employment/Salary (full or part-time):; BlinkLab. **H. Boele:** A. Employment/Salary (full or part-time):; BlinkLab. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlinkLab.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.08/I3

Topic: A.06. Developmental Disorders

Support: NIMH and NHGRI

Title: Transcriptome-wide Profiling of Alternative Splicing in ADHD Brain Reveals Isoform-level Dysregulation

Authors: *D. NAMMI;
Genomic Functional Analysis Section, NHGRI, Natl. Inst. of Hlth., BETHESDA, MD

Abstract: Background: Attention-deficit/hyperactivity disorder (ADHD) is a heritable neurodevelopmental condition that results in symptoms of inattention, hyperactivity, and impulsivity that impair daily functioning. About 5-7% of children worldwide are affected, often into adulthood. In the United States, roughly one in nine children (6.5 million) has been diagnosed. Despite its prevalence, the underlying biological mechanisms remain unclear. ADHD commonly co-occurs with anxiety, mood, autism spectrum disorder and conduct disorders, and learning disabilities, further impacting quality of life and increasing risk for adverse outcomes. Few ADHD studies have examined transcriptome-wide alternative splicing. We aimed to identify differential alternative splicing events (DASEs), associated genes, and enriched pathways to better understand ADHD molecular mechanisms.
Methods: DASEs were identified using rMATS-turbo in postmortem brain transcriptomes from ADHD cases and controls. Five event types were analyzed: skipped exon (SE), alternative 5′ splice site (A5SS), alternative 3′ splice site (A3SS), mutually exclusive exon (MXE), and retained intron (RI). Analyses were performed in anterior cingulate cortex (ACC; 24 cases, 29 controls) and caudate nucleus (CAU; 24 cases, 32 controls). Significant events met uniform filtering thresholds: average read count ≥ 10, false discovery rate (FDR) ≤ 0.05, and percent spliced-in (PSI) difference ≥ 0.05. Pathway enrichment was conducted using the cluster Profiler package.**Results:** In the ACC, 1,413,082 novel splicing events were detected within significant genes: SE (4,835), MXE (8,854), A3SS (1,623), A5SS (1,578) and RI (308). Pathway enrichment identified 1,620 significant pathways, including 75 neurological pathways. In CAU 1,647,033 novel splicing events were identified within significant genes: SE (5,572), MXE (10,481), A3SS (1,843), A5SS (1,768) and RI (329). Pathway analysis revealed 888 enriched pathways including 24 neurological pathways. Notably, 12 key splicing-related pathways were shared between regions.
Conclusion: These results suggest that disruptions in RNA splicing are linked to ADHD. The enrichment of dopaminergic and glutamatergic pathways, consistent with previous RNA-seq studies, indicates that dysregulation of RYK, CLN3, GRIA2, PLCB1, and GRIA4 isoform processing is likely to play a key role in the underlying mechanisms of the condition.

Disclosures: D. Nammi: None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.09/I4

Topic: A.06. Developmental Disorders

Title: Iron-Sensitive T2-weighted Differences in the Subcortex of Adolescents with ADHD: A Longitudinal Analysis in the ABCD Cohort

Authors: *J. AHERN[1], B. J. H. AHN[2], S. ALI[3], A. BAIM[4], S. CHANG[5], D. V. DEMETER[6], E. KOITHAN[9], S. PARK[1], A. M. DALE[10], C. MAKOWSKI[7], R. LOUGHNAN[10], D. GREENE[8]; [1]UCSD, La Jolla, CA; [3]Cognitive Sci., [2]UCSD, San Diego, CA; [4]Cognitive Sci., UCSD, SAN DIEGO, CA; [5]Dept. of Cognitive Sci., UCSD, La Jolla, CA; [6]Cognitive Sci., [7]Psychiatry, Univ. of California San Diego, La Jolla, CA; [8]Cognitive Sci., Univ. of California San Diego, San Diego, CA; [9]Cognitive Sci., UC San Diego, San Diego, CA; [10]J. Craig Venter Inst., La Jolla, CA

Abstract: Attention-deficit hyperactivity disorder (ADHD) is a common psychiatric condition in adolescents. Lower brain iron has been reported in individuals with ADHD compared to controls, and there is evidence of brain iron changes across the lifespan. Prior work has only examined group differences in brain iron in ADHD cross-sectionally. To examine how brain iron changes longitudinally in adolescents with and without ADHD, we modeled the effect of age and ADHD on subcortical T2-weighted intensity (T2w), which is sensitive to brain iron.
Models included 10370 participants (5029 F, Age 12.38 ± 2.3 yrs) from the Adolescent Brain Cognitive Development (ABCD) study. 2852 participants met criteria for ADHD (1049 F, Age 12.46 ± 2.3 yrs) based on the Kiddie Schedule for Affective Disorders and Schizophrenia. Spline regressions were fit with cubic B-splines. We examined the effects of ADHD group on T2w in 6 Freesurfer-defined subcortical regions: the accumbens, brainstem, caudate, pallidum, putamen, and thalamus. Models included fixed effects of sex, scanner, income, 10 genetic principal components, and smooth effect of age, and random effects of participants nested in families. For significant effects of the ADHD group on T2w, additional models were fit to examine potential interactions between ADHD group and the smooth effect of age, and post hoc linear regression sliding-window analysis was used to identify age ranges with a significant difference between the ADHD and non-ADHD groups.
Significant changes in T2w with the smooth effect of age were found across regions. We found a significant ($pFDR \leq 0.03$) increase in T2w in the ADHD group compared to the non-ADHD group in the thalamus ($\beta = 0.03$), putamen ($\beta = 0.02$), and pallidum ($\beta = 0.02$). There was only a significant interaction between ADHD group and T2w in the putamen ($\chi^2 = 10.89$, $p < 0.01$). Sliding window analysis found significant differences between ADHD groups in the putamen and pallidum in all but a few windows (window centers span 10 to 16.5 yrs, $pFDR < 0.05$), but none in the thalamus.
T2w changes dynamically with age, with a significant increase in T2w in the thalamus, putamen, and pallidum of individuals in the ADHD group compared to the non-ADHD group. Differences in T2w may be related to brain iron; other explanations for increased T2w (edema, cysts, hemorrhages, etc.) are less likely in an adolescent dataset. Our findings of increased T2w in the subcortex in the ADHD group are consistent with previous findings of lower brain iron in individuals with ADHD compared to controls, while providing greater insights into the temporal dynamics of this effect using a large, longitudinal, nationally representative sample.

Disclosures: J. Ahern: None. **B.J.H. Ahn:** None. **S. Ali:** None. **A. Baim:** None. **S. Chang:** None. **D.V. Demeter:** None. **E. Koithan:** None. **S. Park:** None. **A.M. Dale:** None. **C. Makowski:** None. **R. Loughnan:** None. **D. Greene:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.10/I5

Topic: A.06. Developmental Disorders

Support: NIH NIA 5R01AG090302
NIH 1S10OD034414

Title: Consistent thalamic neural correlates of tics in multiday intracranial EEG analysis

Authors: *K. SHENOY;
Neurol., Mass Gen. Brigham, Boston, MA

Abstract: Consistent thalamic neural correlates of tics in multiday intracranial EEG analysis Krishma Shenoy, Peter Hadar, Tamir Avigdor, Devang Sehgal, Sydney S. Cash and Rina Zelmann
Figure1. a. Intracranial reconstruction; b. Power plots at bipolar contacts indicate involvement of thalamus during tic initiation.; TF plot was normalized to the resting state period 1. clustered facial tics 2. Shoulder Shrugs. Note increased theta and beta power during eyeblink and decreased beta power during shoulder shrug.c. Statistical test identified most involved bipolar contacts for facial tics, confirming involvement of pulvinar & CM.What are the neural correlates of tics? To date tics have only been studied with scalp EEG or deep brain electrodes with a limited montage, limiting our understanding of deep structures' involvement within the larger brain network. A patient with Epilepsy and Tourette's syndrome, implanted with depth electrodes, including in the thalamus, offered the first-in-human opportunity to study the initiation of tics.We analyzed the intracranial EEG (iEEG) of 6 distinct motor tics over 7 days, recording from N=176 contacts implanted bilaterally with thalamic coverage. Tics studied were eyeblinks with mouth twitches, right shoulder shrugs or similar movement on the left. EEG segments consisted of clusters of the most frequent tics along with a resting state period. We computed time – frequency plots for each channel and normalized to a tic-free period. These plots deduced the most active bipolar contacts and narrow down anatomical regions of interest. For each contact, we quantified the magnitude of activity change during facial tics using the Mann-Whitney U test and Cliff's delta.The most frequent tics, facial twitch, theta-band activity increased ~150% over baseline at bilateral pulvinar and CM contacts, with involvement of frontal cortical areas ($\delta > 0.6$; $p<=0.001$), while broader cortical areas decreased ~60%. Other tics engaged similar contacts in the beta band with more variability; future analyses will focus on unraveling this.This is the first confirmation in humans where we have seen larger pulvinar and CM activity in tic generation along with broader correlation in some cortical structures. This work provides the first demonstration of specific thalamic biomarkers of tics, supporting clinical usefulness of thalamic neuromodulation for Tourette's syndrome and tic disorders.Supported by NIH NIA 5R01AG090302, NIH 1S10OD034414, Peter Hadar: American Academy of Neurology, American Brain Foundation, American Epilepsy Society, Epilepsy Foundation Susan S. Spencer Clinical Research Training Scholarship

Disclosures: K. Shenoy: A. Employment/Salary (full or part-time):; Full time.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.11/I6

Topic: A.06. Developmental Disorders

Support: DFG
Glazer Foundation

Title: War Exposure Alters the Neural Regulation of Screen Use in Children: A Limbic-Attentional Pathway

Authors: *T. HOROWITZ-KRAUS;
Technion Israel Inst. of Technology/Kennedy Krieger Inst., Baltimore, MD

Abstract: War Exposure Alters the Neural Regulation of Screen Use in Children: A Limbic-Attentional Pathway Prof Tzipi Horowitz-Kraus, PhD Educational Neuroimaging Group, Faculty of Education in Science and Technology , Faculty of Biomedical Engineering, May-Blum-Dahl Technion Human MRI Research, Technion, Haifa, Israel Background: War exposure is associated with limbic dysregulation and altered executive function, yet neural mechanisms linking chronic stress to screen-seeking remain unknown. Method: Forty-two war-exposed Israeli children (scanned 2023-2024) were compared to 37 non-exposed peers (scanned 2018-2022), ages 5-13, using resting-state fMRI, behavioural EF, and parent-reported screen exposure. Serial moderated mediation tested whether limbic connectivity predicted screen frequency via VAN-DAN coupling and rapid automatised naming (RAS), with group moderating both pathways. Age and nonverbal IQ were controlled. Results: Subcortical-amygdala connectivity predicted VAN-DAN coupling ($\beta = +0.36$, $p = .003$), which in war-exposed children predicted slower RAS naming ($\beta = -0.47$, $p = .016$) and greater screen use. The complete serial indirect effect was significant in exposed children (ab = +0.048, 95% CI [+0.005, +0.145]) but absent in non-exposed peers. Conclusion: War exposure recruits a bottom-up limbic-attentional pathway driving screen-seeking as a stress-regulatory strategy, with direct implications for trauma-informed screen intervention.

Disclosures: T. Horowitz-Kraus: None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.12/I7

Topic: A.06. Developmental Disorders

Title: Delineating multiomic and network-level architecture of caudate and putamen in early-onset attention deficit/ hyperactivity disorder

Authors: *R. PATEL, S. WANG, J. B. WILLIAMS;
Univ. at Buffalo, Buffalo, NY

Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable and heterogeneous neurodevelopmental disorder affecting ~11.4% of school-aged children in the U.S., with increasing prevalence. Although ADHD typically emerges during childhood or adolescence, transcriptomic studies have often underrepresented two major sources of clinical heterogeneity: age of onset and ADHD subtype, with many cohorts primarily composed of adults. To address this gap, we established a strictly phenotyped early-onset ADHD cohort defined by age ≤18 years, clinical diagnosis, and combined or inattentive subtype classification. Using postmortem caudate and putamen tissues, we integrated bulk RNA sequencing, LC-MS metabolomics, gene co-expression network analysis, pathway enrichment, and cross-study transcriptomic meta-analysis to investigate molecular dysregulation in early-onset ADHD. Our bulk RNA sequencing identified 279 up- and 35 downregulated differentially expressed genes (DEGs) in caudate, and 110 up- and 89 downregulated DEGs in putamen. LC-MS identified dopamine, arginine, succinate, and 6 additional metabolites. To move beyond DEG-level interpretation, we performed MEGENA using the top 2,500 ranked genes, of which ~88% were not individually significant DEGs, enabling identification of coordinated gene networks associated with ADHD. This analysis identified 26 ADHD-associated modules in caudate and 33 in putamen. Integration of MEGENA module-derived biological pathways with DEG-based GSEA pathways revealed region-specific and shared molecular signatures, including neuroimmune dysregulation in putamen, ciliary dysfunction in caudate, and ATP metabolism alterations in both regions, alongside canonical pathways related to synaptic transmission and neuronal circuitry, each linked to specific co-expression modules. Cross-comparison of our transcriptomics, an independent caudate transcriptomics, and their meta-analyzed results identified AQP7, CALHM1, and 3 additional genes as consistently dysregulated. We further identified 42 genes shared between early-onset ADHD and broader ADHD caudate transcriptomic signatures. Finally, comparison with the largest ADHD GWAS, reporting 27 risk loci and 31 associated genes, showed that none of these GWAS-prioritized genes were significantly dysregulated in caudate or putamen transcriptomic data. These findings highlight the importance of brain-region-specific transcriptomic studies and suggest that ADHD pathophysiology extends beyond canonical neurotransmission pathways to include neuroimmune signaling, ciliary biology, cell adhesion, and energy metabolism.

Disclosures: R. Patel: None. **S. Wang:** None. **J.B. Williams:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.13/I8

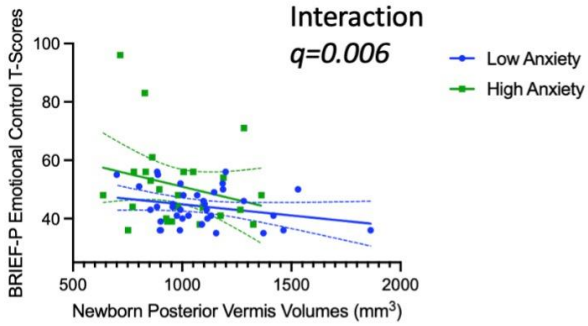
Topic: A.06. Developmental Disorders

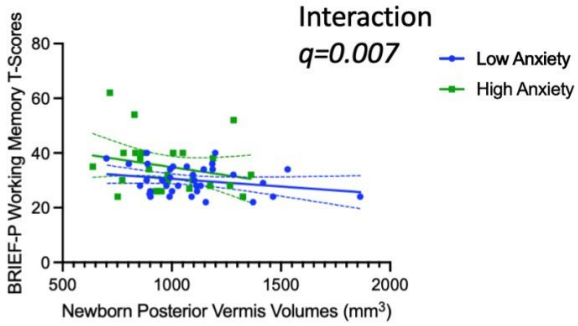
Support: NIH Grant R01HD118702
NIH Grant R01HL116585

Title: Prenatal Maternal Anxiety Moderates the Relationship Between Newborn Posterior Vermis Volumes and Early Childhood Executive Function

Authors: *S. WEINER[1], J. CHENG[4], K. KAPSE[2], A. MEARS[5], H. LATIF[2], E. ADEGBULUGBE[5], C. LIMPEROPOULOS[3], N. N. ANDESCAVAGE[2];
[1]Children's Natl. Hosp., Arlington, VA; [2]Children's Natl. Hosp., Washington, DC; [3]Diagnos. Imaging & Radiology/Developing Brain Res. Lab., Children's Natl. Hosp., Bethesda, MD; [4]Children's Natl. Hopsital, Washington, DC; [5]Childrens Natl. Hosp., Washington, DC

Abstract: Background Early childhood neurodevelopmental outcomes are closely linked with prenatal influences, including elevated maternal prenatal anxiety. Both anxiety and executive functioning in the child are closely associated with the development of the cerebellar vermis. **Objective**To determine the relationship between the newborn cerebellar development and attention-hyperactivity at preschool age following exposure to prenatal maternal anxiety.**Design/Methods**We prospectively recruited healthy mother-baby dyads, excluding mothers using tobacco, alcohol or other drugs during pregnancy. Prenatal maternal anxiety (PMA) was measured using the Spielberger State-Trait Anxiety Inventory, with scores >40 indicative of high anxiety. Neonates underwent non-sedated brain MRI, and images were segmented into 3D volumes; The BRIEF-P was used to assess executive function between 3-4 years of age. Linear regression models were used to assess the relationships between PMA, newborn cerebellar volumes, and performance on the BRIEF-P subdomains. An interaction analysis was subsequently performed to assess the relationship between the newborn cerebellar volumes and performance on the BRIEF-P in the presence of high PMA. **Results**High levels of PMA were associated with smaller posterior vermis volumes on newborn MRI (p<0.01); in toddlers, elevated PMA was associated with higher risk scores on the emotional control (p<0.001), shift (p<0.05), working memory (p<0.001), and planning/organization (p<0.05) domains of the BRIEF-P. In children who were exposed to high levels of PMA, there is a significant negative association between newborn posterior vermis volumes and performance on the working memory (p<0.01*)* and emotional control (p<0.01 subscales of the BRIEF-P, such that smaller volumes are associated with higher risk scores.**Conclusion(s)**Exposure to high levels of PMA moderates a significant relationship between smaller posterior cerebellar vermis volumes on newborn MRI and high-risk executive dysfunction in the domains of emotional control and working memory at ages 3 and 4.





Anxiety Level	Adjusted Slope	95% CI	*p*-value
Low	-0.01	-0.01 to 0.01	0.371
High	**-0.03**	**-0.06 to -0.03**	**0.030**

Anxiety Level	Adjusted Slope	95% CI	*p*-value
Low	-0.01	-0.02 to 0.01	0.366
High	**-0.05**	**-0.09 to -0.01**	**0.024**

Disclosures: S. Weiner: None. **J. Cheng:** None. **K. Kapse:** None. **A. Mears:** None. **H. Latif:** None. **E. Adegbulugbe:** None. **C. Limperopoulos:** None. **N.N. Andescavage:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.14/J1

Topic: A.06. Developmental Disorders

Support: STI 2030-Major Projects 2022ZD0211300
National Natural Science Foundation 82472059of China
Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences 2025-I2M-XHJC-056
Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences 2024-RC416-02

Title: Developmental deviations of association-network structural connectivity in youths with ADHD predict symptom and treatment outcomes

Authors: *X. XU[1], J. CONG[2], A. S. KELLER[3], T. XU[4], W. CAI[5], Z. CUI[1];
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Abstract: Attention-deficit/hyperactivity disorder (ADHD) lacks validated biomarkers to track symptom development or guide treatment selection in youth. This disorder involves distributed

neural alterations, implying that white-matter structural connectivity (SC) linking these regions may capture its substrate. However, the SC alterations in ADHD remain unclear. Here, we aim to investigate how SC deviations evolve across development and track symptoms or inform treatment selection in youth with ADHD. We quantified per-connection deviations in SC strength from normative trajectories in two independent cohorts: the Adolescent Brain and Cognitive Development (ABCD) study (6,687 TD; 1,114 ADHD) and a Chinese cohort (355 TD; 477 ADHD). ABCD data were collected from September 2016 to January 2022, and Chinese cohort data from July 2015 to February 2026. Age effects on deviations were modeled with generalized additive mixed models and generalized additive models. Brain-symptom links were tested using correlation and mediation analyses. A subset of youth with ADHD (n=112) from the Chinese cohort completed 12-week pharmacological treatment with pre/post symptom assessments. Treatment effects were tested using repeated-measures ANOVA, and baseline SC deviations were used to predict response via linear regression. The primary outcome was ADHD diagnosis, and secondary outcomes were ADHD symptoms measured by the Child Behavior Checklist and the ADHD Rating Scale. We found that youth with ADHD showed pronounced SC deviations, especially in higher-order association pathways. A subset of association connections showed ADHD-specific developmental reductions in deviations beyond typical developmental patterns, and these changes mediated the age-related decline in ADHD symptoms. Longitudinal within-individual analyses demonstrated that decreases in deviation over two years tracked symptom improvement. Baseline deviations also predicted 12-week treatment response to atomoxetine, but not methylphenidate, and follow-up imaging revealed treatment-related reductions in deviation. In conclusion, SC deviations, particularly in frontoparietal and default-mode circuits, may serve as neurodevelopmental biomarkers for ADHD. These findings suggest that tracking SC deviations could help monitor symptom progression and guide treatment decisions, with potential applications for precision psychiatry in ADHD.

Disclosures: X. Xu: None. **J. Cong:** None. **A.S. Keller:** None. **T. Xu:** None. **W. Cai:** None. **Z. Cui:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.15/J2

Topic: A.06. Developmental Disorders

Support: the Brain Science and Brain-like Intelligence Technology - National Science and Technology Major Project (2022ZD0211300),
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Non-profit Central Research Institute Fund of Chinese Academy of Medical

Sciences (2024-RC416-02)
Chinese Institute for Brain Research, Beijing (CIBR) funds

Title: White-matter functional connectivity uniquely predicts brain age, cognition, and psychopathology beyond gray matter

Authors: *J. CONG[1], X. XU[2], H. LI[3], T. XU[4], Z. CUI[1];
[1]Chinese Inst. for Brain Research, Beijing(CIBR), Beijing, China; [2]Chinese Inst. for Brain Research, Beijing, Beijing, China; [3]Univ. of Pennsylvania, Philadelphia, PA; [4]Child Mind Institute, Ctr. for the Integrative Developmental Neurosci., New York, China

Abstract: White-matter pathways form the structural backbone for communication across the human connectome, yet whether functional interactions within these tracts carry information beyond gray-matter networks remains unclear. Here, we test whether white-matter functional connectivity (WM-FC), including gray-white (G-W) and white-white (W-W) connectivity, uniquely predicts brain age, cognition, and psychopathology. Resting-state fMRI data were analyzed from five independent neurodevelopmental cohorts. Age prediction was examined in the Philadelphia Neurodevelopmental Cohort (PNC, n = 1,124, aged 8.1 to 23.0 y), the Lifespan Human Connectome Project in Development (HCP-D, n = 531, aged 8.0 to 22.0 y), the developmental component of the Chinese Color Nest Project (devCCNP, n = 193, aged 6.0 to 18.9 y), and the Executive Function and Neurodevelopment in Youth (EFNY, n = 522, aged 6.4 to 23.5 y) study. To assess the behavioral relevance of white-matter FC, we further leveraged the Adolescent Brain Cognitive Development (ABCD) Study, a large and demographically diverse cohort of children aged 8.9-11.0 years (cognition: n = 4,388; psychopathology: n = 4,465) with harmonized cognitive and psychopathology assessments. Functional connectivity was estimated among 100 cortical gray-matter parcels and 68 white-matter regions, generating gray-gray (G-G), gray-white (G-W), and white-white (W-W) feature sets. Partial least-squares regression with nested five-fold cross-validation was used for prediction. Across multiple independent cohorts, both gray-white and white-white connectivity contributed unique information about brain age and cognition, whereas gray-white connectivity further explained unique variance in ADHD symptoms beyond that captured by gray-matter connectivity alone. Feature-weight analyses revealed that commissural, projection, superficial, and association pathways contributed to the predictions, indicating a structured white-matter functional architecture that parallels yet remains distinct from gray-matter networks. These results extend current models of large-scale brain function by showing that functional organization emerges not only from cortical networks but also from coordinated interactions involving white matter. Together, these findings position white-matter functional connectivity as a distinct and behaviorally meaningful component of the human connectome, extending models of neurodevelopment beyond gray-matter functional organization.

Disclosures: J. Cong: None. **X. Xu:** None. **H. Li:** None. **T. Xu:** None. **Z. Cui:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.16/J3

Topic: I.04. Executive Functions

Title: Repetitive visual stimulation at 10 Hz improves cognitive performance in people with ADHD

Authors: *E. E. BENDER, A. SCHIELKE;
Reed Col., Portland, OR

Abstract: Attention Deficit/Hyperactivity Disorder (ADHD) has an estimated global prevalence of 2% to 7% in children and 4% to 5% in adults, and is marked by deficits in attention and/or impulse control. Available pharmaceutical and behavioral interventions help manage these symptoms, however, their relief is only partial. Oscillatory neuronal activity between approximately 8 to 12 Hz (alpha-band activity) is associated with cortical inhibition and excitation, sensory perception, and cognitive function. ADHD is associated with altered alpha-band activity during tasks that require (prolonged) allocation of attention or response inhibition, as well as during resting state EEG measurements. Here we used 10 Hz repetitive visual stimulation (RVS) to induce neuronal activity that falls within the alpha-band, with the goal to improve performance during a psychomotor vigilance task (PVT) and during the Stop-Signal Task (SST). We recruited 30 college students (15 with ADHD and 15 without ADHD) between the age of 18 and 24 years to complete a behavioral experiment on two separate days. On one of the two days participants received 10 Hz RVS and on the other day they received steady light (control) for 10 minutes. The experiment took place in a room with standard overhead lighting turned on. We administered peripheral RVS through a small light box located below the computer monitor while participants fixated a cross displayed at the center of the monitor. Participants performed both tasks (PVT and SST) before and multiple times after the RVS/steady light block. We found that compared to steady light, 10 Hz RVS increased reaction times for participants without ADHD during the PVT, but improved performance of people with ADHD by decreasing attentional lapses. For the SST, we found that 10 Hz RVS improved inhibitory control more for participants with ADHD than for participants without ADHD. However, we only detected RVS induced changes in performance during the PVT and SST measurements that directly followed the sensory stimulation. These findings support the role of alpha-band activity in cognitive performance of people with ADHD and suggest that repetitive visual stimulation at 10 Hz could promote cognitive performance in this population.

Disclosures: E.E. Bender: None. **A. Schielke:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.17/J4

Topic: I.04. Executive Functions

Support: Student Research and Travel Grant (SRTG)

Title: EXAMINING EXECUTIVE FUNCTIONS IN ADHD STUDENTS DURING EXPLICIT SEQUENCE LEARNING: AN ERP STUDY

Authors: *K. HENSON;
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Abstract: Executive functions (EFs) are commonly impaired in individuals with attention-deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder characterized by inattention, inhibitory difficulties, and hyperactivity that can negatively impact social and academic functioning. EFs are essential for goal-directed behavior and include inhibition, working memory, attention, and performance monitoring. Performance monitoring involves detecting and evaluating errors and is reflected by the error-related negativity (ERN), an event-related potential (ERP) associated with early, automatic error detection, and the error positivity (Pe), which reflects conscious error awareness and evaluation. Attention was examined using the P300, an ERP component associated with attentional allocation and stimulus evaluation processes. Previous research has demonstrated impairments in these executive processes in individuals with ADHD, particularly in top-down attentional control. Because executive functions are critical for explicit learning, which involves the conscious acquisition of information with awareness of what is being learned, the present study examined whether individuals with ADHD would demonstrate evidence of explicit learning. Electrophysiological measures revealed greater variability in ERN and Pe among participants with ADHD compared to non-ADHD controls. P300 latency also differed between groups, suggesting slower stimulus processing in the ADHD group. Unexpectedly, participants with ADHD elicited a possible N200 component, an ERP associated with implicit learning paradigms. Evidence for explicit learning was more limited in the ADHD group than in the non-ADHD control group. However, electrophysiological findings suggest that ADHD participants may have relied more heavily on implicit learning processes despite instructions designed to promote explicit learning. These findings indicate that individuals with ADHD may engage different learning mechanisms.

Disclosures: K. Henson: None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.18/J5

Topic: I.04. Executive Functions

Support: NRF-2021R1A2C1011385
RS-2024-00353254
RS-2022-NR070031
RS-2023-00262321

Title: Comprehensive behavioral profiling in male spontaneously hypertensive rats: latent trait mapping supports a valid multidomain ADHD model

Authors: *H. KIM[1], Y. CHOI[2], R.-S. WOO[1];
[1]Dept. of Anat. and Neurosci., Eulji Univ., Daejeon, Korea, Republic of; [2]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder marked by inattention, impulsivity, and hyperactivity. Although the spontaneously hypertensive rat (SHR) is widely used to model ADHD, intra-strain behavioral heterogeneity and its neurobiological relevance remain insufficiently defined. We conducted a comprehensive multidomain behavioral assessment of male adolescent SHR and Wistar-Kyoto (WKY) rats spanning locomotion/exploration, anxiety- and risk-related behavior, compulsive-like activity, cognition, and sensorimotor gating. Across tasks, SHR rats exhibited increased impulsive and repetitive exploratory behaviors, context-dependent alterations in anxiety-related measures, reduced spontaneous alternation, and impaired prepulse inhibition. Exploratory factor analysis of 26 behavioral variables identified five interpretable latent dimensions, including exploratory-attentional engagement and impulsivity/disinhibition, and revealed substantial heterogeneity within the SHR population. Using WKY-referenced factor-score deviation, SHR were stratified into normative-range and combined-deviant subtypes. The combined-deviant subtype exhibited convergent circuit-level alterations, including reduced parvalbumin (PV)/glutamate decarboxylase 67 (GAD67)-associated inhibitory features and decreased synaptic marker signals in prelimbic and infralimbic medial prefrontal cortex, together with increased dopamine transporter expression (DAT) in the striatum without changes in tyrosine hydroxylase (TH). Complementary principal axis factoring, bootstrap resampling, and split-sample analyses supported the robustness of the factor structure. These findings link multidimensional behavioral subtypes in SHR to distinct prefrontal-striatal signatures, strengthening the translational utility of SHR-based ADHD research.

Disclosures: H. kim: None. **Y. Choi:** None. **R. Woo:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.19/J6

Topic: A.06. Developmental Disorders

Support: NINDS R01NS126108
SFARI Bridge to Independence Award
Cincinnati Children's Trustee Grant Award to JER
Children's Tumor Foundation Young Investigator Award to Zoe Cappel

Title: Brain circuits contributing to ADHD-like phenotypes in NF1 model mice

Authors: *Z. CAPPEL[1,2], K. E. RENEAU[2], S. D'SOUZA[2], E. COTELLA[2], D. FERNANDEZ[4], N. K. EVANSON[3], G. W. SCHWARTZ[5], R. R. WACLAW[2], J. E. ROBINSON[2];
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Abstract: **Background and purpose:** The neurocognitive symptoms of neurofibromatosis type 1 (NF1) include impaired executive functioning, autistic features, speech and language delays, and sensory processing abnormalities. NF1 patients also have a high incidence of attention deficit/hyperactivity disorder, which is characterized by hyperactivity, impulsivity and distractibility, whereby individuals assign exaggerated stimulus salience to novel yet irrelevant environmental stimuli and are less able to suppress reactions to visual stimuli that are emotionally arousing. Similarly, our lab previously demonstrated that Nf1 haploinsufficient mice (*Nf1*$^{+/-}$) and mice with a gain of function mutation in the terminal MAPK protein, ERK2, are hyperreactive to a visual looming stimulus that simulates an approaching aerial predator. However, the brain circuits contributing to ADHD-like phenotypes in NF1 model mice are unknown. **Methods:** To address what region of the brain is sensitive to upregulated MAPK activity, we generated Cre-inducible mice with constitutive MEK activity in a region- and cell lineage-specific manner and performed a battery of behavioral assays. Visual hyperreactivity was assessed using the looming stimulus assay, which simulates an approaching aerial predator and evokes rapid flight to shelter responses. The acoustic startle assay was used to measure sensorimotor gating, or the response to sudden loud noises. The locomotor activity assay was used to assess motor hyperactivity. Lastly, the cliff avoidance assay was used to screen for risk-taking behavior. **Results and conclusions:** We found that upregulating MAPK in forebrain inhibitory interneurons (*Dlx1-Cre;MEKDD*) or the midbrain and cerebellum (*En1-Cre;MEKDD*) does not produce visual hyperreactivity. Instead, sustained MAPK activity in excitatory neurons and glia of the cortex and hippocampus (*Emx1-Cre;MEKDD*) was sufficient to drive visual hypersensitivity. Additionally, *Emx1-Cre;MEKDD* mice are hyperactive and show a non-significant trend toward an enhanced acoustic startle response. Furthermore, preliminary evidence suggests that *Emx1-Cre;Nf1*$^{flox/+}$ and *Emx1-Cre;Nf1*$^{flox/flox}$ mice phenocopy the attentional deficits of Cre-inducible MEK mutants such as visual hyperreactivity and impulsive-like behavior. Our findings suggest that attentional phenotypes are driven by enhanced MAPK activity in the cortex, but future work will further parse the role of distinct cell types within the *Emx1* lineage using *Olig1-CreERT2* and *Vglut1-Cre* mice.

Disclosures: Z. Cappel: None. **K.E. Reneau:** None. **S. D'Souza:** None. **E. Cotella:** None. **D. Fernandez:** None. **N.K. Evanson:** None. **G.W. Schwartz:** None. **R.R. Waclaw:** None. **J.E. Robinson:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.20/J7

Topic: A.06. Developmental Disorders

Support: NINDS/NIH: R01NS107428 (S.R.)

Title: CIB2 overexpression modulates behavioral and anatomical neurological phenotypes in Pten conditional mutant mice

Authors: *A. A. ZAIB[1], Z. M. AHMED[2], S. RIAZUDDIN[1], S. RIAZUDDIN[2];
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Abstract: Phosphatase and tensin homology (PTEN) dysfunction-associated neurodevelopmental disorders are characterized by upregulation of PI3K-AKT-mTOR signaling and are frequently associated with macrocephaly, neuronal abnormalities, and behavioral dysfunction. The *Pten-GFAP* conditional knockout (cKO) mouse is an established mTORopathy model that recapitulates several neurological and structural features associated with PTEN deficiency. Our recent studies implicated calcium and integrin binding protein 2 (CIB2) as a negative regulator of mTORC1 signaling, suggesting potential therapeutic relevance in mTOR hyperactivity disorders. Here, we evaluated systemic AAV9-CAPB10-mediated *hCIB2* overexpression in the *Pten-GFAP* cKO mouse brain in both preventive (P30) and post-disease (P60) paradigms. Behavioral analyses performed at P90 using Light/Dark assays demonstrated increased dark-compartment preference in untreated cKO mice compared to WT and heterozygous controls, consistent with anxiety-like behavior. Gross anatomical characterization further revealed enlarged brain size and increased brain weight in cKO mice. Preliminary histological analyses suggest potential alterations in Purkinje neuron organization and hippocampal morphology in cKO mice; however, quantitative analyses are ongoing. Next, to test our hypothesis, we delivered AAV9-CAPB10 capsid containing either *eGFP* or *hCIB2-IRES-eGFP* through tail vein injections in *Pten-GFAP* cKO mice. Sustained GFP expression in the cerebral cortex was detectable up to P180 following systemic delivery, indicating long-term transgene persistence. Intriguingly, cKO mice with *hCIB2* overexpression in the brain exhibited improved exploration of the light compartment in both intervention groups. Furthermore, *hCIB2*-treated animals displayed reduced brain size relative to untreated cKO littermates. Ongoing studies include region-specific morphometric quantification, RNA sequencing, and optimized molecular analysis of mTOR signaling pathways. Overall, our preliminary findings support further investigation of *CIB2* as a potential modulator of mTOR-associated neurodevelopmental phenotypes.

Disclosures: A.A. Zaib: None. **Z.M. Ahmed:** None. **S. Riazuddin:** None. **S. Riazuddin:** None.

Poster

PSTR002: ADHD, SLI, Dyslexia, and Other Specific Disorders of Neurobehavior

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.21/J8

Topic: A.06. Developmental Disorders

Support: NIH grants R01NS97846
R01NS097846-02S1
R01NS092876 and NIAAA of NIH grant R01AA031319 to MS

Title: Neuronal and Astrocytic Injury and microRNA Signatures in Fetal Brain Exosomes as Early Indicators of Fetal Alcohol Spectrum Disorders.

Authors: *T. SA NGUANPHO[1], L. DRAK[1], M. HAMPE[1], U. BHARAI[1], J. HAMZE[1], J. HU[1], S. HASSAN[1], E. OLIVER[2], R. MOSSABEB[4], M. MORRISON[3], L. HART[2], N. DARBINIAN[1], M. E. SELZER[1], H. ZHAO[1];
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Abstract: Introduction. Astrocyte-neuron communication plays a critical role in synaptic development, metabolic support, and neurotrophic signaling during fetal brain maturation. Prenatal alcohol exposure disrupts these interactions, yet early, non-invasive biomarkers of such alterations remain limited. This study investigates microRNAs involved in astrocyte-neuron communication within fetal brain-derived exosomes (FB-Es) isolated from maternal blood as potential early predictors of fetal alcohol spectrum disorders (FASD).Methods. FB-Es were isolated using neural-specific immunoaffinity approaches and analyzed for microRNAs regulating neuronal injury, synaptic stability, and neurotrophic pathways (e.g., BDNF, GFAP-regulated signaling) using qRT-PCR and ELISA for miRNA targets.Results. Preliminary findings reveal significant dysregulation of key astrocyte-neuron microRNAs, including miRNA-9, in pregnancies exposed to alcohol compared to controls, reflecting early impairments in glial-neuronal crosstalk and synaptic maturation. Changes in miRNA expression, including miR-9, were correlated with changes in fetal eye diameter, a characteristic feature of FASD.Conclusions. These results support the feasibility of using FB-E microRNA signatures as novel, non-invasive biomarkers for early detection of FASD, providing insight into the cellular mechanisms underlying alcohol-induced disruptions in fetal brain development.

Disclosures: T. Sa Nguanpho: None. **L. Drak:** None. **M. Hampe:** None. **U. Bharai:** None. **J. Hamze:** None. **J. Hu:** None. **S. Hassan:** None. **E. Oliver:** None. **R. mossabeb:** None. **M. Morrison:** None. **L. Hart:** None. **N. Darbinian:** None. **M.E. Selzer:** None. **H. Zhao:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.01/K1

Topic: A.08. Adolescent Development

Support: Whitehall Foundation Grant awarded to LC

Title: Fronto-striatal function in the development of social behavior during adolescence.

Authors: *K. LIN, L. COUTELLIER;
The Ohio State Univ., Columbus, OH

Abstract: Adolescence is a critical developmental period during which prefrontal cortex (PFC) connectivity with downstream brain regions undergoes extensive refinement. However, how adolescent circuit maturation contributes to the emergence of adult-typical behavior remains poorly understood. This period is also characterized by heightened social reward sensitivity and risk-taking social behavior, implicating striatal reward circuits as key contributors to adolescent-typical behavior. Previous work from our lab shows that activity in PFC neurons projecting to the ventral striatum (vSTR) decreases from adolescence to adulthood, indicating developmental remodeling of this pathway. Together, these findings suggest that the PFC-vSTR circuit links adolescent brain maturation to the development of social behavior. We hypothesize that adolescence represents a sensitive period during which PFC-vSTR circuit activity is required for the proper development of adult social function. To test this, we chemogenetically inhibit vSTR-projecting PFC neurons in either adolescence or adulthood in male and female C57Bl/6J mice. Social motivation and interaction were assessed in adulthood to determine long-term effects of circuit perturbation. Preliminary data show that adolescent, but not adult, PFC-vSTR inhibition reduces social motivation, indicating that maturation of this pathway during adolescence is critical for normal social development. In contrast, inhibition in adulthood produces only transient changes in social investigation, suggesting that PFC-vSTR circuit can modulate social behavior without altering overall patterns of behavior. These results support the idea that adolescence is a sensitive period for PFC-vSTR refinement, which guides the emergence of adult social behavior. These findings have implications for understanding neurodevelopmental disorders characterized by social dysfunction.

Disclosures: K. Lin: None. **L. Coutellier:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.02/K2

Topic: A.08. Adolescent Development

Support: R01MH127737
R01MH136381

Title: Persistent effects of adolescent social isolation on emotional discrimination and prosocial behavior

Authors: *H. LEE[1], J. LU[2], Y. ZUO[1];
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Abstract: Prosocial behavior, actions directed toward the well-being of others, is a fundamental component of social interaction. Adolescence represents a particularly sensitive developmental window for the emergence of social behaviors, yet how experiences during this period shape prosociality remains incompletely understood. Here, we used mouse behavioral assays to investigate how social isolation at different developmental stages influences emotional discrimination and affiliative helping behavior. We found that mice isolated from weaning into adulthood failed to allogroom distressed conspecifics and were unable to distinguish stressed from unstressed individuals in an emotional discrimination task. Notably, just two weeks of post-weaning isolation was sufficient to disrupt both emotional discrimination and prosocial allogrooming, and these impairments persisted even after two months of resocialization. In contrast, a comparable period of isolation in adulthood left emotional discrimination intact but selectively reduced allogrooming toward stressed conspecifics. Together, these results reveal a dissociation between emotional state recognition and prosocial helping behavior. Overall, this study identifies adolescence as a critical period for the development of emotional state recognition and provides a behavioral framework for understanding how early social experience shapes neural circuits underlying empathy and stress buffering.

Disclosures: H. Lee: None. **J. Lu:** None. **Y. Zuo:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.03/K3

Topic: A.08. Adolescent Development

Support: VA CDA2 GRANT BX006528

Title: Transgenerational Inheritance of Trauma-Induced Behavioral Phenotypes in Mice

Authors: *M. MAYEAUX[1], E. HISEY[2];
[1]Behavioral Neurosci., Boston Univ., Boston, MA; [2]Psychiatry, Boston University/VA Boston, Boston, MA

Abstract: Adverse childhood experiences (ACE) are highly prevalent in the US. Based on CDC data from 2011-2020, approximately 64% of American adults report at least one ACE, while 17.3% report 4 or more ACEs with reports of 4 or more ACEs being most common in women (Swedo et. al, 2023). Despite its prevalence, current research has yet to answer key questions regarding the long-term impacts of this exposure. Previousresearch within our lab has identified distinct behavioral and circuit level changes in mice following early-adolescent chronic social defeat stress (eaCSDS) exposure with clear sex differences in observed social behavior post-defeat. In light of these findings and the high prevalence of multiple ACEs reported by adult women in the US, we conducted a study to determine the heritability of these behavioral and anatomical changes observed in female mice with eaCSDS exposure. Control and eaCSDS

exposed dams were bred with wild type male mice at approximately P60. Maternal behavior of dams was recorded to include pre-natal behaviors such as nest size and proximity to resources as well as post-natal behavior such as pup retrieval and cumulative time spent in the nest based on continuous recordings from pup post-natal dates 6-11. Once weaned, offspring of eaCSDS and control dams underwent home cage social interaction experiments (HCSI) at multiple key time points in development (P30, 50, and 70). We have evidence that both male and female offspring of defeated dams exhibit socially avoidant behavioralphenotypes that persist throughout adolescence and early adulthood despite receiving no trauma exposure. These results are not confounded by any meaningful differences observed in maternal rearing behaviors. The existence of socially avoidant behavioral phenotypes in offspring of eaCSDS dams in the absence of variation in maternal care suggests the anatomical and circuit level changes driving the stress-induced behavioral phenotypes seen in eaCSDS mice can be inherited by non-exposed offspring. Future efforts of this study will include comparison of anatomical findings in eaCSDS exposed mice to their offspring to identify specific anatomical changes that may be driving the development and spontaneous extinction of these social behavioral phenotypes.

Disclosures: M. Mayeaux: None. **E. Hisey:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.04/K4

Topic: A.08. Adolescent Development

Support: NIH R21MH121836
NIH R01MH131053

Title: Periadolescent loss of synaptic adhesion molecule IgSF9b in the mPFC results in inhibitory synaptic deficits and globally enhanced theta oscillations

Authors: *J. CLARIN[1], C. ALEXANDROPOULOS[1], A. KEITH[1], S. YANG[2], N. MACK[3], Y. LI[1], W. HUANG[1], D. V. WANG[1], W.-J. GAO[1];
[1]Drexel Univ., Philadelphia, PA; [2]Neurosurg., Fudan Univ. Hushan Hosp., Shanghai, China; [3]Princeton Neurosci. Inst., Princeton Univ., Philadelphia, PA

Abstract: Refinement of synaptic structure and function is an essential component of postnatal neural development. The prefrontal cortex undergoes dramatic circuit-wide maturation during the adolescent period, disruptions in which are theorized to underly psychiatric conditions including schizophrenia. To better understand prefrontal circuit development during adolescence and the molecular factors driving psychiatric disease etiology, we focused on the disease-linked synaptic adhesion molecule IgSF9b. First, we set out to understand the expression dynamics of IgSF9b in the medial prefrontal cortex (mPFC) in mice, between the juvenile period and early adulthood. Employing fluorescent in situ hybridization, we discovered an upregulation of IgSF9b

mRNA expression late in adolescence (P50-56). Next, we sought to understand the circuit and behavioral consequences of IgSF9b loss during this period of upregulated expression. Using IgSF9b shRNAs targeted to the mPFC at ~P40, we found that knockdown (KD) animals exhibited behavioral phenotypes across multiple cognitive and affective tasks in adulthood. In concordance with these behavioral changes and the previously established role of IgSF9b at inhibitory synapses, we found a reduction in miniature inhibitory postsynaptic potential frequency in mPFC pyramidal neurons. Finally, to understand the network disruptions that bridge these synaptic and behavioral findings, we assessed prefrontal oscillations. Across all behavioral contexts, we surprisingly observed an increase in prefrontal theta oscillation power (6-12Hz), suggesting a more rigid network state due to decreased IgSF9b expression. Future experiments will delve further into the prefrontal interneuron subtypes and pathways that explain these changes in network activity and behavior.

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Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.05/K5

Topic: A.08. Adolescent Development

Title: Enrichment alters sound-induced seizures and related lateral amygdala activity in adolescent rats

Authors: G. M. WRIGHT, T. S. SMITH, J. V. STONE, ***M. C. ZRULL**;
Appalachian State Univ., Boone, NC

Abstract: Epilepsy, whether inherited or acquired, is a progressive disorder that can include generalized convulsive seizures. In rodent models of reflex epilepsy, in which audiogenic responses and seizures (AGRs, AGSs) are evoked by sound, AGSs generalize as the lateral amygdala (LA) relays abnormal neural activity to forebrain areas. Seizures can have an injurious impact on brain and behavior, and environmental enrichment (EE) can mitigate the effects of brain injury, particularly during development, through periodic interaction with objects and conspecifics. We revisited a study in which AGS-prone Long Evans rats (n=9) lived in standard cages and received 1.5 h of EE every 2 days between postnatal days (pnd) 32 and 46 and control AGS-prone rats (n=8) remained in standard cages, received no EE, but were briefly picked up to control for handling effects. Six AGRs were induced (Tests 1 to 6) with 120 dB broadband noise similarly for all rats between pnd 32 and 46. Severity of the AGS disorder was measured as latency to AGR (wild running, shorter is more severe) and the duration of a clonic AGS (longer is more severe), if one occurred. Only data from rats showing no hearing loss across tests were used to examine the impact of EE on AGS severity and LA neuron activation on acquired AGSs through adolescence. At Test 6, 96% of control rats had AGSs, and only 64% of EE rats had

seizures. The latency to an AGR decreased for control rats (-29%, p=.028) and increased for EE rats (+32%, p=.004) with AGS duration increasing for controls (+58%) and decreasing (-7%) for EE rats having AGSs. One hour after Test 6, rats were sacrificed and brains processed to visualize c-FOS protein in the LA. Counts of c-FOS containing LA neuron (c-FOS+) were standardized using brains from age-matched naive rats (n=6). Rats tested for AGSs exhibited 382% more c-FOS+ neurons than in LA of naïve brains. Expectedly, LA of EE rats not having seizures had less active LA neurons than controls not having AGSs (-111%, p=.010). However, LA of EE rats having seizures exhibited 67% more (p=.002) activated neurons than found in LA of unenriched controls with seizures. Behaviorally, EE sessions reduced frequency and severity of the seizures suggesting enrichment may provide a relatively simple, non-invasive "treatment" for this type of seizure disorder during adolescence. The LA data are intriguing with EE enhancing rather than suppressing LA activity evoked by AGR induction, as the behavioral data might predict, in EE animals still having seizures. Given the reduced severity of AGSs, perhaps EE promotes enhanced inhibitory processes in LA that, in turn, impact severity of sound-induced seizures.

Disclosures: G.M. Wright: None. **T.S. Smith:** None. **J.V. Stone:** None. **M.C. Zrull:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR003.06/K6

Topic: A.08. Adolescent Development

Support: NSF OIA-2242771
NIH R21AA030086
Veterans Affairs BX005403

Title: Defining Adolescent Tripartite Synapse Maturation Through Integrated Spatial Transcriptomics and Super-Resolution Imaging

Authors: *G. ANGELONA[1], N. KUMAR[1], M. JONES[1], A. WALLS[1], T. MUCK[1], F. MALONE[1], O. COULTER[1], H. G. SEXTON[1,2], K. DENNING[3], S. AKTER[1], M.-L. RISHER[1,2]; [1]Marshall Univ., Huntington, WV; [2]Hershel 'Woody' Williams Veterans Affairs Med. Ctr., Huntington, WV; [3]Dept. of Pathology, Joan C Edwards Sch. of Med., Huntington, WV

Abstract: Adolescence is a critical period of brain development characterized by extensive synaptic remodeling that supports cognitive function, decision-making, and flexibility. Many synapses are ensheathed by peripheral astrocyte processes (PAPs), forming the tripartite synapse, where astrocyte-synapse interactions regulate neuronal communication. Our laboratory has previously demonstrated that adolescent intermittent ethanol exposure (AIE) produces a subregion-dependent loss of PAP-synaptic proximity within the orbitofrontal cortex (OFC). We propose that developmental differences in tripartite synapse maturation may contribute to

alcohol-induced dysfunction; however, the normal developmental trajectory of tripartite synapse maturation remains poorly characterized. To investigate structural and molecular changes during adolescence in the developing tripartite synapse, male and female C57BL/6 mice were euthanized at postnatal day (PND) 31 (early adolescence), PND 46 (late adolescence), or PND 72 (adulthood). Brain tissue was collected for stimulated emission depletion (STED) microscopy and Visium HD spatial transcriptomics (10x Genomics). STED imaging quantified developmental changes in PAP-synaptic proximity, while spatial transcriptomics characterized age-dependent gene expression patterns associated with tripartite synapse maturation. Transcriptomic data were processed using Space Ranger and analyzed in Seurat using sample integration, quality control filtering, normalization, dimensionality reduction, clustering, and marker identification. Preliminary findings show that when comparing male PND 31 and PND 72 samples, spatial transcriptomic clustering identified 28 spatial clusters, including three astrocyte-associated clusters. Seurat differential expression analysis identified significant differentially expressed genes in C7 (257 genes), C16 (25 genes), and C22 (108 genes). Reactome over-representation analysis of directionally regulated genes revealed significant PND 72-enriched pathways only in C22, including transmission across chemical synapses, neurotransmitter and ion channel regulation, and GPCR signaling pathways. By integrating nanoscale structural imaging with spatially resolved transcriptomics, this study will establish a developmental framework for tripartite synapse maturation and identify molecular signatures that may predict maturation-dependent vulnerability to AIE-induced disruption of astrocyte-synapse communication. These findings may provide insight into why the adolescent brain is particularly susceptible to the long-term effects of alcohol exposure.

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Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.07/K7

Topic: A.08. Adolescent Development

Title: Exploring a novel space with and without objects evokes neural activity in entorhinal cortex of adolescent rats

Authors: *S. N. BALKUS[1], E. M. ACUNA[1], M. C. ZRULL[2];
[2]Psychology, [1]Appalachian State Univ., Boone, NC

Abstract: Neurons of the entorhinal cortex (EC) build a representation of an animal's environment globally (i.e., as a whole, medial EC, MEC) and of non-spatial or local features within the context of the environment (lateral EC, LEC). Superficial layers of EC (sMEC, sLEC) receive input from various cortical areas and deep EC, and deep EC layers (dMEC, dLEC)

receive hippocampal output initiated by respective superficial EC neurons. Thus, while neurons of MEC are thought to help build a representation of the immediate environment as a whole, activity of neurons in LEC may represent more local features of a space, such as object location. In the current study, we used c-FOS to examine neural activity evoked by time spent in a novel, multilevel environment with or without objects. Naïve adolescent Long-Evans hooded rats spent 1.5 h in groups in an enclosure with ramps and platforms and objects (YesObj, n=5) or in the same enclosure but without objects (NoObj, n=6), and 5 rats remained in the home cage (control). To assess neural activity, brain tissue was collected after the exploration session and processed to visualize the c-FOS protein in neurons. FOS+ neurons in sample frames were quantified using light and digital microscopy and stereological techniques, and all cell counts were standardized to control counts to yield active neuron densities. While densities of c-FOS+ neurons in sMEC (+383%) and sLEC (+55%) of YesObj and NoObj rats exceeded those in control sMEC and sLEC, the differences were not statistically significant due to variability in active neurons among animals from both groups exploring the space, and no difference between c-FOS+ neurons in superficial EC was seen between the exploration groups. These results suggest that activity in superficial EC may be dependent upon individual differences in perceptual processing of an environment's features by neural systems providing input to EC. In contrast, significant differences in c-FOS+ neuron densities were observed between animals exploring a space and controls in dMEC (+303%, $p<.001$), suggesting neural activity reflecting that environment globally, and in dLEC (+194%, $p=.036$) suggesting neural activity that may reflect local features of the space. Supporting this latter idea, it is notable that a 128% increase in active neuron densities in dLEC of YesObj rats over that in dLEC of NoObj rats was observed ($p=.057$). Overall, our results provide some support for the idea of differential global and local representation of space in regions of the EC.

Disclosures: S.N. Balkus: None. **E.M. Acuna:** None. **M.C. Zrull:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR003.08/K8

Topic: A.08. Adolescent Development

Support: NIH 1ZIAMH002984-03

Title: Lasting Molecular Consequences of Neonatal Medial Pulvinar Perturbation on Cortical Development

Authors: *N. M. KUEHN[1,2], J. SCOTT[1], A. FAN[1], Y.-J. ZHANG[3], E. DAVIS[4], J. IBEN[4], V. MAHADEVAN[4], T. J. PETROS[3], J. A. BOURNE[1];
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[4]Mol. Genomics Core, Eunice Kennedy Shriver Natl. Inst. of Child Hlth. And Human Develop., Bethesda, MD

Abstract: Primate cortical development is characterized by prolonged and asynchronous maturation across regions, a feature thought to support the emergence of higher cognitive function. While thalamocortical interactions are essential for early sensory development, far less is known about how higher-order thalamic nuclei influence extended postnatal cortical development in primates. The medial pulvinar (PM), a primate-specific thalamic nucleus with dense frontal cortical connectivity, is a strong candidate for regulating late-developing cortical gene programs, yet its developmental role remains largely unexplored. To investigate whether early PM perturbation produces lasting molecular consequences in the cortex, we performed bilateral excitotoxic lesions of the PM in neonatal (~postnatal day 14) common marmosets (*Callithrix jacchus*). Animals were allowed to mature to adulthood (>18 months), at which point we assessed cortical gene expression using single-nucleus RNA sequencing and spatial transcriptomics across PM-connected and non-connected cortical regions. Neonatal PM lesions produced persistent, areal and laminar selective alterations in cortical transcriptional landscapes. Differentially expressed genes were enriched in pathways associated with neuronal differentiation, synaptic organization, and cellular maturation, with distinct effects across cortical layers and cell classes. Importantly, transcriptional changes were not uniform across the cortex but were preferentially localized to cortices recipient of PM input, indicating long-term circuit-dependent modulation of developmental gene expression. These findings demonstrate that disruption of a primate-specific thalamic nucleus during early life leads to enduring molecular reorganization of cortical development. By revealing how higher-order thalamic perturbation reshapes cortical developmental trajectories, this work provides new insight into the systems-level mechanisms that may contribute to vulnerability in neurodevelopmental disorders involving thalamocortical dysfunction.

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Poster

PSTR003: Adolescent Development: Animal Models

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.09/L1

Topic: A.08. Adolescent Development

Support: P50 AA017823
R01 AA028566
T32 AA025606

Title: The effects of combined prenatal and adolescent alcohol exposure on mechanical sensitivity and anterior cingulate cortex physiology

Authors: *C. CIRAFESI[1], A. KARKHANIS[2], M. R. DIAZ[2];
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Abstract: Exposure to alcohol during early development is associated with chronic health complications, but the underlying neurobiological mechanisms remain largely unknown. Prenatal alcohol exposure (PAE) has also been linked to increased alcohol use in adolescence, potentially contributing to the prevalence of alcohol misuse. However, the combined effects of both prenatal and adolescent alcohol exposure are underexplored. This project first aims to investigate the impact of PAE and adolescent alcohol exposure on mechanical sensitivity using a preclinical rodent model. In this study, pregnant Long Evans dams were given access to either a bottle of 10% v/v ethanol or tap water for 12 hours each night from gestational day (GD) 17 to 20. Offspring were randomly assigned to receive either air or adolescent chronic intermittent ethanol (aCIE) exposure for 12 hour sessions, occurring on a 2 days on/2 days off schedule from postnatal day (PD) 25/28 through PD65/68. This created 4 experimental groups: prenatal control and adolescent control (Water+Air), PAE and adolescent control (PAE+Air), prenatal control and aCIE (Water+aCIE), and PAE+aCIE ("double hit"). After 3 weeks of abstinence from aCIE, offspring were assessed for mechanical sensitivity using the Von Frey test. aCIE produces a transient increase in mechanical sensitivity during early abstinence (3-4 weeks post aCIE), while mechanical sensitivity persists through week 6 of abstinence in PAE+aCIE males and females. These findings suggest PAE offspring may be more vulnerable to the effects of aCIE on pain sensitivity. Since previous research has linked increased excitability in the anterior cingulate cortex (ACC) to pain processing, glutamate transmission and intrinsic excitability of layer 2/3 pyramidal neurons in the ACC was measured via whole cell patch-clamp electrophysiology in behaviorally-naive offspring. Preliminary data show increased intrinsic excitability of ACC layer 2/3 pyramidal neurons in PAE+aCIE females between weeks 3-6 of abstinence from aCIE. These findings highlight the ACC as a potential contributor to the pain sensitivity observed in PAE+aCIE offspring.

Disclosures: C. Cirafesi: None. **A. Karkhanis:** None. **M.R. Diaz:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.10/L2

Topic: A.08. Adolescent Development

Support: The Jean Phillips Shibley Endowment and Penn State University
Minciencias Fulbright Colombia

Title: Adolescent social stress alters anxiety, locomotion, body weight, sensitivity to nicotine, and increases cumulative corticosterone, a comparison of C57BL6J and C57BL6NJ mice

Authors: C. NOVOA[1], ***T. J. GOULD**[2];
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Abstract: Adolescent psychosocial stress has lasting effects on affective behaviors and vulnerability to substance use. This study investigated the role of genetics in the multidimensional effects of adolescent social stress on behavior and HPA axis activity in two closely related mouse strains. We hypothesized that adolescent social instability stress would alter anxiety, locomotion, decrease body weight, increase sensitivity to nicotine, and increase corticosterone levels in a strain-dependent manner. Subjects were male C57BL/6J (B6J) and C57BL/6NJ (B6NJ) mice from Jackson Laboratory (Bar Harbor, ME, USA). The B6J and B6NJ strains have 34 single-nucleotide variants (SNV), 2 indels, and 15 structural variants across their genomes. From post-natal day (PND) 35 to 48 mice were exposed to social instability stress. Mice were then tested in a behavioral battery that included elevated plus maze, novelty suppressed feeding test, sucrose splash test, social approaching test, forced swim test, and acute nicotine hyperlocomotor test. Hair and blood were collected for corticosterone analysis. Adolescent social instability disrupted body weight gain, decreased time in the open arms of the elevated plus maze, increased locomotor activity, and increased sensitivity to nicotine. Hair corticosterone levels were increased in mice that underwent adolescent social instability, reflecting elevated cumulative levels of the stress hormone. The genetic background of mice influenced distance traveled, anxiety, and sensitivity to nicotine. Our results indicate that genetic factors segregating in the B6J and B6NJ substrains contribute to individual differences in spontaneous locomotion, anxiety- and depression-like behaviors, and acute nicotine in adolescent male mice. Additionally genetic factors captured by these substrains moderate the responses to adolescent social instability stress in anxiety-like and nicotine-related behaviors. Adolescent social stress also resulted in elevated levels of hair corticosterone but contrary to our expectations, cumulative hair corticosterone did not appear to directly mediate the effects of adolescent social instability stress on phenotypes. Together, these results suggest that two weeks of adolescent social instability stress leads to repeated activation of the HPA axis and adaptations of affective behaviors, body weight, and sensitivity to nicotine. These effects could have implications for mental and physical health.

Disclosures: C. Novoa: None. **T.J. Gould:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.11/Web Only

Topic: A.08. Adolescent Development

Support: PROSNII-2026

Title: DeltaFosB expression in the Nucleus Accumbens following adolescent social isolation in mice

Authors: *L. BURGOS-CONTRERAS[1], A. GALINDO-SILLER[2], E. LIRA-DIAZ[1], G. GUDIÑO-CABRERA[1], J. PEREGRINA-SANDOVAL[1], T. CAMPOS ORDONEZ[1];
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Abstract: Evidence indicates that prolonged social isolation can alter the reward circuitry of the nucleus accumbens (NAcc), a region critical for motivation, social reward processing, and adaptive responses to stress. ΔFosB, a stable member of the Fos family of transcription factors, accumulates following repeated or chronic stimulation and serves as a marker of persistent, plasticity-related changes in the central nervous system. The aim of this study was to examine ΔFosB expression in the NAcc of mice using immunohistochemical techniques. To this end, mice exposed to a post-weaning social isolation protocol (PND 21-48) were compared with a control group maintained under group housing conditions (four individuals per cage). Results revealed that isolated mice had a greater number of ΔFosB-positive cells in the NAcc than controls. This finding suggests that social isolation induces long-lasting transcriptional adaptations in reward-related circuits, reflected in increased ΔFosB accumulation. Given that the NAcc is particularly sensitive to stress during adolescence and that ΔFosB plays a role in chronic stimulation and long-term neuronal adaptations, the observed increase may reflect a molecular mechanism by which social isolation affects reward processing, stress vulnerability, and social behavior.

Disclosures: L. Burgos-Contreras: None. **A. Galindo-Siller:** None. **E. Lira-Diaz:** None. **G. Gudiño-Cabrera:** None. **J. Peregrina-Sandoval:** None. **T. Campos Ordonez:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.12/L3

Topic: A.08. Adolescent Development

Support: NIMH Intramural Program
Center for Compulsive Behaviors
Comparative Brain Physiology Consortium

Title: Lifespan changes in striatal dopamine release capacity in macaque and mouse

Authors: *S. R. WHITE[1], M. ANDUJAR[2], H. C. GOLDBACH[4], J. SHIN[5], E. SWANSON[6], L. ANDERSON[7], R. RIMONDINI[3], S. E. CERVENY[1], P. HARMON[2], S. LEE[1], A. CARR[8], A. CUMMINS[9], A. TANGEN[10], B. B. AVERBECK[11], V. A. ALVAREZ[3];
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Bethesda, MD; [4]NIMH, Washington, DC; [5]NIAAA, Natl. Inst. on Alcohol Abuse and Alcoholism, Elkridge, MD; [6]Northwestern Univ., Chicago, IL; [7]NIH/NIMH; Stanford Univ., Bethesda, MD; [8]Vanderbilt, Washington, DC; [9]Natl. Institue of Mental Hlth., Bethesda, MD; [10]Carnegie Mellon Univ., Pittsburgh, PA; [11]NIMH/NIH, Bethesda, MD

Abstract: We experience innumerable changes over the course of our lifetimes. Understanding the trajectory of biological processes, especially during critical windows of development like puberty and post-fertility, is crucial to characterize vulnerable windows in which disorders can develop. In this study, we aimed to characterize the lifespan trajectory of striatal dopamine signaling, a critical system for regulating neural circuit plasticity and adaptive behavior, in two common research models: macaque and mouse. We examined the dorsal striatum, a central hub for cortical excitatory and midbrain dopaminergic inputs, given its role in behavioral regulation and pathology. We used fast-scan cyclic voltammetry, a well-established electrochemical technique, to measure dopamine availability under identical conditions to directly compare species across four developmental stages (prepuberty, postpuberty, postmaturity, and postfertility). We also investigated the modulation of dopamine release by cholinergic interneurons and GABA receptors using pharmacology. We found that baseline dopamine release follows a non-linear developmental trajectory across both species. Dopamine release was significantly predicted by age group, species, and their interaction indicating divergent developmental trajectories across species. In mice, dopamine release was lowest during prepuberty and peaked after postmaturity. In contrast, macaques showed the opposite pattern, with dopamine highest in postpuberty and declining through postmaturity. Dopamine clearance differed by species. In macaques, clearance was faster in prepuberty relative to postmaturity with no change observed in mice. GABAergic modulation of dopamine signaling was significantly predicted by age group, with prepuberty showing the lowest response in both species. This was the only pharmacological measure to show developmental change. Neither α6-nicotinic acetylcholine receptor modulation nor total nicotinic receptor contribution to dopamine release changed across age groups in either species, though species differences in overall nicotinic tone were present. Together, these findings reveal that dopamine system maturation involves both conserved and species-divergent features. The prepubertal dopamine system is consistently characterized by reduced GABAergic modulation and, in macaques, faster clearance, suggesting a functionally immature dopaminergic state regardless of species. The divergent trajectories of dopamine release across development highlight the value of cross-species comparisons for characterizing the full landscape of dopamine system maturation.

Disclosures: S.R. White: None. **M. Andujar:** None. **H.C. Goldbach:** None. **J. Shin:** None. **E. Swanson:** None. **L. Anderson:** None. **R. Rimondini:** None. **S.E. Cerveny:** None. **P. Harmon:** None. **S. Lee:** None. **A. Carr:** None. **A. Cummins:** None. **A. Tangen:** None. **B.B. Averbeck:** None. **V.A. Alvarez:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.13/L4

Topic: A.08. Adolescent Development

Support: R01-MH086507
R01-MH127850

Title: Late-adolescent disruption of prefrontal NMDA-GABA control of thalamic inputs following maternal separation early life adversity

Authors: *D. D. NEAL[1], H. C. BRENHOUSE[2], K.-Y. TSENG[1];
[1]Anat. and Cell Biol., Univ. of Illinois Chicago, Chicago, IL; [2]Psychology, Northeastern Univ., Boston, MA

Abstract: Late-adolescent disruption of prefrontal NMDA-GABA control of thalamic inputs following maternal separation early life adversity
Demetria D. Neal[1], Heather C. Brenhouse[2], and Kuei Y. Tseng[1]
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Keywords: Mediodorsal thalamus, early life adversity, development
Exposure to early life adversity (ELA) is known to disturb neural development and interfere with neural circuit function, causing long-lasting adverse effects on cognitive and affective behaviors. The basis for this is thought to be linked to developmental disruption of neural circuits underpinning these behaviors such as the prefrontal cortex (PFC), which receives inputs from various brain regions, including the mediodorsal thalamus (MD). Thus, it's conceivable that ELA exposure during a sensitive window of MD development may disrupt the trajectory of PFC maturation. Here we employed in-vivo electrophysiology to assess the functionality of the MD-PFC pathway following maternal separation ELA exposure. We found that adolescent rats (P35-45) exposed to ELA displayed a normal NMDAR-mediated facilitation of PFC LFP response to 10Hz-MD stimulation characteristic of this developmental period. The typical patterns of GABA-AR-mediated suppression of PFC LFP response to 20Hz- and 40Hz-MD stimulation were indistinguishable between control and ELA-exposed adolescent rats. However, after P50, the normal PFC LFP facilitation response at 10Hz was absent following ELA and the typical late adolescent gain of PFC LFP suppression at 20-40Hz failed to occur in ELA rats. Of note, the disruption observed in P50-60 ELA rats persists into adulthood. Collectively, these results show that exposure to ELA can elicit a protracted loss of NMDAR recruitment in the PFC by thalamic inputs after P50 in tandem to a diminished prefrontal inhibitory control due to a lack of gain of GABA-AR function that typically occurs late in adolescence.
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Disclosures: D.D. Neal: None. **H.C. Brenhouse:** None. **K. Tseng:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.14/L5

Topic: A.08. Adolescent Development

Title: Disruption of mouse embryonic vasopressin 1a receptor or oxytocin receptor signaling does not affect female adolescent behavior

Authors: *A. REED[1], H. K. CALDWELL[2];
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Abstract: The neuropeptides arginine vasopressin (Avp) and oxytocin (Oxt) play a significant role in the neural modulation of social behavior. In juveniles and adults, Avp signaling through the Avp 1a receptor (Avpr1a) and Oxt signaling the Oxt receptor (Oxtr) have sex- and species-specific behavioral effects. Beyond these neuromodulatory roles, the Avp and Oxt systems also contribute to early brain development. Our lab has identified embryonic day (E) 16.5 as a critical timepoint in development of both systems in the mouse brain. Microinjection of either an Avpr1a antagonist (Avpr1aA) or an Oxtr antagonist (OxtrA) appears to alter the trajectory of brain development such that there are measurable changes in adult social behavior. Specifically, Avpr1aA-treated adult males have subtle changes in affiliative behavior while OxtrA-treated males have increases in social investigation, agonistic, and depressive-like behaviors; these same effects are not observed in females. More recently, we have found that disruption of Avpr1a or Oxtr signaling at E16.5 affects male adolescent behavior as well, with Avpr1aA treatment decreasing anxiety-like behavior and OxtrA treatment increasing social investigation durations. Thus, we wanted to determine the effects of our intervention on female adolescent behavior. We hypothesized that the effects of Avpr1aA and OxtrA treatment on female play, anxiety-like, and depressive-like behaviors would be minimal. Consistent with this expectation, we found that unlike adolescent males, adolescent females were not sensitive to disruption of Avpr1a or Oxtr at E16.5. These results are aligned with the observation that female appear to be more resilient, or males more vulnerable, to perturbations on Avpr1a or Oxtr signaling at E16.5, and suggest that these two systems directly contribute to sex-specific embryonic brain development.

Disclosures: A. Reed: None. **H.K. Caldwell:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR003.15/L6

Topic: A.08. Adolescent Development

Support: Wood Next Foundation
SMART T32 DA057922
NIDA R01DA039865 (McClung)

Title: Adolescent Circadian Rhythm Disruption Leads to Increased Risk-Taking and Transcriptional Changes in Adulthood

Authors: *K. PETERSEN[1], L. DEPOY[3], C. A. VADNIE[4], T. STOWE[1], L. H. NELSON[1], M. R. SCOTT[2], C. A. MCCLUNG[5];
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Abstract: Circadian rhythm disturbances have long been associated with the development of psychiatric disorders, including mood and substance use disorders. Adolescence is a particularly vulnerable time for the onset of psychiatric disorders and for circadian rhythm disruptions (CRD). The goal of this study was to determine the long-term effects of adolescent CRD. We exposed mice to four 12 h shifts in the light/dark cycle over the course of adolescence (P28-P37). 4 weeks following the last shift, mice either underwent behavioral testing or were sacrificed across 4 times of day for RNA sequencing or electrophysiology. To identify possible mechanisms by which CRD during adolescence affects behavior later in life, we measured gene expression in the SCN, PFC and NAc and performed *ex-vivo* recordings in the PFC. We first identified that adolescent CRD alters behavior later in life, namely increasing reward and risk-taking. We measured differential expression (DE) between control and adolescent CRD mice across time of day in male and female mice and found that the transcripts affected by CRD were largely distinct across time, sex, and brain region. The SCN was particularly affected, with the most DE transcripts identified at $q<0.05$. These transcripts were largely involved in circadian rhythms, adipogenesis, and intracellular signaling. We also observed significant changes in the PFC of males at ZT0. Transcripts with altered gene expression were associated with neuronal activity, translation, and the extracellular matrix. This could indicate electrophysiological changes in the PFC, which are currently being investigated. Overall, these studies suggest that adolescent CRD in mice is sufficient to persistently increase risk-taking behavior and alter gene expression long-term.

Disclosures: K. Petersen: None. **L. Depoy:** None. **C.A. Vadnie:** None. **T. Stowe:** None. **L.H. Nelson:** None. **M.R. Scott:** None. **C.A. McClung:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.16/L7

Topic: A.08. Adolescent Development

Title: Persistent sex-specific regulation of affective behaviors following adolescent acetaminophen exposure.

Authors: B. BIELECKI[1], I. LESANTE[1], J. HARE[1], S. LATEEF[1], Y. MATOS[1], A. PARKER[2], D. RUBENSTEIN[1], K. SABLE[1], N. TOMASSACCI[1], I. STULL[1], M.-E. YUZVYAK[1], *J. L. SANTERRE-ANDERSON[1];
[1]Wilkes Univ., Wilkes Barre, PA; [2]Wilkes Univ., Canton, PA

Abstract: Adolescence is a critical period of development during which environmental factors can significantly influence neurodevelopment, neuroimmune signaling, and long-term behavior. Acetaminophen (APAP) is a widely used over-the-counter analgesic with an incompletely understood mechanism of action in the central nervous system. While controversial, prenatal APAP exposure has recently been associated with behavioral phenotypes resembling neurodevelopmental disorders. This study aims to determine whether APAP exposure during adolescence contributes to long-term behavioral and neurobiological changes in adulthood. Adolescent rats received a weekly injection of 10 mg/kg APAP or saline for 3-weeks. Following the exposure period they aged to adulthood before testing on the elevated plus maze and successive alley. The current study suggests that adolescent APAP exposure produces sex-dependent behavioral changes, including increased anxiety-like behaviors in males, and impulsivity in females. Ongoing research aims to explain these behavioral differences through molecular examination of amygdalar tissue.

Disclosures: B. Bielecki: A. Employment/Salary (full or part-time):; Wilkes University. **I. Lesante:** A. Employment/Salary (full or part-time):; Wilkes University. **J. Hare:** None. **S. lateef:** None. **Y. Matos:** None. **A. Parker:** None. **D. Rubenstein:** None. **K. Sable:** None. **N. Tomassacci:** None. **I. Stull:** None. **M. Yuzvyak:** None. **J.L. Santerre-Anderson:** A. Employment/Salary (full or part-time):; Wilkes University.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.17/L8

Topic: A.08. Adolescent Development

Title: The effects of early life stress on evoked dopamine release and locomotion

Authors: *E. MAKOWICZ[1], A. R. HUROWITZ[3], E. V. MOSHAROV[2], D. L. SULZER[2];
[1]Columbia Univ., New York, NY; [2]Columbia Univ., Columbia University, NY; [3]Div. of Systems Neurosci., New York State Psychiatric Inst., New York, NY

Abstract: Early life stress (ELS) markedly elevates lifetime risk for psychiatric disorders, and converging evidence implicates dysregulated dopaminergic signaling in this vulnerability. ELS is known to alter reward processing, emotional regulation, and stress responsivity later in life, yet the developmental trajectory of these alterations remains poorly understood. Here, we combined longitudinal locomotor monitoring, high-performance liquid chromatography (HPLC), and fast-scan cyclic voltammetry (FSCV) to probe how ELS reshapes dopamine system function during

early adolescence (P21) and whether these changes persist into adulthood (P75-100). Our data reveal that ELS exposed C57BL/6J mice display disrupted locomotor activity, with significantly elevated activity during both light and dark phases in ELS females, suggesting heightened arousal or altered sleep-wake regulation. These behavioral changes emerge early and remain detectable across development, indicating that ELS produces long lasting alterations in activity patterns. Neurochemical analyses further demonstrate that ELS induces age-specific effects on monoamine systems. HPLC at P21 revealed significant changes in dopamine and metabolite concentrations in the midbrain and striatum, pointing to altered dopamine synthesis or turnover during a critical developmental window. In contrast, adult HPLC profiles showed no major differences, suggesting that these metabolic disruptions normalize with maturation. Complementing these findings, FSCV recordings in adulthood indicate that ELS females exhibit higher evoked dopamine release in the dorsal striatum and nucleus accumbens, revealing a persistent enhancement of presynaptic release capacity despite normalized metabolite levels. Together, these results suggest that ELS produces transient neurochemical perturbations during adolescence that may reorganize dopaminergic circuits in ways that persist into adulthood.

Disclosures: E. Makowicz: None. **A.R. Hurowitz:** None. **E.V. Mosharov:** None. **D.L. Sulzer:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.18/M1

Topic: A.08. Adolescent Development

Support: NIH Grant R34DA061483

Title: Implications of Neonatal Adversity in Substance Use

Authors: *N. M. BROWN[1], D. A. BANGASSER[1], A. Z. MURPHY[2];
[1]Neurosci. Inst., Georgia State Univ., Atlanta, GA; [2]Neurosci. Inst., Georgia State Univ. Neurosci. Inst., Atlanta, GA

Abstract: Every year, 1 in 10 infants are born pre-term and require a stay in the Neonatal Intensive Care Unit (NICU). Here, infants experience upwards of 15 painful and invasive procedures each day, including surgeries and endotracheal intubation, the majority of which are performed without analgesia. In addition to untreated pain, NICU infants are isolated in incubators and receive minimal caregiver contact. Further, over 45% of infants born prematurely are from low socioeconomic status households, presenting the additional stressor of limited resources. Existing preclinical models typically examine single stressors and fail to recapitulate the multifaceted nature of the NICU experience. There is growing evidence that former NICU infants exhibit impaired ability to form social bonds, an established risk factor for substance use. Social behavior and reward motivation are modulated by the prefrontal cortex (PFC), and

dependent on the activity of the endocannabinoid system. These studies test the hypothesis that cumulative neonatal adversity - including pain, maternal separation, and resource scarcity - disrupts endocannabinoid signaling in the developing PFC and reward-associated brain regions, thereby establishing a mechanistic pathway linking early NICU-like experiences to maladaptive social behaviors and heightened vulnerability to substance use during adolescence. This hypothesis is tested using a novel rodent model combining the stressors of the NICU experience. Social behavior and motivation are assessed using a social behavior assay and operant social self-administration across adolescence. As adolescents, NICU rats do not show the characteristic age-associated decline in play behavior, suggesting a delay in the maturation of social circuitry. We are currently assessing reward and substance use motivation using operant sucrose and ethanol self-administration tasks. Quantification of CB1 receptor density and endogenous ligand concentrations in corticolimbic regions is also underway. These experiments will identify mechanisms by which neonatal adversity influences substance use.

Disclosures: N.M. Brown: None. **D.A. Bangasser:** None. **A.Z. Murphy:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.19/M2

Topic: A.08. Adolescent Development

Support: NIH Grant MH136708

Title: Sex and age-dependent alterations in cognitive and hedonic processing in a two-hit early-life scarcity and adult chronic stress rat model

Authors: *K. BOSWELL[1], D. R. OLIVEIRA, Sr.[1], J. R. MANTSCH[2];
[2]Pharmacol. and Toxicology, [1]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Stress-related mental health outcomes in human populations have transdiagnostic manifestations that disproportionately affect populations who experience early life adversity through resource scarcity. It is established that experiences during critical developmental periods play a consequential role in shaping the brain. This project investigated the effects of early life scarcity (ELS) on cognitive function and hedonic processing in adolescent and adult Sprague-Dawley rats. Moreover, the effects of ELS were examined in combination with adult chronic stress in a two-hit model. ELS was assessed using a heavily restricted limited bedding and nesting (LBN) approach on PD2-9. Control litters received normal bedding and nesting conditions. Male and female rats from each litter were assigned for behavioral testing and brain dissection during adolescence (PD 40-46) or adulthood (PD 80-86). Adult rats were tested under chronic unpredictable stress (CUS), where animals receive two stressors daily or control conditions for 14 days. Cognition was assessed using the novel object recognition test (NOR). Hedonic processing was assessed using a two-bottle sucrose preference test. Following testing,

nucleus accumbens and prelimbic prefrontal cortex were dissected for transcriptional analysis using RNAseq and DNA methylation. We hypothesized that early life adversity would 1) alter novel object recognition and sucrose preference in adolescent and/or adult rats and 2) influence the behavioral effects of CUS. Moreover, we hypothesize that these effects will be associated with unique transcriptional signatures that are attributable in part to epigenetic priming in response to LBN. LBN produced age-dependent effects of NOR. A 3-way LBN*age*sex ANOVA showed a significant interaction of LBN*age. LBN disrupted NOR in adolescent, but not adult rats as observed as a reduction in discrimination index (P=0.002). By contrast, LBN alone showed no alterations of sucrose preference. In the two-hit model, CUS in adult rats did not affect NOR. However, CUS produced sex-dependent reductions in sucrose preference that were prevented by LBN. A 3-way LBN*CUS*sex ANOVA showed a trending interaction of LBN*CUS*sex (P=0.070). CUS reduced sucrose intake, measured as sucrose preference percentage, in male but not female rats. Reduction was not observed in rats that received LBN. Altogether these effects that LBN can have both deleterious and protective effects, producing cognitive deficits in adolescents and preventing CUS-induced hedonic deficits in males. Analysis of transcriptional signatures and DNA methylation in the prelimbic cortex and nucleus accumbens is in progress.

Disclosures: K. Boswell: None. **D.R. Oliveira:** None. **J.R. Mantsch:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR003.20/M3

Topic: A.08. Adolescent Development

Support: NIH R01 MH131592
NIH F31 MH136684
Portland VA Research Foundation

Title: Cortical perineuronal nets are necessary for pair bond expression in the socially monogamous prairie vole

Authors: *N. E. MILMAN[1], J. LOEUNG[2], L. S. BUENO-JUNIOR[4], N. MCGUIRE[3], P. T. WICKHAM[1], A. GHIMIRE[5], B. O. WATSON[6], C. J. TINSLEY[7], B. A. SORG[8], M. M. LIM[9]; [2]Dept. of Neurol., [3]Neurol., [1]OHSU, Portland, OR; [4]Dept. of Psychiatry, Univ. of Michigan Med. Sch., Ann Arbor, MI; [5]Psychiatry, Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [6]Dept. of Psychiatry, Univ. of Michigan, Ann Arbor, MI; [7]Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [8]Neurobio., Legacy Res. Inst., Portland, OR; [9]Veterans Affairs Portland Hlth. Care Syst., Portland, OR

Abstract: Early life sleep, which is maximal during development, is essential for species-typical neurodevelopment, including the formation of functional networks and display of affiliative

social behavior. The emergence of specific interneurons (Parvalbumin positive interneurons - PVIs) and their surrounding extracellular matrix (Perineuronal Nets - pnns) is a critical milestone of cortical maturation. Prairie voles (*Microtus ochrogaster*) are highly affiliative, maximally so during adolescence, and as adults, exhibit monogamous pair bonding. We found that early life sleep disruption (ELSD) via selective reduction of rapid-eye-movement (REM) sleep during the 3rd post-natal week (P14-21) impaired pair bond expression between opposite-sex adults and altered PVIs. We first characterized typical maturation of PVIs and pnns in the prairie vole. We built an atlas of PNN expression across the adult brain and found elevated expression of pnns within the somatosensory cortex (S1).ELSD males had significantly fewer pnns in the S1 which was related to impairments in huddling with their partner during the partner preference test (PPT). However, it is unclear how late-maturing cortical structures are sensitive to interventions relevant to improving social attachment.To test the functional importance of pnns on social behavior, we exposed siblings to acute environmental enrichment (EE) for one week after weaning. EE advanced the maturation of pnns. Next, we found that EE following ELSD, was sufficient to rescue both the molecular and behavior consequences of sleep loss during development. Compared to standard housed ELSD males, EE ELSD males had intact partner preference and increased huddling with their partner during PPT. ELSD EE males also had higher levels of pnns than ELSD SH, equivalent to Control SH males.Lastly, we tested whether pnns are required for typical expression of a pair bond. We injected an enzyme to temporarily deplete pnns within the cortex, chondroitinase (ChABC) or a control enzyme, penicillinase (Pen) in adults, and found ChABC lead to impairment in huddling behavior during PPT and changes in sensory processing via the whiskers. This work supports further research into how both early life sleep and the sensory environment may shape typical social development via modulation of later-maturing cortical circuits involved in attachment.

Disclosures: N.E. Milman: None. **J. Loeung:** None. **L.S. Bueno-Junior:** None. **N. McGuire:** None. **P.T. Wickham:** None. **A. Ghimire:** None. **B.O. Watson:** None. **C.J. Tinsley:** None. **B.A. Sorg:** None. **M.M. Lim:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.21/M4

Topic: A.08. Adolescent Development

Title: The Role of Dopamine Balance in Regulating Acute Social Isolation-Induced Social Play Rebound in Juvenile Rats

Authors: *Z. ZHANG[1,2], Z. WANG[3,2];
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Abstract: Social play behavior is a fundamental aspect of neurodevelopment, characterized by dynamic, reciprocal interactions such as pouncing and pinning. While acute social isolation is known to potentiate subsequent social play—a phenomenon referred to as the "rebound effect"—the precise neural substrates governing this motivational surge remain unclear. This study aims to delineate the causal role of dopamine receptor-expressing neurons in the medial shell of the nucleus accumbens (mShNAcc) in regulating juvenile social play. Utilizing a juvenile rat model, we compared baseline social play with behavior following acute social isolation. We employed stereotaxic surgery to deliver viral vectors for the chemogenetic inhibition of either $Drd1^+$ or $Drd2^+$ neurons within the mShNAcc, and validated the efficacy of neuronal silencing through whole-cell patch-clamp recordings. To control for potential confounding effects on locomotor activity and anxiety, open field tests (OFT) were additionally conducted. Our results indicate that acute social isolation reliably induces a robust rebound in social play behavior. Furthermore, chemogenetic inhibition of mShNAcc $Drd1^+$ neurons significantly suppressed social play, whereas the inhibition of $Drd2^+$ neurons led to a significant increase in this behavior. Crucially, neither manipulation altered total locomotor distance or anxiety-related metrics in the OFT, confirming that the observed changes in play were not secondary to generalized motor alterations. These findings demonstrate a functional double dissociation within the mShNAcc, where $Drd1^+$ neurons act as a positive driver and $Drd2^+$ neurons act as a negative regulator of social play motivation. Ultimately, this D1-D2 balance provides a mechanistic explanation for the dynamic control of social motivation and offers specific neural substrates for the social play rebound following acute social deprivation.

Disclosures: Z. Zhang: None. **Z. Wang:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.22/N1

Topic: A.08. Adolescent Development

Title: Cross-Species Studies Implicate Early Life Sleep Disturbances and Extracellular Matrix Molecules in Autism Spectrum Disorder (ASD)

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Abstract: A growing number of studies implicate the amygdala-hippocampal circuit in Autism Spectrum Disorders (ASD). This circuit is involved in several processes in ASD including emotional valence, facial recognition, social learning, and anxiety. Brain imaging studies demonstrate altered amygdala development in children with ASD, associated with impairment in social behavior and anxiety. Altered hippocampal volume and deficits in memory for person and emotion related stimuli are also implicated. Our previous study of the hippocampus of children with ASD identified increased expression of extracellular matrix molecules (ECM) including matrix metalloproteases and immune signaling molecules, along with decreased synaptic signaling molecules. In the present study we conducted RNAseq profiling on postmortem amygdala samples from male children (4-14 yrs old) with ASD (n=8) and normotypic male children (n=6). We conducted drug repurposing analysis to identify compounds predicted to reverse the transcriptomic signatures to identify potential therapeutic targets. Sleep compounds were one of our top therapeutic compounds, and early life sleep disturbances (ELSD) have been previously implicated as a risk factor for ASD. Therefore, we used a prairie vole model of ELSD to examine the effects of ELSD on ECM molecules.Full transcriptome pathway analysis identified enriched expression of molecular pathways involved in neuroimmune signaling, matrix metalloproteases, neurodevelopment, and synaptic signaling in children with ASD. Drug repurposing analysis identified sleep modifying compounds and anti-inflammatory compounds as top predicted therapeutic compounds. In prairie voles with ELSD, we observed increased MMP9 neurons in CA1 stratum oriens (SO) of adolescent voles ($p<0.04$) along with decreased PNNs ($p<0.05$). In adult voles that experienced ELSD, we observed decreased PNNs in CA1 SO ($p<0.05$) together with increased MMP9 expression in PNNs ($p<0.02$). Approximately half (49%) of the PNNs in CA1 SO of adult prairie voles were colocalized with wisteria floribunda agglutinin labeled PNNs, suggesting a highly plastic state of neurons surrounded by PNNs in this sector that may be particularly vulnerable to neurodevelopmental factors. Collectively, our studies indicate alterations in ECM organization, immune signaling, and synaptic signaling in the amygdala-hippocampal circuit of children with ASD. Our drug repurposing analysis and prairie vole ELSD studies highlight the role of early life sleep disturbances in these neurodevelopmental processes.

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Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.23/N2

Topic: A.08. Adolescent Development

Support: NIH R01 MH131592 to MML, BOW, CT, LS
NIH F31 MH136684 to NEPM
Portland VA Research Foundation

Title: Identifying Sensitive Windows of Sleep in Early Life on Social Attachment in Prairie Voles

Authors: *J. M. LOEUNG[1], P. T. WICKHAM[1], N. E. P. MILMAN[2], N. M. MCGUIRE[1], A. GHIMIRE[4], L. S. BUENO-JUNIOR[4], B. O. WATSON[4], C. J. TINSLEY[3,1,5], M. M. LIM[5,2,1,3]; [1]Portland VA Res. Fndn., Portland, OR; [2]Dept. of Behavioral and Systems Neurosci., [3]Dept. of Neurol., Oregon Hlth. and Sci. Univ., Portland, OR; [4]Dept. of Psychiatry, Univ. of Michigan, Ann Arbor, MI; [5]Veterans Affairs Portland Hlth. Care Syst., Portland, OR

Abstract: Sleep is vital for healthy brain development, with early life sleep disruption (ELSD) leading to detrimental effects on mental, social, and emotional wellbeing. The precise postnatal period when ELSD maximally shapes social attachment is unknown. We have previously shown, in the highly social prairie vole (*Microtus ochrogaster)*, that ELSD during the third postnatal week (ELSD-3) impairs social bonding behavior in both adolescence and adulthood. Moreover, we have shown that parvalbumin inhibitory interneurons (PVIs) in prairie voles mature during postnatal week 3, timestamping the functional maturation of the cortex. The present study tested whether earlier or later windows outside ELSD-3 impacted social development later in life. Prairie voles were part of the undisrupted control group or underwent ELSD for one week at one of three possible timepoints: postnatal weeks 2, 3, or 4. Following sleep disruption, social behavior was then assessed longitudinally in same-sex sibling dyads across development. Finally, in adulthood, voles underwent pair bonding followed by the partner preference test, a three-chambered social choice test used to assess preference for a familiar over a novel opposite-sex conspecific. Consistent with the PVI maturation time window revealed in our prior work, adult partner preference was selectively reduced by ELSD during postnatal week 3, but not during postnatal week 4, compared to controls. This work identifies a period in early life during which sleep quality is particularly consequential for brain development and social behavior. This may provide insight into how ELSD contributes to long-term vulnerability in social functioning.

Disclosures: J.M. Loeung: None. **P.T. Wickham:** None. **N.E.P. Milman:** None. **N.M. McGuire:** None. **A. Ghimire:** None. **L.S. Bueno-Junior:** None. **B.O. Watson:** None. **C.J. Tinsley:** None. **M.M. Lim:** None.

Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.24/N3

Topic: A.08. Adolescent Development

Support: NIH Grant 4RF1MH131592-03

Title: State-specific changes in prairie vole prefrontal cortical activity during pair bond formation

Authors: *A. GHIMIRE[1], L. S. BUENO-JUNIOR[2], N. E. MILMAN[3], C. J. TINSLEY[5], P. T. WICKHAM[4], M. M. LIM[6], B. O. WATSON[7];
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Abstract: The formation of long-lasting social bonds, as seen in humans, is rare among laboratory mammals. However it can be investigated in socially monogamous prairie voles (Microtus ochrogaster), which prefer opposite-sex partners over strangers (pair bonding). Most prairie vole studies have examined pair bonding using the partner preference test (PPT), in which a test animal is allowed to differentially engage with a familiar opposite-sex conspecific and a stranger opposite-sex conspecific. However, the PPT is a short-term assay (~3 hours) and captures only the expression or strength of a pair bond without measuring the process of bond formation. Here, we quantified the multi-day process leading to pair bond formation, including ultradian sleep-wake state dynamics per animal, measured using multi-day synchronized overhead video recording (keypoint tracking, SLEAP) and chronic electrophysiology (silicon probe) in the medial prefrontal cortex (mPFC). The experimental timeline included a baseline single-housed recording (24 hours, male and female in separate cages) followed by a cohabitation recording (48 hours, male and female in the same cage, separated by a wire-mesh divider). We initially observed that the ultradian incidence of sleep-wake states was largely preserved throughout this timeline, despite intense behavioral activity in the initial hours of cohabitation. Subsequently, through video analysis, we divided WAKE epochs into four “social WAKE substates” defined by degree of engagement based on quantification of body direction and animal-animal distance: toward-near, opposite-near, toward-away, opposite-away, further enriching mPFC state classification. Within each sleep state (REM and nonREM) and social WAKE state (four, as above), overall mPFC power spectral slope remained stable over the cohabitation timeline. In contrast, theta activity decreased over that timeline, specifically within the “toward-near” WAKE substate on day 1 of cohabitation, potentially reflecting a shift from novelty-driven social engagement to familiarity. Together, these findings suggest that the development of pair bonding involves state-specific mPFC dynamics that are not apparent from sleep-wake architecture and aperiodic LFP spectral features alone. These preliminary results provide a longitudinal framework for exploring the neural dynamics of pair bond formation, informing ongoing analysis of spiking activity and studies of how neurodevelopmental conditions affect social attachment.

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Poster

PSTR003: Adolescent Development: Animal Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.25/N4

Topic: A.08. Adolescent Development

Support: NIH Grant ES35851
P20GM139753

Title: Effects of subtoxic methylmercury exposure on redox homeostasis and parvalbumin-expressing interneuron development

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Abstract: Methylmercury (MeHg) is a neurotoxin prevalent in marine food chains that negatively impacts the developing brain. Evidence suggests that MeHg preferentially targets selenol groups within antioxidant systems. Selenium (Se) is an essential trace element that is incorporated into selenoproteins as the catalytic amino acid selenocysteine. Optimal levels of Se are crucial for maximizing the activity of redox-regulating selenoproteins such as glutathione peroxidase (GPX) and thioredoxin reductase (TXNRD), which are vital for brain development. There is evidence that MeHg induces conditions reminiscent of Se deficiency *in vitro,* and studies in rodents have shown that additional Se supplementation can mitigate MeHg toxicity.Parvalbumin Interneurons (PVIs), a subtype of GABAergic interneuron that expresses the calcium-binding protein parvalbumin, are increasingly vulnerable to oxidative damage due to their high metabolic activity. PVIs are vital for proper excitatory/inhibitory tone in neural networks and modulation of gamma oscillations. During development, PVIs are preferentially surrounded by perineuronal nets (PNNs), extracellular matrix structures that protect PVIs from oxidative insults and stabilize synaptic input. Elevated levels of ROS during development have been shown to impair PVI and PNN development *in vivo,* leading to lasting alterations in excitatory/inhibitory balance. Furthermore, abnormalities in PVIs and PNNs are well documented in neuropsychiatric disorders.Here, we examined the interactive effects of Se and MeHg on PVI and PNN maturation *in vitro* and *in vivo*. Mixed primary cortical cultures were challenged with a subtoxic dose of MeHg (200 nM) from DIV14-DIV28 (days in vitro), a critical period when cortical networks and PNNs stabilize. At DIV28, TXNRD activity was reduced by MeHg exposure, whereas GPX activity was reduced under Se-deficiency. Electrophysiological analysis using microelectrode arrays (MEA) revealed that MeHg treatment disrupted neural network connectivity and impaired synaptic plasticity. Immunofluorescent analysis demonstrated decreased density of PVIs with PNNs following the MeHg challenge. Additionally, mice were placed on a diet with MeHg in two-fold molar excess to Se from weaning (3 weeks) to 8 weeks old. Utilizing immunofluorescent labeling, reduced density of PVIs with PNNs was observed in the anterior cingulate cortex, reflecting results produced *in vitro*. Altogether, these results demonstrate the effects of Se and MeHg on redox homeostasis and GABAergic maturation.

Disclosures: M. Watanabe: None. **C. Ma:** None. **K. Roshto:** None. **M.W. Pitts:** None.

Poster

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.01/N5

Topic: A.10. Schizophrenia

Title: Replication of Cobenfy's clinical cognitive benefits in a schizophrenia mouse model

Authors: *S. WAGNER, E. POIRAUD, F. LAUGA, **E. ANDRIAMBELOSON**; NEUROFIT, ILLKIRCH, France

Abstract: Cognitive impairment is a core symptom of schizophrenia and a critical predictor of patient prognosis, yet no pharmacological treatments are specifically approved to address it. Cobenfy, a groundbreaking combination of xanomeline and trospium, is the first FDA-approved drug for schizophrenia with a non-dopaminergic mechanism, offering a novel approach to treatment. To our knowledge, preclinical evidence for Cobenfy's cognitive-enhancing effects has not been reported, highlighting the need to evaluate its efficacy in translational models. To replicate Cobenfy's clinical cognitive benefits in an MK-801 mouse model of schizophrenia and to ensure that improvements in cognition were not secondary to attenuation of positive symptom-like behaviors, as typically observed with standard antipsychotics. We assessed the effect of Cobenfy on cognitive performance in a mouse model of schizophrenia. MK-801 (an NMDA receptor antagonist) was used to induce cognitive deficits, as measured by reduced spontaneous alternation in the mouse T-maze paradigm. To ensure that any observed cognitive benefits were not secondary to reductions in positive symptom-like behaviors, locomotor activity was simultaneously monitored, since MK-801 reliably induces hyperlocomotion, a preclinical correlate of positive symptoms. As a starting point for dose translation, [10 mg/kg xanomeline + 4 mg/kg trospium] was estimated as the mouse equivalent dose, derived using body surface area scaling for a single Cobenfy (50 mg/20 mg) capsule taken by a 60 kg man. In addition, we explored lower doses corresponding to one-half, one-third, one-fourth, and one-tenth of the reference dose. Cobenfy demonstrated a significant dose-dependent improvement in spontaneous alternation performance, reversing the cognitive deficits induced by MK-801. Maximal reversal was observed at 5/2 mg/kg, with a 59% reversion of the MK-801-induced deficit. A slight decline was noted at the 20/4 mg/kg (reference dose), but the reversal effect remained significant, with a 44% reversion. Notably, Cobenfy had no effect on MK-801-induced hyperlocomotion, confirming that the observed cognitive benefits occurred independently of any attenuation of positive symptom-like behaviors. These preclinical findings support the translational validity of the MK-801-induced cognitive deficit model and replicate the clinical cognitive benefits of Cobenfy with selectivity for cognition over positive symptom-like behaviors. Together, these results highlight the model's utility for future mechanistic investigations and preclinical evaluation of therapies targeting cognitive dysfunction in schizophrenia.

Disclosures: S. Wagner: None. **E. Poiraud:** None. **F. Lauga:** None. **E. Andriambeloson:** None.

Poster

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.02/N6

Topic: A.10. Schizophrenia

Title: Antipsychotic Efficacies and Side Effects Evaluation and Head-To-Head Comparison of Xanomeline and KarXT in Preclinical Rodent Models of Schizophrenia

Authors: *L. WANG[1], J. TAN[2];
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Abstract: Introduction: In 2024, KarXT, a novel co-formulation of xanomeline and trospium chloride, was approved by FDA for the treatment of schizophrenia in adults. While xanomeline provides central muscarinic agonism for antipsychotic efficacy, it was historically limited by intolerable peripheral cholinergic side effects, including diaphoresis, hypersalivation, and severe vomiting. The addition of trospium, a peripherally restricted muscarinic antagonist, effectively mitigates xanomeline's peripheral toxicity without compromising its central antipsychotic activity. However, centrally mediated side effects like dizziness and somnolence persist, alongside new anticholinergic effects induced by trospium. While the preclinical profile of xanomeline monotherapy is extensively documented, studies investigating the pharmacological dynamics of the combined KarXT formulation remain sparse. This study aims to systematically verify the antipsychotic-like effects of xanomeline in preclinical models of schizophrenia, and to conduct a head-to-head comparison against KarXT regarding antipsychotic efficacies and sides effects. Acute xanomeline dose dependently attenuated amphetamine induced hyperactivity in both mice and rats, and PCP induced hyperactivity and DOI induced head twitch response in mice. Xanomeline also reversed apomorphine induced climbing in mice. In rats, xanomeline dose dependently reduced CAR rate and increased escape latency in CAR test, and dose dependently reversed ketamine induced PPI deficit . Furthermore, xanomeline induced hypoactivity, salivation, lacrimation, hypothermia and constipation in mice, with similar but milder effects observed in rats. Xanomeline also dose dependently impaired rotarod performance. On the other hand, a combination of xanomeline and trospium completely eliminated xanomeline induced salivation, without affecting all other side effects in mice. The combination regimen neither affected the motor suppression effects of xanomeline in rat rotarod test, and antipsychotic-like effects in mice amphetamine induced hyperactivity, as well as in rat CAR test. This study validated the antipsychotic efficacies of xanomeline in various preclinical rodent models of schizophrenia representing positive and cognitive symptoms, alongside its side effect profiles. Importantly, our head-to-head comparison demonstrates that KarXT selectively eliminates peripheral hypersalivation while fully preserving central antipsychotic efficacies. These findings provide critical, previously uncharacterized *in vivo* validation for this newly approved therapeutic combination.

Disclosures: 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

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.03/N7

Topic: A.10. Schizophrenia

Title: SUVN-M8036, a multimodal receptor antagonist that exhibits antipsychotic and anti-aggressive like effects in animal models

Authors: *R. ABRAHAM, V. GOURA, S. PETLU, H. BOBBILI, A. DUDHAL, U. ANNADEVARA, A. MOHAMMED, R. NIROGI;
Suven Life Sci. Ltd., Hyderabad, India

Abstract: Psychosis is a complex neuropsychiatric disorder characterized by dysregulation of serotonergic neurotransmission, the treatment of which with dopaminergic agents is generally accompanied by side effects such as motor disorders, metabolic disorders, and unwanted cardiac effects. SUVN-M8036 is the lead compound from a multimodal project with potent affinity for serotonin and dopaminergic receptors. The in-vitro binding and functional activities of SUVN-M8036 were evaluated using both radioligand binding assays and cell-based reporter gene functional assays. The pharmacokinetic characteristics of SUVN-M8036 were evaluated in Wistar rats and Beagle dogs. Receptor occupancy of SUVN-M8036 at 5-HT1A, 5-HT2A, and dopaminergic D2 receptors was evaluated in Wistar rats using non-radiolabeled tracers. The antipsychotic profile of SUVN-M8036 was evaluated across several preclinical models in Wistar rats, with olanzapine serving as the positive control in these studies. Antipsychotic-like activity was assessed in MK-801 and amphetamine-induced hyperlocomotion in the open field test, as well as in the 2,5-dimethoxy-4-iodoamphetamine (DOI) induced head-twitch assay. Additionally, the anti-aggressive properties of SUVN-M8036 were examined using the resident-intruder task in Swiss albino mice. Finally, its side-effect profile was characterized by evaluating the propensity to induce tardive dyskinesia and motor impairment using the rotarod test. SUVN-M8036 is a novel antipsychotic that binds to serotonin 5-HT1A, 5-HT2A, and dopaminergic D2 receptors, showing dose dependent occupancy in rats. It exhibits favorable oral bioavailability (15 ± 3% in rats; 34 ± 13% in dogs). In behavioral assays, SUVN-M8036 reduced aggression and blocked MK-801 and amphetamine induced hyperlocomotion. It also inhibited DOI induced head twitches, confirming 5-HT2A antagonism. SUVN-M8036 showed no evidence of tardive dyskinesia, or motor deficits in the rotarod assay. These findings demonstrate that SUVN-M8036 exhibits antipsychotic efficacy without the typical adverse effects of standard therapies.

Disclosures: R. Abraham: A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD, Full-time Employment. **V. Goura:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Petlu:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **H. Bobbili:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Dudhal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **U. Annadevara:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd..

Poster

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR004.04/N8

Topic: A.10. Schizophrenia

Support: NSFC Grant 32571149
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Fundamental and Interdisciplinary Disciplines Breakthrough Plan of the Ministry of Education of China Grant JYB2025XDXM604

Title: Mitochondrial Redox Dysfunction Links Maternal Immune Activation to Schizophrenia-Relevant Neuronal Stress and Behavioral Abnormalities

Authors: X. ZHANG[1,2], J. ZHANG[1,2], ***M. SHEN**[3,2];
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Abstract: Maternal immune activation (MIA) is a well-established prenatal environmental risk factor for neurodevelopmental and psychiatric disorders, including schizophrenia. However, the cellular stress mechanisms that translate prenatal immune disturbance into long-lasting brain dysfunction remain unclear.In this study, we investigated whether mitochondrial redox disruption contributes to persistent neuronal abnormalities and schizophrenia-relevant behavioral deficits in MIA offspring. Transcriptomic analysis of the hippocampus revealed a prominent suppression of oxidative phosphorylation and mitochondrial respiratory pathways, together with activation of endoplasmic reticulum protein-processing and stress-related programs. Consistent with these molecular changes, hippocampal neurons from MIA offspring displayed increased oxidative injury and ER stress, accompanied by fragmented mitochondrial morphology, reduced mitochondrial membrane potential, and impaired respiratory activity. Similar stress-related remodeling was also observed in the prefrontal cortex, where MIA altered mitochondrial and ER-associated transcriptional programs and was associated with mitochondrial structural defects and enhanced inflammatory signaling. Importantly, treatment with the mitochondria-targeted antioxidant MitoQ improved mitochondrial respiratory function and alleviated anxiety-like and social behavioral abnormalities in MIA offspring. These findings suggest that mitochondrial redox imbalance represents a central mechanism through which prenatal immune challenge induces sustained neuronal stress responses and schizophrenia-relevant behavioral dysfunction. Our results further support mitochondrial redox modulation as a potential therapeutic strategy for neurodevelopmental and psychiatric disorder-related phenotypes.

Disclosures: X. Zhang: None. **J. Zhang:** None. **M. Shen:** None.

Poster

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR004.05/O1

Topic: A.10. Schizophrenia

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The Brain Foundation grant to M. K.

Title: Targeting Neuronal Bioenergetics in Genetic Mouse Models of Schizophrenia

Authors: *M. KAMBALI[1], M. WANG[1,2], R. NAGARAJAN[1], J. LYU[1,2], S. TRUSHIN[3], E. TRUSHINA[3], U. RUDOLPH[1,2,4];
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Abstract: Schizophrenia remains one of the best genetically characterized yet therapeutically stagnant psychiatric disorders. Across diverse genetic risk models, convergent evidence points to disrupted neuronal bioenergetics, including impaired mitochondrial biogenesis and oxidative phosphorylation. We examined neuronal bioenergetics as a strategic target for drug development in a genetically defined mouse model for schizophrenia with four copies of glycine decarboxylase (4cG mice), which leads to reduced extracellular glycine levels affecting synaptic function, synaptic plasticity-related signaling pathways, mitochondrial function, and cognitive performance. We tested whether compounds modulating mitochondrial function can reverse the phenotype of the 4cG mice: metformin (FDA-approved antidiabetic agent) and the tricyclic pyrone CP2, both with AMPK-dependent effects, and lactate, a natural substrate of an astrocyte-neuronal lactate shuttle, which is required for ATP production. For all these compounds, we found restoration of PGC1α and BDNF protein levels, and of mitochondrial gene expression, consistent with increased mitochondrial biogenesis and function, as well as increased synaptic plasticity and function. We plan to extend these studies to other genetic mutant mouse models, such as 1q21.1 deletion and duplication, and 15q13.3 deletion and duplication. By linking a genetic risk factor to mitochondrial vulnerability, synaptic deficits, and behavioral impairments and demonstrating their reversal by compounds targeting neuronal oxidative metabolism, this work provides evidence that targeting neuronal bioenergetics may provide a pathway for repurposing FDA-approved drugs, which could accelerate the development of novel mechanism-based treatments for schizophrenia.

Disclosures: M. Kambali: None. **M. Wang:** None. **R. Nagarajan:** None. **J. Lyu:** None. **S. Trushin:** None. **E. Trushina:** None. **U. Rudolph:** None.

Poster

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.06/O2

Topic: A.10. Schizophrenia

Support: NIH Grant DA037327
Deutsche Forschungsgemeinschaft AM 488 /1-1/-2

Title: Haloperidol suppresses accumbens core D2-MSN activity in-vivo

Authors: *M. MASSMANN[1], J. PARRILLA-CARRERO[3], A. KRUYER[1], R. W. NALL[4], R. M. CHALHOUB[5], D. AMATO[2];
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Abstract: Striatal D2 receptor blockade is considered central to antipsychotic drug action, yet it poorly predicts clinical and neurophysiological responses. One possible explanation is the limited resolution of conventional approaches for tracking defined striatal neuronal populations under in-vivo conditions. To determine how antipsychotics rapidly alter striatal subcircuits, we used single-cell in-vivo calcium (Ca2+) imaging in freely moving mice to record D1- and D2-receptor-expressing medium spiny neurons in the nucleus accumbens core (NAcc) before and after acute administration of haloperidol, a high-affinity D2 receptor antagonist. Given the inhibitory signaling mediated by D2 receptors, we expected D2 receptor blockade to disinhibit D2-expressing neurons. Contrary to this prediction, haloperidol rapidly and persistently suppressed Ca2+ events in D2-MSNs, while producing only transient excitation followed by reduced activity in D1-MSNs. After haloperidol administration, D2-MSN activity, but not D1-MSN activity, correlated with spontaneous locomotion, indicating a shift in the neuronal population most closely associated with psychomotor output. These findings identify a rapid, cell-type-specific neuronal response to haloperidol, in which D2 receptor blockade in the NAcc suppresses D2-MSN activity in vivo. This suppression, rather than D2 receptor blockade alone, may represent a key circuit mechanism through which haloperidol alters psychomotor output.

Disclosures: M. Massmann: None. **J. Parrilla-Carrero:** None. **A. Kruyer:** None. **R.W. Nall:** None. **R.M. Chalhoub:** None. **D. Amato:** None.

Poster

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.07/O3

Topic: A.10. Schizophrenia

Support: Korea–US Collaborative Research Fund (KUCRF), funded by the Ministry of Science and ICT and the Ministry of Health & Welfare, Republic of Korea (grant number RS-2025-02293110)

Title: Akt-mediated translational reprogramming drives expression of plasticity-related synaptic proteins following clozapine-induced AMPK-mTORC1 suppression in mouse perfrontal cortex

Authors: *Y. KIM[1], S. KIM[2];
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Abstract: Clozapine is an antipsychotic agent with superior efficacy. Its effects on the metabolic system showed that clozapine affects mTOR and AMPK signaling pathways. However, the findings are inconsistent as well. In this study, we examined the effect of systemic injection of clozapine on mTOR and protein translation in the mouse prefrontal cortex (PFC). Clozapine decreased phosphorylation of S6 (S240/244, S235/236). Together, AMPK-responsive phosphorylation of Raptor (S792) and TSC2 (S1387) was increased by clozapine. The findings suggest that clozapine reduced global translation in the metabolic-stressed state in PFC. The protein synthesis activity slightly decreased in the whole fraction of PFC by clozapine. However, clozapine increased phosphorylation of AKt (S473), GSK-3beta (S9), p70S6K (T389), and mTOR (S2481, S2448). The phosphorylation of 4E-BP1 (T36/S47) and eIF4B (S422) was also increased, and co-immunoprecipitation showed increased binding of eIF4E with eIF4G, indicating the increased translation initiation. In the synaptosomal fraction, the protein level of Arc, CaMKII, and GluA2 was increased with reduced phosphorylation of eIF2Bε (Ser540) and eIF2α (Ser51), indicating eIF2B activation, which demonstrated local synaptic translation increase. Systemic injection of MK-2206, an AKt inhibitor, decreased a clozapine-induced increase in protein level of Arc, CaMKII, and GluA2, accompanied by the reduced phosphorylation of GKS-3beta, eIF4B, and 4E-BP1. The findings demonstrate that clozapine-induced suppression of canonical mTORC1 signaling via AMPK activation, which paradoxically triggers a compensatory AKt-mediated feedback loop that drives the selective local translation of synaptic proteins such as Arc in PFC.

Disclosures: Y. Kim: None. **S. Kim:** None.

Poster

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.08/O4

Topic: A.10. Schizophrenia

Support: 1R01MH134074 (NIMH)
The Branfman Family Foundation

Title: Characterization of the specific dopamine D_2 receptor agonist MCL-524 as a tool to monitor pathophysiological striatal D_2 dysregulation in schizophrenia

Authors: *A. SHANMUGAVADIVU[1,2], W. B. RUZICKA[3,2], S. SUBBURAJU[4,2];
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Abstract: Despite their limitations, antipsychotic medications are the cornerstone of the clinical management of schizophrenia (SZ). One adverse outcome of antipsychotic exposure is the emergence of secondary treatment resistance and dopamine supersensitivity psychosis (DSP), seen in ~30% of SZ patients, characterized by rebound psychosis, tardive dyskenesia, escalating medication requirements, and poor long-term outcomes. DSP occurs when chronic or inconsistent dopamine blockade by antipsychotic medications induces a compensatory overexpression of the D2 receptor, resulting in an increased response to dopamine stimulation. To effectively manage SZ symptoms while avoiding DSP there is an optimal range of D_2 receptor antipsychotic occupancy, determined by patient-specific changes in D_2 density. A specific D_2 agonist for use in PET would facilitate early, accurate diagnosis of DSP and enable careful, precise titration of antipsychotics dosage to maximize therapeutic benefit in managing psychosis while minimizing unwanted side effects. The aporphine D_2 agonist MCL-524 has sub-nanomolar affinity to D_2, low or no affinity to other DA or non-DA receptor families, readily crosses the blood brain barrier, and is readily labelled as a [^{18}F] radiotracer. The *in vitro* and animal studies presented here establish the safety, reliability, sensitivity, and specificity of MCL-524 toward its development as a first-in-class diagnostic tool for monitoring dopaminergic neurotransmission in the clinical management of SZ.
Metabolic stability: in plasma, MCL-524 had a half-life of 33.2 (human), 48.4 (rat) and 11.4 (mouse) minutes. In liver microsomes, half-lives were 69.9 (human), 30.5 (rat) and 26.2 (mouse). In hepatocytes, half-lives were 90.5 (human), 126.3 (rat) and 73.3 (mouse). These results indicate adequate metabolic stability for a typical imaging session timeframe.
Plasma protein binding (PPB) indicating potential availability of the ligand for binding to its target was determined by the ultrafiltration method. PPB was 88.79% and 88.64% (mouse), 88.17% and 86.74% (rat), 83.96% and 84.4% (monkey) and 81.52% and 84.86% (human) in plasma at incubation temperatures of 25 °C and 37 °C, respectively.
I*n vivo* selectivity of [^{18}F]MCL-524 was assessed using specific D2 or D_3 antagonists (benperidol, SB277011A) and quantified by PET imaging. In SD rats [^{18}F]MCL-524 bound to D_2 in regions of interest (basal ganglia, Nucleus accumbens, cortex). Binding in females was slightly higher. The specific D_2 receptor antagonist benperidol very efficiently abolished binding of MCL-524 in the striatum.

Disclosures: A. Shanmugavadivu: None. **W.B. Ruzicka:** None. **S. Subburaju:** None.

Poster

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.09/O5

Topic: A.10. Schizophrenia

Support: Dalhousie Psychiatry Research Fund Grant, awarded to Derek Fisher

Title: Caffeine Effects on Beta and Gamma Auditory Sensory Gating in Early-Phase Schizophrenia

Authors: *C. Q. DENG[1], T.-J. ANDERSON[2], K. J. MCKEARNEY[2], P. G. TIBBO[3], D. FISHER[2], S. VAN NOORDT[1];
[1]Psychology, Wake Forest Univ., Winston-Salem, NC; [2]Psychology, Mount St. Vincent Univ., Halifax, NS, Canada; [3]Psychology, Dalhousie Univ., Halifax, NS, Canada

Abstract: A hallmark of chronic schizophrenia (SZ) is difficulty filtering repeated or redundant information, referred to as sensory gating. Sensory gating has been linked to coordinated gamma and beta dynamics between frontal and auditory regions as a possible mechanism that supports the suppression of redundant sensory information. Caffeine is the most commonly consumed psychoactive substance and is known to impact several cognitive functions such as processing speed and working memory. However, despite its widespread use, and elevated consumption rates in the SZ population, the effects of caffeine on sensory gating remains largely unknown. The present study examined the effects of caffeine on oscillatory auditory sensory gating in healthy controls (HC) and individuals with early-phase SZ, focusing on beta- and gamma-band dynamics. Using a randomized, double-blind, placebo-controlled, repeated-measures design, 15 HC and 17 individuals within five years of a primary SZ diagnosis (mean age = 25.6 years) completed two EEG sessions following counterbalanced 200 mg caffeine and placebo. EEG was collected during an auditory paired-click paradigm consisting of an initial click (S1) followed by a repeated click (S2; 128 pairs of 1000 Hz clicks, 500 ms apart). Source-level evoked beta and gamma dynamics were extracted from auditory and frontal regions, and sensory gating was quantified as the change in power from S1 to S2.We observed a significant caffeine × group interaction ($p = .047$) on gating for gamma dynamics in auditory cortex sources. This effect was driven by caffeine-related attenuation of gamma gating in SZ, with no reliable change in HC. Beta showed robust gating effects from S1 to S2, in both frontal and auditory regions ($p < .001$), but it was not affected by caffeine or group. In addition, both frontal beta gating ($p = .010$) and auditory beta gating ($p < .001$) were significant predictors of auditory gamma gating. The auditory beta-gamma relationship was further moderated by group, indicated by significant positive cross-frequency in SZ.These findings highlight auditory gamma-band activity as a candidate marker of altered auditory information processing in early-phase SZ and suggest that coordinated frontal-auditory beta-band dynamics may represent a neural mechanism that supports the gating of auditory gamma responses.

Disclosures: C.Q. Deng: None. **T. Anderson:** None. **K.J. McKearney:** None. **P.G. Tibbo:** None. **D. Fisher:** None. **S. van Noordt:** None.

Poster

PSTR004: Schizophrenia Therapeutics: Animal and Human Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.10/O6

Topic: A.10. Schizophrenia

Support: RS-2023-00266120
RS-2026-25470841
25-BR-05-05

Title: Effective connectivity in the mismatch negativity network associated with positive symptom improvement following electroconvulsive therapy in psychosis

Authors: *E. CHOE[1], M. HA[2], M. KIM[3];
[1]Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of; [2]Inst. of Human Behavioral Medicine, Seoul Natl. Univ. - Med. Res. Ctr., Seoul, Korea, Republic of; [3]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Electroconvulsive therapy (ECT) produces rapid improvement of symptoms in psychotic disorders, yet how it acts at the level of neural circuits remains largely unknown. Positive symptoms have increasingly been framed through predictive coding, which formulates the brain as a hierarchy that generates sensory predictions and signals prediction errors. The mismatch negativity (MMN) network offers a tractable reflection of this hierarchy and is consistently altered in schizophrenia. We explored whether ECT is related to change in the effective connectivity of this network and whether such changes are related to symptomatic improvement. We analyzed electroencephalography data recorded during a passive auditory oddball task. Patients with schizophrenia or schizoaffective disorder treated with ECT plus medication (n = 23) or medication alone (n = 24), and healthy controls (n = 52) underwent recordings. MMN was quantified at Fz, and dynamic causal modeling with parametric empirical Bayes were utilized to estimate effective connectivity among bilateral primary auditory cortices (A1), superior temporal gyri (STG), and inferior frontal gyri (IFG). MMN amplitude diverged between the patient groups over time (group-by-time interaction t=-3.17, $P = 0.003$): it increased after ECT but decreased under medication alone. Within the ECT group, greater improvement on the Positive and Negative Syndrome Scale (PANSS) positive subscale was related to strong evidence (posterior probability > 0.95) of changes in effective connectivity involving both lower (A1-STG) and higher (STG-IFG) levels of the hierarchy, including ascending, descending and intrinsic connections. No connection showed strong evidence of association with improvement in the PANSS total score. These connectivity changes were shown to be specific to the ECT group, by group-by-time interaction effects. In psychotic disorders, ECT is related to changes in the effective connectivity within the MMN circuit, which is implicated in predictive coding, and these changes correlate specifically with positive symptom improvements. These findings may provide background for future neuromodulation that targets the full cortical hierarchy of neural circuit that subserves positive symptoms.

Disclosures: E. Choe: None. **M. Ha:** None. **M. Kim:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.01/O7

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

Title: Glial peptides regulate reversal behaviors in C. elegans

Authors: *A. RAHMAN[1], C. SHEELER[2], A. FRAKES[2];
[1]Section on Glial Biol., Natl. Inst. of Hlth. (NIH) - Brown Univ., Bethesda, MD; [2]Section on Glial Biol., NIH, Bethesda, MD

Abstract: Glia orchestrate central nervous system function by synthesizing and releasing many neuroactive molecules. Despite their name, neuropeptides are also expressed in glia across invertebrates and mammals, yet whether glial-derived neuropeptides modulate neuronal circuits and behavior remains unknown. Therefore, we utilized *C. elegans* to identify glial-derived neuropeptides and characterize their role in sensorimotor behavior. *C. elegans* is a powerful system for dissecting glial neuropeptide function due to its optical transparency, genetic tractability, and quantifiable behavioral outputs. Its genome encodes 160 neuropeptide genes giving rise to over 300 peptides, many of which are phylogenetically conserved. By integrating single-cell RNA sequencing datasets with fluorescent transcriptional reporter strains, we confirmed that *nlp-16* is expressed in a subset of glia. To determine whether *C. elegans* glia possess the molecular machinery required for neuropeptide secretion, we characterized glial expression of proprotein convertases. While most glia lacked the predominant neuronal proprotein convertase, *egl-3*, many glia expressed *bli-4*, suggesting *bli-4* is the primary peptide processing enzyme in glia. Fluorescence microscopy of an endogenous dense core vesicle marker confirmed that *C. elegans* glia harbor the secretory vesicles required for neuropeptide release. Once released, neuropeptides bind to G-protein coupled receptors (GPCRs) to regulate physiological and behavioral processes, such as food-seeking. Therefore, we investigated whether NLP-16 contributes to this conserved behavioral program. Using WormLab tracking software, we compared behavior between *nlp-16* loss-of-function (LOF) and wild-type animals in the presence and absence of food. Upon removal from food, *C. elegans* perform an area-restricted search, exhibiting increased reversals and reorientations during a local search phase (0-20 min), followed by a reduction in these behaviors during a global search phase (>20 min). We found that *nlp-16* LOF animals spent significantly less time in reverse locomotion and performed fewer reversals than wild-type animals during both local and global search in the absence of food. No behavioral differences were observed in the presence of food. This suggests that NLP-16 functions specifically in regulating reversal during food-seeking. These data demonstrate that glia, not just neurons, can modulate behavioral programs through neuropeptide signaling. Future work will identify the receptor and downstream cellular targets of NLP-16 to resolve the mechanism by which glial neuropeptide signaling alters food-seeking behavior.

Disclosures: A. Rahman: None. **C. Sheeler:** None. **A. Frakes:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.02/O8

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

Title: Distributed INS-1 signaling through the candidate noncanonical receptor NTR-1 tunes the ASER-AIY axis to drive high-salt ethanol avoidance in Caenorhabditis elegans

Authors: *Y. WANG[1,2,3], J. ZHANG[1], X. HUANG[1], Y. RUAN[1], Y. YU[4];
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Abstract: Context-dependent neuromodulation can reverse the behavioral response from the same chemical cue. Ethanol valence in *Caenorhabditis elegans* is salt-dependent: ethanol is attractive under low salt but aversive under high salt. In day-1 adult hermaphrodites, we found that loss of the insulin-like neuropeptide INS-1 completely reversed high-salt ethanol avoidance into attraction, suggesting that INS-1 is central to assigning negative valence to ethanol under high-salt conditions.

We next used cell-specific perturbations to identify the sources of INS-1 that regulates ethanol valence. These experiments implicate ASEL, AIY, AIZ, and AIB as candidate INS-1-releasing nodes. ASEL was supported by cell-specific *ins-1* deletion and rescue, and its ethanol response was largely unchanged by *ins-1* loss, consistent with a primary role as an INS-1 source. AIY was supported by deletion, rescue, and PH-miniSOG-mediated ablation, indicating a robust role in INS-1-dependent ethanol valence control. AIZ was implicated by rescue, while AIB by rescue and ablation. Together, INS-1 appears to be released from a distributed network rather than a single dedicated source.

Calcium imaging further showed that *ins-1* loss shifted ethanol sensitivity in the ASER-AIY circuit. In *ins-1* mutants, ASER exhibited a right-shifted response profile, responding only to higher ethanol concentrations, while AIY showed reduced ethanol-evoked negative calcium transients. Consistent with these neural changes, increasing ethanol concentration partially restored avoidance behavior in *ins-1* mutants, suggesting that *ins-1* deficiency elevates the threshold for aversive detection rather than complete sensory loss.

At the receptor level, canonical insulin-pathway mutants, including *daf-2*, *age-1*, *akt-1/2*, *daf-16*, and *daf-18*, failed to recapitulate the *ins-1* phenotype, whereas mutants of the neurotensin-like GPCR *ntr-1* did. Protein-docking analysis further predicted a favorable INS-1-NTR-1 interaction. Together, these results support a mechanistically integrated model in which distributed INS-1 release, potentially through the noncanonical receptor NTR-1, tunes ASER state and downstream AIY output to drive high-salt ethanol avoidance.

Disclosures: Y. Wang: None. **J. Zhang:** None. **X. Huang:** None. **Y. Ruan:** None. **Y. Yu:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.03/P1

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

Support: NIH Grant R15GM155985

Title: Molecular and Activity-Dependent Mechanisms Regulating Dense-Core Vesicle Trafficking, Capture, and Neuropeptide Release

Authors: *K. O'CONNOR[1], T. HANA[1], B. YUN[1], O. ALSHEHAB[1], M. HASSAN[2], K. ORMEROD[1];
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Abstract: Intercellular communication is one of the most fundamental and critical processes in biology, where almost all cells in organisms respond to and send signals to other cells. Within the nervous system, intercellular communication relies on the regulated release of small molecules like neurotransmitters and neuropeptides (NPs) from synaptic vesicles and dense-core vesicles (DCVs), respectively. Unlike synaptic vesicles, which are synthesized and recycled locally at synapses, DCVs are generated in the neuronal soma and transported along axons by motor proteins before being captured within synaptic boutons for regulated release. Despite the importance of this process for neuronal signaling, the molecular mechanisms governing DCV uncoupling from molecular motors and subsequent capture at synapses remain poorly understood. We hypothesize that activity-dependent increases in intracellular calcium at the bouton-axon interface activate a kinase signaling cascade that promotes DCV capture by disrupting the interaction between kinesin and its cargo adaptor proteins. To test this, we took advantage of the genetic, molecular, and microscopy-based tools available in Drosophila melanogaster. Live fluorescence imaging and immunohistochemistry in third-instar larvae expressing genetically encoded, fluorescently labeled NPs was conducted in conjunction with targeted genetic disruption of candidate motor proteins, adaptor proteins, and critical members of major kinase pathways. Highly novel, computer learning-integrated software was used to track individual DCVs to quantify changes in velocity, flux, directional persistence, run length, and bouton capture frequency. Our investigations have identified several key motor proteins, adaptors, and kinases critically involved in NP trafficking, capture, and release. Together, these studies will define the molecular and activity-dependent mechanisms that regulate DCV capture at synaptic boutons and provide new insight into how neuropeptide signaling is controlled within neural circuits.

Disclosures: K. O'Connor: None. **T. Hana:** None. **B. Yun:** None. **O. Alshehab:** None. **M. Hassan:** None. **K. Ormerod:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.04/P2

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

Support: NIH Grant R15GM155985

Title: Genetic disruption of Dynactin in the nervous system of Drosophila melanogaster leads to impaired intracellular transport, and synaptic malfunction

Authors: *O. ALSHEHAB[1], T. HANA[2], K. O'CONNOR[1], M. HASSAN[3], B. YUN[1], K. ORMEROD[1];
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Abstract: Intracellular cargo trafficking is a fundamental cellular process required for the maintenance of cellular homeostasis and viability. Neurons are particularly reliant on efficient intracellular transport due to their high metabolic demands and highly polarized morphology, which necessitates the movement of proteins, organelles, and signaling molecules over long distances. A key component of the retrograde transport machinery is dynactin (DCTN), a heteromultimeric protein complex that functions as an essential cofactor for cytoplasmic dynein, the primary minus-end-directed microtubule motor. Dynactin interacts directly with dynein to form an active transport complex, thereby enhancing motor processivity and enabling sustained movement along microtubules without frequent detachment. Structural analyses using cryo-electron microscopy have revealed that dynactin is composed of 23 distinct subunits organized into a highly ordered macromolecular assembly. Together, dynein and dynactin mediate the retrograde transport of diverse cargoes, including dense-core vesicles (DCVs), synaptic vesicles (SVs), and membrane-bound organelles, facilitating their movement from distal axonal regions toward the neuronal soma. Despite considerable advances in our understanding of dynein-dynactin structure and function, the specific contributions of individual dynactin subunits to vesicular trafficking and neuromuscular junction (NMJ) development and maintenance in motor neurons remain incompletely characterized. Here we take advantage of the strong genetic, molecular, and imaging advantages of Drosophila melanogaster to examine the role dynactin. Using a targeted genetic approach, we knocked down 5 different dynactin subunits, and explored the impacts on intracellular organelle trafficking, and putative impacts on the structure/function of individual neurons. Live imaging revealed that knocking down dynactin subunits 2 and 4 caused intracellular organelles to aggregate, significantly impairing the rate of trafficking, flux, and coordinateness of cargo transport. Cargo localization at synapses was also significantly impaired in larvae with disrupted dynactin subunit expression. Our current work is exploring whether these disruptions lead to synaptic structural or functional impairments, and ultimately whether changes in behavior are observed. These findings highlight the essential roles of individual dynactin subunits in neuronal cargo transport and establish a framework for understanding how disruptions in dynein-dynactin function contribute to nervous system dysfunction in both normal physiology and human disease.

Disclosures: O. Alshehab: None. **T. Hana:** None. **K. O'Connor:** None. **M. Hassan:** None. **B. Yun:** None. **K. Ormerod:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.05/P3

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

Support: WWTF Grant VRG21-015

Title: Cell-type-specific PACAP-PAC1 signaling in temporal cortex circuits

Authors: *S. HEIMBACH, S. MELZER;
Med. Univ. of Vienna, Vienna, Austria

Abstract: PACAP-PAC1 signaling has been implicated in stress-related behaviors and emotional memory, yet the intracellular signaling pathways and circuit-level consequences of this neuromodulatory system in higher-order cortical areas remain poorly understood. Here, we investigated PACAP-PAC1 signaling in the temporal neocortex. Using fluorescence *in situ* hybridization, publicly available single-cell RNA sequencing datasets, acute slice imaging, electrophysiology, tracing approaches, chemogenetic manipulation, and *in vivo* fiber photometry, we identify PAC1-expressing cells across multiple neuronal populations and astrocytes in TeA. Acute slice imaging revealed substantial heterogeneity in PACAP-evoked signaling across neuronal populations, indicating that PAC1 receptor activation engages distinct intracellular signaling programs in different cell types and circuits. We further characterized the output connectivity of *Adcyap1r1*$^{+}$ expressing neurons and investigated the recruitment and behavioral relevance of cortical cell populations targeted by PACAP signaling during fear learning and memory retrieval. Together, these findings reveal PACAP-PAC1 signaling as a heterogeneous, cell-type- and circuit-specific modulatory system in the temporal cortex, providing new insights into how neuromodulatory GPCR signaling shapes cortical function during emotional learning.

Disclosures: S. Heimbach: None. **S. Melzer:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

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Program #/Poster #: PSTR005.06/P4

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

Support: ERC 101041941

Title: CRH-CRHR1 signaling in the thalamic reticular nucleus

Authors: *A. CREAMER, C. LÜGERING, S. MELZER;
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Abstract: Corticotropin-releasing hormone (CRH) signaling through CRHR1 has been implicated in anxiety, stress-related behavior, arousal, and adaptive responses to salient environmental cues, yet the region-specific signaling pathways and behavioral effects are not fully understood. Here, we investigated CRH-CRHR1 signaling in the thalamic reticular nucleus (TRN), a GABAergic structure that regulates thalamocortical transmission, sensory processing, attentional gating, and behavioral responses to threats. Using cross-species gene-expression analyses, fluorescence *in situ* hybridization (FISH), *ex vivo* cAMP fluorescent imaging, whole-cell patch-clamp electrophysiology, optogenetic circuit physiology, CRISPR-mediated *Crhr1* deletion, and behavioral testing, we examined the role of CRH-CRHR1 signaling in the TRN in anxiogenic contexts.
Cross-species gene-expression analyses indicated that CRHR1 expression in the TRN is conserved across mouse and human datasets, and RNAscope FISH in mouse TRN showed that *Crhr1* is broadly expressed across *Pvalb*- and *Sst*-expressing neurons. We next examined how CRH-CRHR1 signaling modulates key electrophysiological and molecular properties of TRN neurons, including cAMP signaling, intrinsic excitability, hyperpolarization-activated cyclic nucleotide-gated (HCN) channel activation, calcium channel activation, and GABAergic output from TRN neurons. To assess the behavioral relevance of TRN CRHR1 signaling, we examined how cell-type-specific *Crhr1* deletion influences behavior across classical anxiety-related assays. Together, our results highlight CRH-CRHR1 signaling as a functionally relevant neuromodulatory pathway in the TRN and provides a framework for understanding how GPCR-mediated signaling in thalamic inhibitory circuits may influence adaptive behavioral responses.

Disclosures: A. Creamer: None. **C. Lügering:** None. **S. Melzer:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.07/P5

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

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Grants-in-Aid for Scientific Research JP23K27324

Title: Intracellular trafficking of endocytosed Reelin and its regulatory mechanism in mature cerebellar Purkinje cells

Authors: *M. HIRADE, S. TOKUNAGA, T. KOHNO, M. HATTORI;
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Abstract: [Background and Purpose] Reelin is a secreted glycoprotein that is essential for the proper migration and positioning of cerebellar Purkinje cells (PCs) during development. Although Reelin continues to be secreted by cerebellar granule cells after PC migration is complete, and its receptors remain highly expressed in mature PCs, its functions in the adult cerebellum are largely unknown. In cerebral cortical neurons, endocytosed Reelin undergoes proteolytic cleavage within endosomes, resulting in signal termination. However, whether a similar mechanism operates in mature PCs remains unclear. In this study, we investigated the intracellular trafficking of endocytosed Reelin and the role of Reelin cleavage in mature PCs. [Methods] Primary cerebellar neurons were isolated from Reelin-deficient mice and cultured until PCs reached maturity. The cultures were then treated with recombinant Reelin-containing medium and incubated at 37°C for a defined period. To analyze the subcellular localization of the molecules, immunocytochemistry was performed. [Results and Discussion] Exogenously applied Reelin bound predominantly to the dendrites of mature PCs and was subsequently endocytosed. To examine the intracellular trafficking of endocytosed Reelin, cells were treated with Reelin-containing medium and then transferred to Reelin-free medium. Immediately after internalization, Reelin was primarily detected in dendrites. Over time, dendritic Reelin signals decreased, whereas somatic signals increased, suggesting that Reelin is internalized in dendrites and transported to the soma. When the same experiment was performed using a cleavage-resistant mutant Reelin, it accumulated more extensively in the soma, suggesting that proteolytic cleavage regulates the dendrite-to-soma transport of endocytosed Reelin. We also examined the intracellular dynamics of Dab1, the primary downstream adaptor protein in the Reelin signaling pathway. Following Reelin uptake, diffusely distributed Dab1 became concentrated into punctate structures within dendrites. Reelin and Dab1 initially co-localized in these puncta; however, the proportion of Reelin+/Dab1- puncta increased over time. These findings suggest that Dab1 transiently associates with Reelin-containing endosomes and is subsequently degraded or dissociates from the complexes. Together, our findings reveal a previously unrecognized intracellular trafficking pathway for Reelin in mature PCs. Reelin may exert distinct functions in the adult cerebellum through cell type-specific trafficking mechanisms.

Disclosures: M. Hirade: None. **S. Tokunaga:** None. **T. Kohno:** None. **M. Hattori:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.08/P6

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

Title: Metabotropic vs ionotropic signaling during neurotransmission at the parabrachioamygdalar synapse enabling behavioral responses to aversive stimuli

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Abstract: Neurotransmitters convey information across synapses either via direct effects on ion channels affecting firing rates (e.g. at ionotropic receptors), or indirectly via second messengers (e.g. at metabotropic receptors). Ionotropic signaling is typically conveyed via release of glutamate or GABA, and metabotropic signaling via neurotrophins, catecholamines and neuropeptides. Ligands for some G-protein coupled receptors, however, may act metabotropically via G-alpha, and ionotropically via G-beta regulation of cation channels. Signaling by the neuropeptide PACAP within the capsular central amygdala (CeC) is involved in processing of aversive stimuli. PACAP is released from PACAPergic/glutamatergic neurons of the extended lateral parabrachial nucleus (elPBn) at axosomatic synapses with PKCδ cells of CeC. PACAP neurotransmission is required for $PKC\delta^{CeC}$ neuronal engagement (fos induction), and for hypophagia, after restraint stress. Silencing of $PKC\delta^{CeC}$ neurons, but not of $PKC\delta^{BNST}$ neurons to which $PACAP^{elPBn}$ neurons also project, blunts restraint-induced hypophagia (Jiang et al., Biol. Psychiatr. GOS 3: 672, 2023). We have also reported that PACAP deletion from this pathway, contralateral to unilateral sciatic nerve cuffing ablates unilateral paw sensitization to cold, pain, pressure and heat (Singh et al., PSTR038.17, 2024 Neuroscience Meeting Planner, Chicago, IL, SfN). PACAP perfusion of amygdalar brain slices is reported to enhance neuronal excitability, but not firing rates, of $CeC^{PKC\delta}$ neurons (Zhang et al., PNAS Nexus 5: pgag083, 2026). $PKC\delta^{CeC}$ neurons receive glutamateric input via both $PACAP^{elPBn}$ axosomatic synapses, and axodendritic input from other sources. Patent glutamatergic transmission at the axosomatic synapses is demonstrated by firing of PKCδ neurons, blocked by application of glutamate receptor antagonists, in slices from mice expressing channelrhodopsin in PACAPergic parabrachioamgdalar neurons. However, deletion of the glutamate vesicular transporter VGluT2 from them (via AAV-cre injection into elPBn of $VGluT2^{fl/fl}$ mice) did not affect restraint stress-induced hypophagia, or induction of fos after restraint, in $PKC\delta^{CeC}$ neurons. We conclude that PKCδ neuronal engagement, measured by fos induction is dependent on PACAP and independent of glutamatergic transmission in this pathway. Based on similar experiments conducted on dopamine signaling to D1 receptor-bearing neurons of nucleus accumbens (Zhang et al., J. Neurochem. 170:e70374, 2026), we hypothesize that cAMP is the second messenger leading to fos induction in PKCδ neurons as well as PKCδ neuron-dependent behavioral effects of stress.

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Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.09/Q1

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

Support: VA Grant I01 BX006921
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Title: Seizure-induced activity-dependent regulation of enkephalin expression in the hippocampus

Authors: *C. P. TRAN[1,2], A. N. ANDERSON[1,2], N. WARIKOO[1,2], E. SCHNELL[1,2]; [1]Anesthesiol. and Perioperative Med., Oregon Hlth. & Sci. Univ., Portland, OR; [2]Portland VA Med. Ctr., Portland, OR

Abstract: Granule cells of the hippocampal dentate gyrus express several different peptide neurotransmitters, one of which is the endogenous opioid peptide, enkephalin. Basal expression of enkephalin in granule cells is very sparse, but the number of enkephalin-expressing cells increases dramatically in epilepsy. To further understand the relationship of granule cell enkephalin expression to seizure activity, we performed intrahippocampal kainic acid injections to activate the hippocampal network. Kainic acid dramatically increased both enkephalin mRNA and peptide expression. Additional characterization of both basal and seizure-induced enkephalin expression was performed with a Proenkephalin-IRES-Cre mouse crossed with a tdTomato reporter mouse, which demonstrated dramatic increases in Proenkephalin gene activation by seizures. TdTomato-positive cells accumulated as mice aged, and in situ hybridization experiments suggested that this was due to sporadic enkephalin expression throughout the mouse lifespan. Ongoing experiments are aimed at obtaining additional insights into the mechanisms and timecourse of enkephalin expression after seizures. Future work will aim to understand the functional roles of enkephalin during both basal and seizure-related activity in the hippocampal dentate gyrus.

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Poster

PSTR005: Neuropeptides and Other Signaling Molecules

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.10/Q2

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

Title: Deep Brain Stimulation at Lateral Habenula Reduces Avoidance Behavior in a Rat Model of Depression via Lateral Hypothalamus Orexin System

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Abstract: Depression is one of the psychiatric disorders affecting millions of people worldwide. The symptoms like anhedonia, reduced motivation and memory impairment studied in the animal model of depression. In addition to these symptoms, avoidance behavior has gained attention as marker of depression phenotype. The orexinergic projection from the lateral hypothalamus (LH) to the lateral habenula (LHb) has been implicated in the regulation of avoidance behavior; however, its role in depression and the effects of deep brain stimulation (DBS) on this pathway remain poorly understood. Although DBS has emerged as a promising treatment for treatment-resistant depression (TRD), the neural mechanisms underlying its antidepressant effects are not fully elucidated. In the present study, we investigated the involvement of orexinergic projection from the LH to the LHb in depression-associated avoidance behavior and examined whether the antidepressant effects of DBS at LHb are mediated through this circuit. We used adult male Wistar rats were exposed to chronic unpredictable mild stress (CUMS) for the induction of depression-like symptoms and were stereotaxically implanted with the electrode targeted at LHb. The CUMS exposed rats showed (a) increased avoidance behavior in the shuttle box, reduced sucrose preference, feed consumption, locomotor activity and increased latency to feed (b) decreased orexin mRNA in the LH (c) reduced orexin receptor 2 (OXR2) and increased vesicular glutamate transporter 2 mRNA in LHb. The application of DBS, targeted unilaterally at the LHb for 1 h/day for 14 days, resulted in the reversal of behavioral and molecular alterations induced by CUMS. To further evaluate the role of orexinergic signaling, orexin A and the OXR2 antagonist TCS OX2-29 were administered into the LHb. Orexin A reduced avoidance behavior and improved depression-like symptoms in CUMS-exposed rats, whereas OXR2 antagonism increased avoidance behavior and countered the antidepressant effects of DBS. These findings suggest that dysregulation of the LH-LHb orexinergic pathway contributes to depression-associated avoidance behavior and the antidepressant effects of DBS at LHb may be mediated, at least in part, through restoration of OXR2-dependent orexinergic signaling within the LHb.

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Poster

PSTR005: Neuropeptides and Other Signaling Molecules

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Program #/Poster #: PSTR005.11/Q3

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

Support: R01MH112739 (NIMH)
R01NS131664 (NINDS)

Title: Mapping the Nanoscale Molecular Organization of Hypocretin/Orexin Synapses

Authors: *J. M. SALVATORE[1], W. P. ARMSTRONG, IV[1], D. MARTINELLI[3], A. C. JACKSON[2];
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Abstract: Mapping the nanoscale molecular organization of hypocretin/orexin synapses**James M. Salvatore[1]**, William P. Armstrong IV[1], David C. Martinelli[2], Alexander C. Jackson[1] [1]Department of Physiology and Neurobiology, University of Connecticut, Storrs CT [2]Department of Neuroscience, University of Connecticut Health Center, Farmington, CT
Funding: R01MH112739 (NIMH), R01NS131664 (NINDS)**Disclosures:** None**Abstract:**Hypocretin/orexin (H/OX) neurons of the lateral hypothalamic area (LHA) are critical regulators of arousal and sleep-wake state stability. Dysfunction of the H/OX system causes profound disturbances in behavioral state control, including the human sleep disorder narcolepsy with cataplexy. Although the circuit-level organization and behavioral functions of H/OX neurons have been extensively studied, the molecular architecture of their excitatory synapses remains poorly understood. In particular, the spatial organization and localization of key synaptic proteins, highly enriched within H/OX neurons, have yet to be systematically characterized. To address this gap, we combined stimulated emission depletion (STED) super-resolution microscopy with high-resolution confocal imaging to map the nanoscale organization of proteins within H/OX synapses in both wild type and epitope-tagged knockin mice. Bassoon and PSD95 were used to define presynaptic and postsynaptic compartments, respectively, allowing putative pre-, post- and trans-synaptic proteins, receptors, and neuromodulatory signaling components to be quantified relative to established synaptic landmarks. We examined the spatial distribution of canonical excitatory synaptic markers, including kainate and AMPA receptors, relative to presynaptic and postsynaptic domains. In addition, we investigated the localization and co-occurrence of putative trans-synaptic proteins at H/OX synapses to assess potential molecular relationships associated with synaptic specialization. We further compared the molecular composition of H/OX synapses across multiple arousal-related target regions including the ventral tegmental area (VTA), tuberomammillary nucleus (TMN), and locus coeruleus (LC) to evaluate regional heterogeneity in H/OX synapse organization. Taken together, these studies provide a framework for understanding the molecular organization of H/OX synapses and establish a foundation for future investigations into how synaptic molecular architecture contributes to H/OX neuron function and the regulation of behavioral state.

Disclosures: J.M. Salvatore: None. **W.P. Armstrong:** None. **D. Martinelli:** None. **A.C. Jackson:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

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Program #/Poster #: PSTR005.12/Q4

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

Support: ERC 101041941

Title: Cell-type-specific opioid modulation of cortical inhibitory microcircuits

Authors: *G. CRUDELI, L. GHIANI, M. KOZLOWSKA, S. MELZER;
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Abstract: Endogenous opioid peptides regulate diverse brain functions, including pain, learning, memory, fear, anxiety, and reward. Despite the broad expression of opioid receptors throughout the cortex, how opioid signaling engages specific cortical cell types to shape network activity and behavior remains poorly understood. Here, we combined molecular mapping, electrophysiology, optogenetics, imaging, and targeted genetic manipulations to investigate opioid signaling in cortical inhibitory circuits. Fluorescence in situ hybridization revealed cell-type-specific peptide and opioid receptor expression across cortical brain regions. Electrophysiological recordings, optogenetic circuit interrogation and imaging approaches were combined to investigate intracellular signaling mechanisms in identified receptor-expressing cells. Cell-type-specific opioid signaling effects in interneuronal microcircuits were largely in line with identified receptor expression levels. Finally, targeted CRISPR-Cas9 strategies were developed to enable spatially restricted manipulation of opioid receptor signaling in defined neuronal populations for functional investigation. Together, these approaches reveal a highly organized cellular architecture of opioid receptor expression and uncover cell-type-specific mechanisms through which endogenous opioid signaling shapes cortical inhibitory networks.

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Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

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Program #/Poster #: PSTR005.13/Q5

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

Support: TÜBİTAK Grant 125Z789
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Title: Functional characterization of neuronal membrane proteasome-derived peptides that modulate neuronal signaling in health and disease

Authors: B. YAZICIOGLU[1], Y. IRI[1], S. S. MARGOLIS[2], ***F. TÜRKER**[1];
[1]Mol. Biol. and Genet., Bilkent Univ., Ankara, Turkey; [2]Dept. of Biol. Chem. and Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Maintenance of protein homeostasis is essential for neuronal health and function. The neuronal membrane proteasome (NMP) is a specialized protein degradation complex localized to

the plasma membrane that regulates neuronal signaling through the generation and extracellular release of proteasome-derived peptides. Previous studies demonstrated that NMP activity promotes canonical excitatory signaling through NMDA receptor activation and is required for normal neuronal function; however, the identity of the bioactive peptide sequences responsible for these effects remains unknown. To identify NMP-derived signaling peptides, primary mouse cortical neurons were stimulated to induce NMP-dependent peptide release. Extracellular peptides were collected, purified, and analyzed using a mass spectrometry-based peptidomics approach. Comparative peptidomic analysis identified 88 candidate peptide sequences significantly enriched following NMP activation. Physicochemical characterization revealed that NMP-derived peptides possess distinct molecular features, including characteristic charge distributions, isoelectric points, and hydrophobicity profiles. To determine whether individual peptide sequences possess biological activity, we *de novo* synthesized a library of candidate peptides. Synthetic peptides were applied individually to naïve cortical neurons, and neuronal activation was assessed by high-content imaging of c-Fos protein expression. We identified two candidate peptides that robustly increased c-Fos levels, indicating that individual NMP-derived peptide sequences are sufficient to promote neuronal activation. These findings characterize endogenous NMP-derived peptides as candidate signaling molecules that may mediate NMP-dependent neuronal responses. In parallel, we are investigating the role of NMP dysfunction in Huntington's disease (HD), a fatal neurodegenerative disorder. Surface biotinylation assays revealed reduced NMP levels in HD mouse and cellular models, suggesting that disruption of NMP-mediated peptide signaling may contribute to disease-associated neuronal network dysfunction. Ongoing studies are examining changes in NMP-derived peptide signatures in HD. Together, these findings provide evidence that NMP-generated peptides constitute a previously unrecognized class of neuronal signaling molecules and identify specific candidate peptide sequences that can modulate neuronal activity. These results establish a foundation for defining the molecular mechanisms of proteasome-derived peptide signaling in both normal brain function and neurodegenerative disease.

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Poster

PSTR005: Neuropeptides and Other Signaling Molecules

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Program #/Poster #: PSTR005.14/Q6

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

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U54-MD007587

Title: Age-dependent redistribution of polyamines and their synthetic enzymes in the retina

Authors: *Y. HERNÁNDEZ[1], A. ZAYAS-SANTIAGO[6], J. M. SANTIAGO[8], C. J. MALPICA-NIEVES[9], D. RIVERA[2], Y. V. KUCHERYAVYKH[7], J. COLON[3], M. P. MÉNDEZ-GONZÁLEZ[10], P. SANABRIA-RAMIREZ[4], R. W. VEH[11], S. N. SKATCHKOV[5];
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Abstract: Background: Polyamines, spermine (SPM) and spermidine (SPD), are essential polycationic molecules implicated in cellular homeostasis, neuroprotection, and memory enhancement. Although traditionally attributed to neuronal function, polyamines have been recently localized predominantly to glial cells rather than neurons in the healthy adult retina, suggesting a distinct glial storage and modulatory role. Objective: To characterize the cellular localization and developmental redistribution of polyamines and their biosynthetic enzymes in rat retina across postnatal maturation and aging, with emphasis on establishing polyamines as gliotransmitters. Methods: Using immunohistochemistry and confocal microscopy, we analyzed SPM and SPD localization alongside their biosynthetic enzymes, spermine synthase (SpmS) and spermidine synthase (SpdS), across postnatal days 3, 21, and 120 in rat retina, correlating changes with age-dependent neuronal decline. Results: SPM and SPD were selectively localized to Müller glial cells endfeet and processes throughout development, while SpmS and SpdS expression remained restricted to neurons. Critically, expression of polyamine biosynthetic enzymes declined with age progression, suggesting reduced neuronal polyamine synthetic capacity during aging. Polyamines colocalized with key glial ion channels, Kir4.1 and connexin-43 (Cx43), in tiny glial processes, positioning them as modulators of channels exquisitely sensitive to polyamine levels. Possibly, polyamines are transported into glia via Cx43 channels and transporters (SLC22A3, SLC18B1, ATP13A2 and ATP13A4), establishing a transporter-mediated uptake mechanism. Conclusions: This developmental redistribution reveals a fundamental reorganization of polyamine metabolism: mature Müller glia act as repositories and regulators of extracellular polyamine levels, functioning as gliotransmitter-releasing cells. The colocalization of polyamines with their ion
channel targets represent an evolutionarily conserved, functionally designed necessity for fine-tuning neuronal excitability and protecting against age-related decline. Given polyamines reported neuroprotective, anti-inflammatory, antioxidant, and memory-enhancing properties, glial polyamine accumulation and redistribution may represent a critical mechanism underlying retinal neuroprotection, neuronal homeostasis, and slowed CNS aging. These findings establish polyamines as novel gliotransmitters and propose glial polyamine metabolism as a therapeutic target for neurodegenerative and neurodevelopmental retinal disorders.

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Poster

PSTR005: Neuropeptides and Other Signaling Molecules

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

Support: NIH Grant NS129675
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Title: CDP-diacylglycerol amplifies TrkB-dependent neurotrophic signaling

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Abstract: Neurotrophins play important biological roles in the growth, differentiation, and survival of neural cells. BDNF is a prototypical neurotrophin that signals through the TrkB receptor. BDNF-TrkB receptor interaction activates multiple downstream mediators of phosphatidylinositol (PI)-3-kinase (PI3K) and phospholipase C (PLC) cascades, resulting in changes in gene expression and enhanced neuronal plasticity and survival. BDNF-TrkB signaling utilizes PI-4,5-bisphosphate (PIP2) as substrate, and availability of PIP2 controls the amplitude of TrkB-dependent signaling. PIP2 levels depend on the rate-limiting synthesis of the nucleolipid CDP-diacylglycerol (CDP-DG) by the enzymes CDP-diacylglycerol synthases 1 and 2 (cds1/2). While CDP-DG is a key intermediate in phosphatidylinositide signaling, little is known about its potential role in regulating neuronal viability pathways. Using various biochemical and immunofluorescence assays, we investigated whether exogenous CDP-DG can modulate PI availability and neurotrophic signaling. ReNcell CX human neural progenitor (ReNCx) cells incubated with CDP-DG were used to assay various indices of CDP-DG metabolism or BDNF/TrkB-dependent signaling cascades. CDP-DG treatment significantly increased membrane PIP2 levels, consistent with enhanced utilization of added nucleolipid for PI synthesis. CDP-DG increased Akt phosphorylation, indicating increased amplitude of BDNF/TrkB signaling. Consistent with the phenomenon of BDNF-induced BDNF transcription, BDNF and downstream cds1/2 expression were increased by cdpdg. Pharmacological inhibition of TrkB with ANA-12 or neomycin-mediated sequestration of PIP2 attenuated CDP-DG-induced signaling and genomic effects. Our results support a model in which CDP-DG functions as a signaling intermediate that engages PI-dependent BDNF/TrkB signaling to enhance PI3K/Akt cascades and promote neural cell growth and resilience. Further studies would investigate the upstream mechanism by which CDP-DG induces BDNF and cds1/2 expression and activity, and whether this pathway promotes in vivo neurotrophic signaling for prophylactic or regenerative applications.

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Poster

PSTR005: Neuropeptides and Other Signaling Molecules

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

Support: NIH R35 GM133802-07
NIH T32 GM133351-06

Title: Uncovering substance P release mechanisms in the dorsal striatum

Authors: *J. CHANG-WEINBERG[1], A. LAYDEN[2], A. LI[4], M. R. BANGHART[3];
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Abstract: While classical neurotransmitter release events are frequent and lead to transient effects in the postsynaptic neuron, neuropeptide release events are thought to be comparatively rare and able to drive robust, long-lasting changes across neural circuits to affect physiological states. Classical neurotransmitter release and bidirectional modulation is well-characterized. However, the mechanisms that control neuropeptide release have remained elusive due to a lack of tractable assays for detecting release. Our lab has established a robust acute slice electrophysiological assay for monitoring endogenous substance P (SP) release from direct-pathway medium spiny neurons (dMSNs) onto the large aspiny cholinergic interneurons (CINs) in the dorsal striatum. In coronal slices taken from both male and female P30-70 Pdyn-Cre+/- x LSL-ChR2-eYFP (Ai32)+/+ mice-- which express channelrhodopsin in dMSNs-- we found that optogenetic stimulation drives SP release in response to physiologically relevant stimuli. The resulting slow excitatory postsynaptic current in striatal CINs is blocked by NK1R (TACR1) antagonists and lost in *Tac1* knock out mice, which lack the gene encoding SP. Using this assay, we have determined that SP release depends on stimulation duration and frequency, and that it relies on voltage-gated calcium channels. Using a minimal stimulus paradigm, we found that SP release is quantal in nature. Additionally, our experiments revealed that SP release can be bidirectionally modulated by GPCR signaling and chronic exposure to drugs of abuse. In this context, we also uncovered evidence for an acetylcholine-mediated negative feedback loop between dMSNs and CINs that tempers SP release. This work provides an unprecedented view into an elusive, yet fundamental form of neural communication that is of universal importance across organisms.

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Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.17/R3

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

Title: A multi-omic atlas of human spinal dorsal horn synaptosomes reveals compartment-specific synaptic architecture

Authors: *K. GABRIEL[1], T. J. PRICE[2];
[1]Univ. of Texas Dallas, Richardson, TX; [2]Sch. of Behavioral and Brain Sci., Univ. of Texas At Dallas Neurosci. Undergraduate Program, Richardson, TX

Abstract: A multi-omic atlas of human spinal dorsal horn synaptosomes reveals compartment-specific synaptic architecture**Authors**Gabriel K[1], Price TJ[1]1.University of Texas at Dallas, Department of Neuroscience and Center for Advanced Pain Studies; Richardson, TX, USA.**Disclosures**KAG: none. TJP: none
AbstractThe first synapse between primary afferent nociceptors and dorsal horn neurons is a major site of plasticity in the pain pathway and signaling at this synapse could be manipulated to create analgesia. Despite its importance, the molecular composition of human dorsal horn synapses remains largely uncharacterized. In this study, we leveraged human spinal cord samples obtained from 23 organ donors (11 males, 12 females) to generate an integrated transcriptomic and proteomic atlas of human dorsal horn synapses. Bulk RNA sequencing, single-synaptosome sequencing, and mass spectrometry-based proteomics were performed on enriched synaptosome fractions. Bulk transcriptomic profiling demonstrated enrichment of synaptic transcripts in synaptosome preparations relative to whole tissue, and immunohistochemistry and RNAscope confirmed spatial localization of candidate synaptic proteins and mRNAs, respectively, within dorsal horn synapses. Proteomic analysis revealed strong enrichment of canonical postsynaptic density proteins involved in synaptic scaffolding, receptor organization, and signaling pathways underlying synaptic plasticity, including HOMER1, SHANK family members, GRIA receptors, CAMK2alpha, and DLG4/PSD95. Single-synaptosome sequencing preferentially captured presynaptic transcripts associated with synaptic vesicle cycling and neurotransmitter release machinery, including SNAP25, SYT1, CPLX1/2, RAB3A, VAMP2, and STX1A/B. Together, these datasets define distinct compartment-specific molecular signatures of human dorsal horn synapses, with proteomics preferentially resolving postsynaptic density architecture and single-synaptosome sequencing capturing presynaptic release programs likely controlled by local translation. This multi-omic atlas provides a foundational resource for defining human nociceptive synapses and identifying candidate molecular targets for pain modulation.

Disclosures: K. Gabriel: None. **T.J. Price:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.18/R4

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

Support: NIH Grant NS129675
NYS DOH Grant C38337GG
NIH Grant MD017979
NYS DOH Grant C37715GG

Title: Neuroprotective and Regenerative Effects of CDP-Diacylglycerol in Neural cells

Authors: *C. C. OLUIGBO[1,2], C. P. OKAFOR[1,2], A. S. UNDIEH[2,1];
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Abstract: Brain-derived neurotrophic factor (BDNF) is a major growth factor that is implicated in CNS cell growth, differentiation, survival, and regeneration. BDNF's primary receptor, TrkB, signals through phospholipase C (PLCγ) or phosphatidylinositol (PI)-3-kinase (PI3K); both of these cascades depend on PI-4,5-bisphosphate (PIP2) as a signaling intermediate. Cellular levels of PIP2, in turn, are regulated by upstream synthesis of cytidine diphosphate diacylglycerol (CDG-DG). Given that CDP-DG synthesis is the rate-limiting step in PI provisioning for the downstream reactions, we aimed to explore how physiologic or pharmacologic manipulations of this critical intermediate could modulate neurotrophic signaling effects. Here, we report the results of our testing of the effects of synthetic stearoyl-arachidonoyl-CDP-DG on various indices of neurotrophic cellular effects in primary cortical neurons and in cultured rodent (B35) and human (ReNCell-Cx) cortical neuroblastoma cells. Biochemical and immunofluorescence assays show that nanomolar concentrations of CDP-DG increase cell metabolic activity and EdU incorporation into dividing cells. This suggests enhanced cell proliferation, which was supported by the parallel observation of increased Cyclin D1 protein expression, a key cell cycle regulator. CDP-DG concentration-dependently increased the survival of lipopolysaccharide-stimulated neural cells. Regenerative effects assessed by measuring regrowth of mechanically injured primary cortical neurons demonstrated that CDP-DG promoted neuronal regrowth in a concentration-dependent manner. To confirm that the CDP-DG effects were mediated through enhanced formation of PIP2 as anticipated by the signaling model, we used immunofluorescence assays to measure PIP2 levels and observed increased membrane PIP2 content in CDP-DG-exposed cells. These results suggest that CDP-DG supports neural cell proliferation, protection, and regeneration by promoting PI-dependent neurotrophic signaling. Hence, pharmacologic or transgenic strategies to manipulate CDP-DG signaling in vivo could substantially impact systemic neurotrophic signaling with potential for multiple therapeutic applications.

Disclosures: C.C. Oluigbo: None. **C.P. Okafor:** None. **A.S. Undieh:** None.

Poster

PSTR005: Neuropeptides and Other Signaling Molecules

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.19/R5

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

Support: NIH Grant NS129675
NYS DOH Grant C38337GG
NIH Grant MD107979
NYS DOH Grant C37715GG

Title: Characterization of ReNCell CX-human neural progenitor cells for nucleolipid signaling studies

Authors: *A. BELLA NKOTTO[1], C. OKAFOR[2,3], A. S. UNDIEH[4,3];
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Abstract: Synthesized by CDP-diacylglycerol synthases CDS1 and CDS2, CDP-diacylglycerol is a nucleolipid that serves an important role in the biosynthesis of phosphatidylinositide (PI) and its polyphosphorylated derivatives, notably PI-4,5-bisphosphate (PIP2). PIP2 availability is critical for diverse CNS functions including neurotrophic control of neurogenesis, neuroresilience, and neuroregeneration. To establish a suitable human cellular model for investigating cds1/2-dependent signaling functions, we sought to characterize the differentiation, neurotransmitter phenotypes, and select gene expression of ReNcell-CX (ReNC) human cortical progenitor cells. ReNC cells maintained under proliferative conditions or differentiated for 7 or 14 days were analyzed for gene expression by RT-qPCR and protein immunofluorescence staining. Transmitter phenotypes were examined by immunostaining targeting vesicular glutamate transporter 1 (VGLUT1) for glutamate and choline acetyltransferase (ChAT) for detection of cholinergic neurons. PCR analysis confirmed expression of cds1 and cds2 in ReNC growing or differentiated ReNC cells. As expected, differentiation resulted in increased neuronal marker expression and morphological features characteristic of neurons. βIII-tubulin immunoreactivity was greater in differentiated cultures compared with undifferentiated cells and was further increased at day 14 relative to day 7, indicating progressive neuronal maturation. Expression of both VGLUT1 and ChAT was detected in ReNC cultures, with differentiated cells exhibiting higher levels of VGLUT1 and ChAT immunostaining than undifferentiated cells, consistent with acquisition of a mix of glutamatergic and cholinergic neuronal phenotypes. SKF38393, a dopamine agonist associated with stimulation of CDP-diacylglycerol accumulation, was found to induce increased expression of cds1 and cds2 message and protein in differentiated ReNC cells. In conclusion, we demonstrated that ReNC cells undergo progressive neuronal differentiation accompanied by increased expression of glutamatergic and cholinergic markers, and increase their expression of cds1/2 in response to D1-like receptor stimulation. These findings imply that ReNC cells are a suitable line for investigating cds1/2-dependent PI signaling and cellular functions.

Disclosures: A. Bella Nkotto: None. **C. Okafor:** None. **A.S. Undieh:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.01/R6

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

Support: KAKENHI 25K19825
KAKENHI 24H02336
KAKENHI 25K09842

Title: Volatile anesthetics sevoflurane suppresses action potentials by inhibiting axonal Na^+ currents in the hippocampal mossy fibers

Authors: *S. OHURA[1], H. KAMIYA[2];
[1]Dept. of Neurobiology, Hokkaido Univ. Grad. Sch. of Med., Sapporo-shi, Japan; [2]Dept. of Neurobio., Hokkaido Univ. Grad. Sch. of Med., Sapporo, Japan

Abstract: Volatile anesthetics are commonly used in surgical procedures to induce and maintain general anesthesia. Their effects are known to suppress neural activity by inhibiting multiple ion channels and neurotransmitter receptors. While most previous studies have focused on somatic or synaptic mechanisms, the effects of volatile anesthetics on axonal excitability remain largely unknown. In this study, we investigated the effect of sevoflurane, a widely used volatile anesthetic, on the excitability of hippocampal mossy fibers, which are one of the best-studied axons in the central nervous system. Direct patch-clamp recordings were performed from the hippocampal mossy fiber terminals identified under observation with IR-DIC optics. In the loose-patch clamp recordings, sevoflurane reduced the amplitude of axonal spikes to 87.1 ± 2.4% of control ($p < 0.05$, n = 6). Furthermore, the whole-cell recordings from single mossy fiber terminals revealed that sevoflurane suppressed the amplitude of action potentials to 94.3 ± 2.1% of control ($p < 0.05$, n = 6) and subsequent afterdepolarizations to 81.5 ± 4.3% of control ($p < 0.05$, n = 6), which lasted for tens of milliseconds after action potentials. Since Na^+ channels shape action potentials and afterdepolarizations, we next examined the effect of sevoflurane on axonal Na^+ currents. Sevoflurane reduced the amplitude of Na^+ currents to 83.2 ± 2.8% of control ($p < 0.05$, n = 6). Taken together, it was concluded that sevoflurane suppresses axonal action potentials in hippocampal mossy fibers by inhibiting axonal Na^+ channels. These findings unveil the inhibitory action of volatile anesthetics on axonal excitability in the central nervous system.

Disclosures: S. Ohura: None. **H. Kamiya:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.02/S1

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

Support: Ministry of Education, India

Title: Dopamine mediated reduction in subthreshold excitability of granule cells enhances pattern separation in degenerate and heterogenous dentate gyrus networks

Authors: *S. SAINI, R. NARAYANAN;
Mol. Biophysics Unit, Indian Inst. of Sci., Bangalore, India

Abstract: Pattern separation, a key computation central to hippocampal memory encoding and retrieval, must remain robust across cellular heterogeneity, synaptic variability, and shifting neuromodulatory states. Although dopamine has been implicated in reward and novelty during hippocampal learning, the question of how dopamine alters the heterogeneous dentate gyrus (DG) microcircuitry or pattern separation there remains unanswered. We address this gap using an integrated computational and electrophysiological framework. Using an exhaustive population-of-networks approach, we constructed heterogeneous DG network models comprising functionally validated populations of granule cells (GCs) and three interneuron subtypes endowed with within-type heterogeneity. Of 20,000 networks generated with random local synaptic weights that preserved an identical divergent architecture, only 47 achieved pattern separation, demonstrating that specific local synaptic weight combinations and not divergent feedforward connectivity mediate pattern separation. Strikingly, disparate synaptic weight combinations yielded similar pattern separation, revealing synaptic degeneracy as a core organizing principle of the DG network. Across these degenerate networks, interneuron contributions were strong but network-dependent, while cellular heterogeneity conferred greater robustness to synaptic perturbations when compared with homogeneous networks. To understand how dopamine shapes pattern separation, we performed in vitro whole-cell patch-clamp recordings to show that 50 μM dopamine transiently and selectively reduced subthreshold GC excitability without altering suprathreshold firing, with substantial cell-to-cell variability in the magnitude of changes. Pharmacological blockers revealed concomitant modulation of G-protein-coupled inwardly rectifying potassium (GIRK), hyperpolarization-activated cyclic nucleotide-gated (HCN), and persistent sodium channels, showing conjunctive multi-channel modulation as the underlying mechanism. Incorporating heterogeneous dopaminergic neuromodulation into our network population revealed that dopamine robustly enhanced pattern separation across all 47 DG networks. Together, we demonstrate that DG pattern separation arises from degenerate circuit mechanisms and is dynamically upregulated by dopaminergic neuromodulation of granule-cell intrinsic properties. Importantly, heterogeneity in GC responses to identical dopamine treatment suggests compositional heterogeneity as a key mechanistic substrate for vectorized feedback of reward prediction errors in learning circuits.

Disclosures: S. Saini: None. **R. Narayanan:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.03/S2

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

Support: NINDS COBRE Center for Nervous System Function
Blackman Family Fund

Title: Visual-Activity-Driven Changes in Intrinsic Excitability and Nav1.6 Levels Are Mediated by Prostaglandin E_2

Authors: S. S. G. ADAM[1], G. ROCCHIO[2], A. C. THOMPSON[3], A. JONES[2], *C. D. AIZENMAN[4];
[1]Brown University, Providence, RI, PROVIDENCE, RI; [2]Neurosci., [3]Dept. of Neurosci., [4]Brown Univ., Providence, RI

Abstract: Developing neural circuits must remain sufficiently plastic to be shaped by sensory experience yet stable enough to function within a useful dynamic range. In the *Xenopus laevis* optic tectum, intrinsic excitability undergoes stereotyped changes that maintain this balance: excitability peaks during a critical developmental period and declines as circuits mature, paralleled by changes in voltage-gated sodium channel expression. Enhanced visual stimulation (EVS) acutely increases intrinsic excitability, offsetting homeostatic decreases in glutamatergic transmission and preserving stable input-output balance. This increase depends on upregulation of sodium channels, particularly Nav1.6. Yet the molecular signal coupling sensory experience to the transcriptional regulation of neuronal excitability has remained unknown.Here we identify prostaglandin E_2 (PGE_2), a lipid classically associated with inflammation, as the upstream mediator coupling visual experience to sodium channel regulation and intrinsic plasticity. We show that pharmacological blockade at every level of the PGE_2 pathway (COX-2, mPGES-1, EP receptors, and PGE_2 transport) prevents EVS from increasing Na^+ currents and action potential firing in tectal neurons, establishing that PGE_2 is **necessary** for experience-dependent increases in intrinsic excitability. Conversely, exogenous PGE_2 alone, without visual stimulation, recapitulates the EVS effect, establishing **sufficiency**. Molecular data corroborate the electrophysiology: ELISA confirms elevated PGE_2 in visually stimulated tecta, and qPCR demonstrates PGE_2-dependent upregulation of Nav1.6.Beyond its acute role, we show that PGE_2 is required for the developmental maturation of intrinsic excitability. Chronic COX-2 inhibition during rearing disrupts the homeostatic trajectory in both directions, preventing the critical period peak in excitability and blocking its subsequent decline. Both excess PGE_2 and synthesis blockade impair schooling behavior, showing that PGE_2 signaling must remain within a tightly regulated range.Together, these results define a pathway in which visual experience drives COX-2-dependent PGE_2 synthesis that acts through EP receptors to transcriptionally upregulate sodium channels and increase intrinsic excitability. These findings reveal an unanticipated convergence of inflammatory and plasticity signaling and show that a prostaglandin mediates experience-dependent homeostatic regulation of neuronal excitability in the developing CNS.

Furthermore, these data show that disrupting this pathway during development results in adverse neurodevelopmental outcomes.

Disclosures: S.S.G. Adam: None. **G. Rocchio:** None. **A.C. Thompson:** None. **A. Jones:** None. **C.D. Aizenman:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.04/S3

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

Support: NIDA Postdoctoral T32 (T32DA060142)
NIDA R01 Grant (DA065668)

Title: Constructing a midbrain dopaminergic neuron model towards understanding the biophysical properties of axonal computation

Authors: *L. R. MADDEN, L. MCNANNEY, P. F. KRAMER;
Molecular, Cellular, and Developmental Biol., Univ. of Michigan, Ann Arbor, MI

Abstract: The role of midbrain dopaminergic neurons in reward learning is a principal focus of addiction research. Notably, these neurons possess thin axons that branch in the striatum into expansive arborizations, giving rise to hundreds of thousands of synapses. Striatal dopaminergic axons express excitatory nicotinic acetylcholine receptors (nAChRs) and inhibitory $GABA_A$ receptors ($GABA_A$Rs) that locally modulate dopamine release. Activated $GABA_A$Rs suppress excitation by nAChR inputs, which can initiate local axonal action potentials without contribution from the soma or initial segment, suggesting $GABA_A$Rs and nAChRs interact functionally through a novel form of axonal computation to regulate dopamine release. A comprehensive theoretical framework describing how dopamine axons perform computations within their arborized terminal regions is lacking. To identify the conditions under which local inputs can mediate axonal action potential transmission and dopamine release, we constructed a biophysical multi-compartment cable model to computationally simulate the axons of midbrain dopamine neurons. Furthermore, we used immunofluorescent labeling to determine the myelination pattern and sodium channel distribution along these axons. Midbrain dopamine axons are generally assumed to be unmyelinated, but recent literature indicates that some are sheathed, and our preliminary imaging results corroborate this. For the computational model, we included an anatomically complete representation of a midbrain dopamine neuron's axon, reconstructed from publicly available 3D trajectory data. Further, we used a hybrid parameter optimization method — a genetic algorithm in conjunction with simulation-based inference — to generate model parameter values and provide insight into the relationships between ion channel expression patterns and functional output. These biophysical simulations are the first to model

the complex physiology of midbrain dopaminergic axons. Our experimental findings, paired with simulated results, aim to elucidate how the electrophysiological properties of these axonal membranes modulate dopamine release and subsequent plasticity.

Disclosures: L.R. Madden: None. **L. McNanney:** None. **P.F. Kramer:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.05/S4

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

Title: Using high-density MEA assays of neuron activity to interrogate mechanism of action and target engagement for drug discovery

Authors: *R. E. PETROSKI[1], D. LIU[2], M. HE[3], S. GRIGORYEV[1], C. PETROSKI[1]; [1]Neuroservices-Alliance, San Diego, CA; [2]Electrophysiology Lab., Neuroservices-Alliance, Oak Park, CA; [3]Biochem. and Cell Biol., Neuroservices-Alliance, San Diego, CA

Abstract: Therapeutic strategies that modulate neuronal activity are used to treat a variety psychiatric, neurodevelopmental, neurodegenerative, epilepsy and pain indications. Measuring the effect of therapeutic candidates on neuronal activity can support drug discovery programs by providing target validation, mechanism of action, and target engagement data used to establish pharmacokinetic-pharmacodynamic relationships. Neuronal action potential firing is driven by excitatory synapses. But the patterns of neuronal activity in brain circuits are sculpted by the activity of inhibitory interneurons. Primary rodent neuron cultures contain both excitatory and inhibitory neurons. Patch clamp recording confirms a high level of both spontaneous excitatory and inhibitory synaptic potentials which ultimately confer the overall pattern of network activity.The high-density microelectrode array (MEA) from MaxWell Biosystems can simultaneously record the activity of up to 1000 neurons per well from 24-wells at time. This scalability provides a great throughput and cost advantage over conventional patch clamp recording. We used the MaxWell MEA to evaluate the responses of neuron cultures to reference compounds known to modulate neuronal activity. Our MEA results show that drugs targeting ion channels and GPCRs affect spontaneous firing and neuron bursting in predictable ways. The MaxWell MEA is a validated platform for interrogating the efficacy and potency novel drugs but can also be adapted to test the effects of other therapeutic modalities including siRNA/shRNA to knock down gene expression and AAV transduction to drive expression of transgenes.

Disclosures: R.E. Petroski: None. **D. Liu:** None. **M. He:** None. **S. Grigoryev:** None. **C. Petroski:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.06/S5

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

Support: NIH NINDS R01NS129622

Title: Neural activity phase lead relative to the endogenous arousal signal as a novel measure of brain excitability: a multi-timescale control framework and preliminary human evidence

Authors: *M. DERVINIS[1], T. J. RICHNER[1], S. AGGARWAL[3], G. A. WORRELL[1], J. VAN GOMPEL[2], B. N. LUNDSTROM[1];
[1]Neurol., [2]Neurosurg., Mayo Clin., Rochester, MN; [3]Physics, Indian Inst. of Sci., Bengaluru, India

Abstract: Brain excitability remains poorly defined at a mechanistic level despite being central to neural function, limiting the development of robust clinical biomarkers. Existing excitability measures are modality-specific, temporally narrow, and difficult to interpret mechanistically. Electrophysiological recordings and neuroimaging studies consistently reveal that brain activity is organized across multiple timescales: power spectra follow 1/f scaling, oscillations at different frequencies are phase-amplitude coupled, and neural fluctuations exhibit long-memory temporal dependencies. These signatures reflect fundamental properties of how excitable tissue regulates itself, yet no unifying framework connects them to excitability and to clinical phenomena arising when excitation-inhibition balance fails.

We propose a control-theoretic framework in which excitability arises from fast amplifying and slower adaptive processes (positive and negative feedback) distributed across overlapping timescales. Grounded in fractional dynamics, the brain is conceptualized as a distributed feedback system whose activity-dependent regulation gives rise to scale-free dynamics and predicts measurable excitability signatures: response-to-stimulus phase lead, frequency-dependent gain scaling, and time-resolved spectral exponent. Neural activity phase lead reflects anticipatory dynamics arising from temporally distributed adaptation, particularly at slow and infra-slow timescales (<2 Hz), providing a direct excitability measure with existing animal support (Lundstrom et al., 2008; Lundstrom et al., 2010; Dervinis and Okun, 2026).

To translate this to humans, we present a theoretical framework of the phase-lead excitability measures and preliminary data from intracranial stereo-EEG recordings in epilepsy patients, where phase advances relative to external stimuli signify increased negative feedback control. Phase leads relative to other signals, such as endogenous arousal signals (e.g., heart rate inter-beat interval fluctuations or non-luminance-mediated pupil dilations) largely generated by the noradrenergic locus coeruleus (Bär et al., 2009; O'Callaghan et al., 2021), may serve as a mechanistically grounded and clinically accessible biomarker of pathological excitability.

References

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Lundstrom et al (2008) Nat Neurosci 11:1335-1342.
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O'Callaghan et al (2021) Philos Trans R Soc Lond B Biol Sci 376:20190699.

Disclosures: M. Dervinis: None. **T.J. Richner:** None. **S. Aggarwal:** None. **G.A. Worrell:** None. **J. Van Gompel:** None. **B.N. Lundstrom:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.07/S6

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

Support: NIH R01# MH107615 to TDG

Title: Ketamine Metabolite (2R,6R)-hydroxynorketamine Increases Excitability of CA1 Pyramidal Neurons

Authors: *M. V. AHERN[1], K. A. BROWN[1], M. I. AJIBOLA[1], T. FRANCIS[1,2,4], T. D. GOULD[1,2,3,5];
[1]Psychiatry, [2]Neurobio., [3]Pharmacol., Univ. of Maryland, Baltimore, Baltimore, MD; [4]Med. Inst. for Neurosci. Discovery (UM-MIND), Univ. of Maryland, Baltimore, MD; [5]Veteran Affairs Maryland Hlth. Care Systems, Baltimore, MD

Abstract: Major depressive disorder is a prevalent debilitating mood disorder. Unfortunately, many antidepressant treatment options have delayed therapeutic effects, require multiple trials and do not provide relief for one-third of patients. Like its parent compound ketamine, (*2R,6R*)-hydroxynorketamine (2R6R), elicits robust and rapid antidepressant-like effects in rodents. We have previously found that one-hour incubation of hippocampal slices with 2R6R followed by a three-hour washout period increases the magnitude of long-term potentiation (LTP) at the Schaffer Collateral-CA1 synapse. 2R6R's actions to enhance synaptic plasticity without being present in the tissue suggests the metabolite engages metaplastic mechanism(s). Cellular excitability, or the cell's readiness to respond to stimuli, is one mechanism that can mediate metaplasticity. We hypothesized that 2R6R will increase intrinsic excitability, priming neurons for enhanced LTP. To measure changes in CA1 pyramidal cell excitability, acute hippocampal slices were collected from 9- to 12-week-old female CD-1 mice and incubated in 2R6R (30μM) or vehicle for one hour followed by a three-hour washout period. Experimenters were blind to treatment conditions. This incubation method models 2R6R's *in vivo* pharmacokinetics while allowing for precise temporal resolution of 2R6R's metaplastic effects. Slices were then used for whole-cell patch-clamp electrophysiology. By utilizing current-clamp recordings, various current injections were used to elicit changes in membrane potential. We measured excitability parameters including firing pattern, action potential characteristics, and hyperpolarization. We

found when treated with 2R6R (n=9) compared to vehicle control (n=14), CA1 pyramidal neurons exhibit increased input resistance and reduced rheobase, increased voltage sag amplitude and hyperpolarized steady-state, and reduced medium afterhyperpolarization. These findings suggest 2R6R incubation leads to increased intrinsic excitability of CA1 neurons, which may act to enhance the magnitude of LTP. Ongoing experiments are assessing whether the changes in excitability occur rapidly after 2R6R application or are delayed. Overall, these studies will identify metaplastic mechanisms utilized by rapid-acting antidepressants to be targeted by future therapeutics, which may exert effects that could increase the capacity to assist with therapies that rely on learning (e.g., behavioral therapies) or neuromodulation.

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Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.08/S7

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

Support: INFR-2016-01268247
SEP-Cinvestav FIDSC2018/77

Title: Exercise regulates acetylcholine neuromodulation of dentate gyrus granule cells

Authors: *G. D. APOSTOL-DEL ROSAL[1], L. ORIHUELA[2], C. VIVAR[3];
[1]Physiology, Biophysics and Neurosci., Cinvestav, Ciudad de Mexico, Mexico; [2]Physiology, Biophysics and Neurosci., [3]Deparment Physiology, Biophysics and Neurosci., CINVESTAV, Mexico City, Mexico

Abstract: Aerobic exercise improves hippocampal-dependent learning and memory, inducing structural and functional neuroplastic changes within the dentate gyrus (DG). While acetylcholine (ACh) is one of the major neuromodulators of hippocampal function, its role in exercise-induced DG improvement remains unknown. To investigate how exercise modulates cholinergic regulation of DG function, we performed whole-cell patch-clamp recordings of DG granule cells (GC) from young adult C57Bl6 mice housed under either control (n = 12) or running (n = 14) conditions for 5-6 weeks. Bath application of the cholinergic agonist carbachol (CBC; 50 μM) significantly depolarized the resting membrane potential, increased the membrane resistance, and decreased the rheobase of GCs in both control and runner mice, compared to basal conditions. CBC also enhanced GCs' excitability across both groups, as indicated by an upward shift in the input-output curve, increased action potential counts, and higher firing frequency. Furthermore, CBC perfusion induced slow rhythmic bursts of action potentials with

plateau suprathreshold depolarization in GCs from both control and runner mice. However, running altered the specific dynamic of DG network activity. Running reduced the overall percentage of GCs exhibiting burst responses (36%, 7/19) compared to controls (60%, 9/15). Strikingly, among the cells that did burst, running significantly increased the proportion of GCs exhibiting double bursts of action potentials (running: 85.7%, 6/7 *vs* control: 11%, 1/9) and decreased the latency to the first burst (running: 243 ± 23s *vs* control: 461 ± 99s). To evaluate the contribution of the local inhibitory network, we pharmacologically interrogated the circuit. Blockade of $GABA_A$ receptors with Bicuculline (20 μM) either before or after CBC prevents further bursting activity. Furthermore, CBC-induced GC rhythmic activity was found to depend on both M1 muscarinic and α7-nicotinic ACh receptors across both groups. Together, our findings indicate that voluntary running modulates the sparse activity of DG GCs by altering how ACh receptors engage both GC and local inhibitory interneurons. We propose that exercise modifies the operation of the DG microcircuit under cholinergic neuromodulation, highlighting ACh as a critical mechanism driving exercise-induced cognitive enhancement.

Disclosures: G.D. Apostol-Del Rosal: None. **L. Orihuela:** None. **C. Vivar:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.09/S8

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

Support: NHMRC Development Grant 203134

Title: Focused Ultrasound Reshapes Intrinsic Excitability Consistent with Outward Potassium Conductance Modulation in CA1 Pyramidal Neurons

Authors: *N. ZOKA[1], S. HOSIE[1], J. DRUMMOND[1], D. B. GRAYDEN[1,2], S. E. JOHN[1,2]; [1]Dept. of Biomed. Engin., [2]Graeme Clark Inst., The Univ. of Melbourne, Melbourne, Australia

Abstract: Focused ultrasound (FUS) is a non-invasive neuromodulation modality with potential for miniaturized neural interfaces capable of spatially precise neural stimulation. Although intracellular studies of action potential (AP) dynamics have typically employed frequencies exceeding 20 MHz to maintain recording stability, the cellular effects of lower high-frequency FUS remain incompletely understood. We therefore used whole-cell current-clamp recordings to investigate how 10 MHz FUS modulates intrinsic excitability and AP kinetics across acoustic intensities and firing states in mouse hippocampal CA1 pyramidal neurons. Sagittal hippocampal slices (200 μm) were prepared from wild-type C57BL/6 mice aged postnatal days 21-35. During depolarising current injection, neurons were exposed to 1.5 s continuous-wave FUS at 12, 27, 48, and 75 W/cm². Both sexes were used; sex-specific effects were not assessed. Analyses were unblinded. Firing rate, membrane potential, AP threshold, amplitude, overshoot, width, rise and

decay kinetics, and input resistance were quantified using paired control-FUS comparisons. Across four acoustic intensities (12-75 W/cm²; n = 10), FUS produced membrane hyperpolarization of ~1.0-1.5 mV, becoming significant at intensities ≥27 W/cm² (paired t-test, $p < 0.01$). At 48 W/cm², the second AP threshold shifted from −16.0 to −27.0 mV, AP amplitude increased from 55.0 to 67.0 mV, AP width decreased from 4.2 to 3.0 ms, and maximum depolarization slope increased from 43.0 to 80.0 mV/ms (paired t-test, $p < 0.01$). Input resistance was unchanged. A separate cohort of 22 neurons was examined at 48 W/cm². FUS produced state-dependent modulation of firing output, with mild suppression near threshold but enhanced firing during suprathreshold depolarization. In neurons approaching depolarization block, FUS restored spike output. FUS also increased AP amplitude and overshoot, increased maximum depolarization and repolarization rates, and reduced AP threshold, width, rise half-width, and decay half-width (paired t-test, $p < 0.01$). These effects were strongest in the second and third APs within a spike train. Thermal measurements demonstrated progressive focal heating with increasing FUS intensity, reaching 0.42 ± 0.22 °C at 75 W/cm². These findings demonstrate that 10 MHz FUS reshapes intrinsic excitability and AP kinetics across acoustic intensities and firing states. The observed electrophysiological signature is consistent with increased outward potassium conductance, potentially involving mechanosensitive K2P-like channels, providing new insight into the cellular mechanisms underlying ultrasound neuromodulation.

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Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

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

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

Title: Functional characterization of CB2 cannabinoid receptors in glutamatergic neurons of the anterior cingulate cortex

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Abstract: Cannabinoid receptor type 2 (rCB2) expression and function in cortical neurons remain controversial despite increasing evidence supporting its role in neuronal excitability and synaptic transmission. The anterior cingulate cortex (ACC) is a key brain region involved in reward processing, decision making, and motivated behaviors, yet the contribution of those canabinoid receptors to the intrinsic excitability of ACC glutamatergic neurons remains poorly understood. To characterize the functional role of rCB2 at the somatic level, whole cell current clamp recordings were obtained from layer V glutamatergic pyramidal neurons in acute rat ACC brain slices. Neuronal excitability parameters were evaluated before and after pharmacological activation and inactivation of rCB2. Activation of rCB2 produced significant changes in intrinsic neuronal excitability. Pharmacological responses elicited by GW405833 (1μM) and AM630 (100 nM) were consistent with the presence of functional rCB2 in ACC pyramidal neurons and were distinguishable from those induced by CB1 receptor activation. Changes were observed in action potential firing properties and excitability-related parameters, supporting a direct somatic effect of rCB2 activation. These findings provide electrophysiological and pharmacological evidence for functional rCB2 in glutamatergic neurons of the ACC and suggest that rCB2 signaling may contribute to cortical regulation of neuronal activity.

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Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.11/T1

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

Support: GCR grant GR1057743

Title: From Retina to Hippocampus: Optimizing Magnetoelectric Nanoparticle-Based Wireless Neuromodulation

Authors: *H. MOKHTARI DOWLATABAD[1], O. SHARAFI[1], N. C. ZEPEDA[2], M. SHOTBOLT[5], V. GARIMELLA[1], S. T. WALSTON[1], J.-M. C. BOUTEILLER[7], M. S. BIENKOWSKI[3], D. J. LEE[4], S. KHIZROEV[6], G. LAZZI[1];
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Abstract: Wireless neuromodulation using magnetoelectric nanoparticles (MENPs) offers a minimally invasive strategy for activating neural tissue through externally applied magnetic fields. We recently demonstrated MENP-mediated stimulation of retinal ganglion cells (RGCs) in ex vivo retinal explants and are now extending this approach to hippocampal slice preparations to identify stimulation paradigms suitable for central nervous system and future in vivo studies.

Core-shell MENPs composed of a magnetic core and a Piezoelectric shell were applied to ex vivo Thy1-GCaMP6f rat retinal explants. Neuronal activity was quantified using calcium imaging during alternating magnetic field stimulation. MENP-treated retinas exhibited significantly greater stimulation-evoked activity than magnetic-core-only and nanoparticle-free controls. Under stimulation at 100 mT, 50 Hz, and a 2-s pulse duration, the percentage of retinal ganglion cells that showed activity increased from 5.7 ± 2.1% before stimulation to 28.1 ± 9.2%in MENP-treated preparations. Approximately 83% of calcium events occurred during stimulation or within a 5.5-second window after stimulus termination, indicating strong temporal coupling between magnetic stimulation and neuronal activation. Systematic exploration of the stimulation parameter space revealed that neuronal activation increased with magnetic field amplitude and pulse duration, reaching a maximum of approximately 65% of active-cell populations (excluding cells without detectable spontaneous or stimulation-evoked activity) at100 mT, 50 Hz, and a 2-s pulse duration. Results were obtained from 8 retinal explants derived from 4 animals and were reproducible across preparations.

Building on these findings, we are evaluating MENP-mediated stimulation in acute hippocampal slice preparations across a range of magnetic field amplitudes, frequencies, pulse durations, and nanoparticle concentrations to determine whether the stimulation paradigms identified in retinal tissue translate to hippocampal networks.

These results demonstrate that MENPs can mediate magnetic-field-induced neuronal activation in retinal tissue. The observed dependence of neuronal responses on stimulation parameters provides a framework for optimizing MENP-based wireless neuromodulation and supports the extension of this approach to hippocampal networks.

Disclosures: H. Mokhtari Dowlatabad: None. **O. Sharafi:** None. **N.C. Zepeda:** None. **M. Shotbolt:** None. **V. Garimella:** None. **S.T. Walston:** None. **J.C. Bouteiller:** None. **M.S. Bienkowski:** None. **D.J. Lee:** None. **S. Khizroev:** None. **G. Lazzi:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.12/T2

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

Support: NPHT GR004596
GR024591

Title: Deep subiculum ovoid neurons are specially equipped to sustain a prolonged, nicotinic mediated response to acetylcholine

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Abstract: Acetylcholine (ACh) is critical for attention and the encoding of new memories. The subiculum (SUB) is distinguished by sharp excitatory cell-type heterogeneity, including deep "ovoid" neurons recently shown to be required for non-spatial object memory (Kinman et al.). Here we show that deep SUB ovoid neurons are specially equipped to respond to ACh, displaying a sustained, nicotinic mediated response to cholinergic receptor activation that distinguishes them from neighboring classical SUB pyramidal neurons. Anatomically, labeling of medial septum/diagonal band of Broca (MS/DBB) cholinergic neurons in ChAT-Cre mice revealed that cholinergic axons preferentially terminate along the deep and proximal SUB, with sparser innervation of distal SUB. Transcriptomically, using the Allen Brain Cell Atlas with spatial validation by MERFISH, deep SUB neurons were enriched for the nicotinic subunits Chrna4 and Chrnb2 (comprising the alpha4beta2 receptor) and the desensitization-attenuating subunit Chrna5 (alpha5). Physiologically, in whole-cell recordings, deep ovoid neurons responded to the ACh receptor agonist carbachol (CCh) with an elevated, sustained depolarization, whereas classical pyramidal neurons returned to baseline. This sustained response was reproduced by a nicotinic (alpha4beta2) but not a muscarinic agonist, and single-pulse optogenetic release of endogenous ACh from ChR2-expressing cholinergic axons drove a prolonged depolarization in deep, but not classical, SUB neurons. Together, these data indicate that deep SUB ovoid neurons are anatomically and molecularly equipped to sustain a prolonged, nicotinic mediated response to cholinergic input, setting them apart from classical SUB neurons.

Disclosures: D. Merryweather: None. **N.P. Vyleta:** None. **M.S. Cembrowski:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.13/T3

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

Support: NIH NIDA R01 DA041705

Title: Markov Models for Na_V Ion channels in Dopamine Neurons

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Abstract: We hypothesize that subpopulation-specific NaV channel diversity accounts for diverse subpopulation-specific responses of midbrain dopamine (DA) to excitation. The initially identified population of conventional DA neurons projecting to the dorsal striatum and lateral shell of the accumbens enters abruptly into depolarization block at low frequencies (~10 Hz) whereas a more recently identified atypical DA population enters depolarization block gradually at significantly higher frequencies (>30 Hz). We previously utilized a phenomenological 5 state Markov model of NaV1.2 with sequential inactivation into a short-term and a long-term inactivated (LTI) state to account for these differences by using a greater rate of entry into LTI for the sodium channels in the conventional DA population. However, we now know the two states to be competitive and likely to be controlled by differential expression of sodium channel beta subunits. One of these factors is the fibroblast growth factor 12 (FGF12). We refined an existing NaV channel Markov model (Dover et al., 2010), which includes competition between the two inactivated states using a genetic algorithm that maximizes the peak open fraction during an action potential in addition to fitting the voltage-clamp data. Our modeling results predict that there are two accessory proteins for the NaV channel that are substrates for long-term inactivation, one being FGF12 and the other has not yet been identified. The ratio between these NaV accessory proteins is predicted to govern the frequency and spike amplitude at entry into depolarization block. Moreover, the model suggests that the atypical subpopulation is responsible for the plateau bursts observed in vivo (Otomo et al 2022).

Disclosures: C.J. Knowlton: None. **J. Roeper:** None. **C.C. Canavier:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.14/T4

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

Support: NIH grant R01MH131721
NIH grant R25NS080686

Title: Examining Functional Differences in Parvalbumin Fast-Spiking Interneurons between the Medial Prefrontal Cortex and Nucleus Accumbens

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Abstract: GABAergic inhibitory interneurons regulate the activity of other neurons by suppressing excessive excitation. Parvalbumin-containing fast-spiking interneurons (PV-FSI) are the largest class of neocortical GABAergic interneurons (~40%) making them an important focal point for circuit function. Their unique intrinsic properties allow them to act as high-speed regulators of local circuit activity, providing fast, precisely timed inhibition to regulate neuronal communication and control the firing of nearby principal neurons. Since they influence spike-timing and circuit synchrony, they are critical for normal cognition, memory, and behavior.PV-FSI share hallmark fast-spiking characteristics, however the functional impact of their powerful inhibition differs across brain regions. For example, PV-FSI in the medial prefrontal cortex (mPFC) intercept and filter sensory information to be conveyed downstream to other brain regions, while PV-FSI in the nucleus accumbens (NAc) shape experience-dependent functional adaptations necessary for behavioral responses. Transcriptomic differences have previously been identified between PV-FSI located in the somatosensory cortex compared to the dorsal striatum. Further, PV-FSI in the dorsal striatum share only 30% overlapping protein-coding transcripts with the NAc, located in the ventral striatum, demonstrating both regional and subregional heterogeneity among PV-FSI. However, the electrophysiological consequences of these diverse transcriptomic profiles have been insufficiently explored. We are therefore interested in examining differences in electrophysiological and morphological properties of PV-FSI in the mPFC and NAc, brain regions strongly implicated in salience processing, sensorimotor gating, and associative learning. Exploring regional heterogeneity in these two brain regions will aid in our greater research interests exploring the pathophysiology of neurodevelopmental disorders such as schizophrenia which feature PV-FSI dysfunction. We used ex vivo whole-cell patch clamp electrophysiology to assess spontaneous excitatory post-synaptic currents (sEPSCs), as well as various action potential features of PV-FSIs in the mPFC and NAc. While results show comparable connectivity, PV-FSI in the mPFC and the NAc exhibit significantly different resting membrane potentials, as well as divergent spiking phenotypes, including spike frequency, latency to first action potential, and spike frequency adaptation. Morphological discrepancies were also analyzed post-hoc via biocytin-filling and immunostaining, followed by sholl analysis to assess arborization of PV-FSIs.

Disclosures: N. Sabena: None. **L. Peeters:** None. **B.A. Grueter:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.15/T5

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

Title: Ankyrin-G Loss Impairs Sustained Neuronal Output in Cortical and Striatal Circuits and Is Associated with Behavioral Dysregulation

Authors: *J. LI[1], J. KIM[2], C. A. ROSS[3];
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Abstract: Ankyrin-G (Ank-G), encoded by the bipolar disorder risk gene **ANK3**, is a core scaffold of the axon initial segment (AIS). Using CaMKIIα-Cre-mediated Ank-G conditional knockout mice, we found that Ank-G-deficient cortical pyramidal neurons showed impaired sustained repetitive firing across multiple cortical regions, with largely preserved rheobase but progressive action potential amplitude failure. These findings suggest defective maintenance of spike output rather than impaired spike initiation. In vivo recordings showed reduced spike firing in regular-spiking neurons in the cortex, while behaviorally the mice displayed persistent hyperlocomotion and impaired habituation in the open field, suggesting that weakened cortical output may impair behavioral state regulation rather than simply reduce locomotion. Spontaneous excitatory transmission was largely unchanged, whereas inhibitory transmission was reduced in a cortical-region-dependent manner. Recent CaMKIIα-Cre;tdTomato mapping revealed Cre expression in cortical excitatory neurons and in a subset of CTIP2-positive striatal medium spiny neurons, suggesting that both cortical dysfunction and direct striatal involvement may contribute to the phenotype. Together, our results demonstrate that Ank-G is essential for maintaining sustained neuronal output in the adult brain and suggest that both cortical and striatal mechanisms may contribute to ANK3-associated behavioral abnormalities.

Disclosures: J. Li: None. **J. Kim:** None. **C.A. Ross:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.16/T6

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

Title: Modulation of Neural Heterogeneity Enables Context-Addressable Network Function

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Abstract: Recent advances in transcriptomics, projection tracing, and multi-neuron recordings reveal that neural heterogeneity — the continuous diversity of cellular, synaptic, and circuit properties — is a pervasive feature of brains. Using mathematical analysis and computational modeling, we recently showed that the degree of neural heterogeneity controls the dynamical regime of networks of spiking neurons: homogeneous populations support computation via distinct attractor states, whereas heterogeneous populations support computation via transient, input-driven dynamics around a single equilibrium state (Gast et al., PNAS 2024). As we

discussed in a recent perspective, this raises the question whether the brain can actively regulate levels of population heterogeneity, thereby switching between localized computational regimes (Dahmen et al., Neuron 2026).
We propose that neuromodulators provide exactly this control. We test this idea in the striatum, where dopamine acts on D1- and D2-receptor-expressing spiny projection neurons (SPNs). Leveraging a dataset of calcium imaging from D1- and D2-SPNs in freely behaving mice subjected to dopaminergic and cholinergic pharmacological manipulations (Yun et al., Nature Neuroscience 2023), we find that drugs reshape not only the mean firing rate of SPN populations but the full shape of the excitability distribution across SPNs—its width, skew, and modality. Crucially, these changes are content-addressable: distinct behavioral features are associated with distinct SPN firing rate distributions, and pharmacological manipulations alter the firing rate distribution associated with specific behavioral features rather than scaling striatal activity independent of behavior.
Based on these observations, we propose that dopaminergic modulation can tune the position of striatal circuits along a heterogeneity axis, shifting them between distinct regimes that allow for different dynamic interactions between D1- and D2-SPNs during ongoing behavior. More generally, we propose that neuromodulators act as a control knob on neural heterogeneity, allowing a single circuit to flexibly switch between distinct computational regimes.

Disclosures: R. Gast: None. **J.G. Parker:** None. **A. Kennedy:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.17/T7

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

Support: NIH Grant 2R01NS115209-06

Title: Ionic mechanisms underlying burst generation in Drosophila cold nociceptor neurons

Authors: *A. SAKURAI[1], S. M. KOROGOD[1], D. N. COX[2], G. S. CYMBALYUK[1];
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Abstract: Bursting activity in peripheral sensory neurons plays an important role in neuronal signaling and sensory coding, yet the underlying biophysical mechanisms remain poorly understood. In *Drosophila* larvae, Class III (CIII) sensory neurons detect nociceptive cold temperatures and respond to rapid cooling with phasic-tonic spiking activity, with approximately half of the neurons generating bursts during rapid temperature decreases. Here, we investigated how bursting can arise from intrinsic membrane properties and examined how ionic perturbations influence burst generation without thermosensory activation. Enhancing the Cl^- gradient by lowering extracellular Cl^- concentration promoted bursting when neurons were

depolarized by steady current injection (N=30). The low-Cl^- saline produced little detectable membrane depolarization despite strongly promoting bursting. In contrast, a fivefold elevation of extracellular K^+ evoked membrane depolarization and induced bursting in 58% of neurons examined (N=7/12), indicating that CIII neurons possess intrinsic burst-generating mechanisms. To further examine the ionic basis of bursting activity, we performed pharmacological manipulations targeting Ca^{2+} and Na^+ currents. Removal of extracellular Ca^{2+} had little effect on the bursting activity. In contrast, tetrodotoxin (TTX) at 20 nM abolished slow membrane-potential oscillations underlying bursting along with spikes, indicating that sodium-dependent membrane mechanisms contribute to burst generation in CIII neurons. Biophysical modeling reproduced the experimentally observed transitions among silence, tonic spiking, and bursting, and suggested that voltage-gated Na^+ current plays a prominent role in sustaining the depolarizing envelope underlying burst generation. Together, our findings show that CIII neurons can generate the full spectrum of activity patterns in the absence of thermosensory stimulation. The results provide new insight into the membrane dynamics underlying thermal sensory coding in peripheral sensory neurons.

Disclosures: A. Sakurai: None. **S.M. Korogod:** None. **D.N. Cox:** None. **G.S. Cymbalyuk:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.18/T8

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

Support: 1R01DA055008

Title: Vagus nerve stimulation facilitates extinction, reduces cocaine seeking, and modulates intrinsic excitability and spontaneous synaptic transmission in the medial prefrontal cortex

Authors: *K. YANG, S. RODRIGUEZ, R. AREZOOMANDAN, L. VU, M. VAHID, Z. HASAN, S. KROENER;
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Abstract: Cocaine use disorder presents a persistent global public health burden, in part because drug-associated environmental cues acquire strong motivational salience and reliably trigger craving and relapse. Extinction training seeks to weaken these cue-drug associations by establishing a competing memory, yet extinction alone frequently fails to prevent relapse in clinical and preclinical settings. Previous work from our lab demonstrated that coupling extinction training with vagus nerve stimulation (VNS) enhances extinction and reduces subsequent cue-induced reinstatement of cocaine seeking in rats. The present study investigates the cellular mechanisms mediating this effect, with a focus on the prelimbic (PL) and infralimbic

(IL), two subregions of medial prefrontal cortex (mPFC) that are thought to exert opposing effects on drug-seeking behavior. Adult male and female Sprague-Dawley rats (3-7 months) underwent cocaine self-administration followed by extinction training paired with either VNS or sham stimulation, and were subsequently tested for cue-induced reinstatement. Whole-cell patch-clamp recordings were done at two timepoints (after the final day of extinction and following reinstatement) to characterize VNS-induced changes in intrinsic excitability and spontaneous excitatory (sEPSC) and inhibitory (sIPSC) postsynaptic currents. Group comparisons were performed using two-way ANOVA or independent-samples t-tests as appropriate. Relative to extinguished rats, rats that underwent reinstatement showed significantly reduced current-evoked firing in deep-layer IL pyramidal neurons, suggesting that relapse is associated with diminished IL output. Critically, VNS increased firing rates and depolarized the action potential threshold of IL pyramidal neurons after both the extinction and reinstatement compared with sham controls, a pattern consistent with the established role of the IL in consolidating extinction memory and suppressing drug seeking. VNS also reduced sIPSC frequency in IL neurons following reinstatement, indicating that a reduction in local inhibitory tone may partly account for the observed increase in IL excitability. Preliminary data from a subset of animals further suggest that VNS differentially regulates excitatory/inhibitory (E/I) balance across subregions: after extinction, VNS appeared to decrease the E/I ratio in the PL while increasing it in the IL. In summary, extinction and cue-induced reinstatement engage distinct adaptations within the mPFC and support a model in which VNS reduces cocaine seeking by enhancing IL activity and potentially dampening PL activity.

Disclosures: K. Yang: None. **S. Rodriguez:** None. **R. Arezoomandan:** None. **L. Vu:** None. **M. Vahid:** None. **Z. Hasan:** None. **S. Kroener:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.19/T9

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

Support: 26-BR-02-02
NRF-2026-25481379

Title: Dissociable neuronal substrates for acute responses and delayed plasticity after psilocybin treatment in mice

Authors: *J. LEE[1,2], M. KANG[3], J. LEE[5,3], J. LIM[3], N. CHOU[4], J. KIM[3];
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Abstract: Psychedelic compounds have shown strong and long-lasting therapeutic efficacy in preclinical models and clinical studies of psychiatric disorders. However, it remains unclear whether these effects arise from the acute hallucinogenic state or from distinct neurobiological mechanisms. Here, using psilocybin, we systematically compared acute and delayed cortical responses in mice across sex, dose, cortical region, cortical layer, and neuronal cell type. Psilocybin induced robust head-twitch responses (HTRs) and produced region- and cell-type-specific patterns of acute cortical activation, as assessed by c-Fos expression 60 min after administration. Notably, acute c-Fos induction varied across cortical regions and inhibitory interneuron populations. To examine whether acutely responsive populations overlap with those showing delayed plasticity, we performed whole-cell patch-clamp recordings 24 h after psilocybin treatment. Delayed electrophysiological alterations were not simply predicted by acute c-Fos activation, but instead emerged in distinct cortical regions, layers, and neuronal cell types. In particular, visual cortical pyramidal neurons and PV interneurons showed prominent delayed changes in intrinsic excitability, whereas somatosensory cortical pyramidal neurons showed limited electrophysiological changes despite acute activation. *In vivo* electrocorticogram (ECoG) recordings further revealed region-specific acute network responses. Together, these findings indicate that the immediate and 24-h effects of psilocybin are mediated by distinct cortical regions and cell types, supporting separable neurophysiological substrates for its hallucinogenic and therapeutic actions.

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Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

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

Support: Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 24K15104
Japan Agency for Medical Research and Development (AMED) AMED-CREST 26gm1510005s0206

Title: Axon initial segment plasticity reconciles increased excitability with reduced network synchrony

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Abstract: Homeostatic plasticity is thought to restore neuronal activity after reductions in intrinsic excitability caused by injury or other perturbations. However, compensatory enhancement of single-neuron excitability can increase the susceptibility of neuronal populations to pathological synchronization, including epileptic seizures. How neurons regain spike-generating capacity while preserving network stability remains unclear. Here, we theoretically show that plasticity of the axon initial segment (AIS), through adaptive changes in its distance from the soma, can reconcile these competing requirements. Using a biophysically detailed neuron model implemented in the NEURON simulator, we demonstrate that distal relocation of the AIS lowers the rheobase, thereby enhancing intrinsic excitability. Paradoxically, the same structural change lengthens the firing period under sustained input and reduces the susceptibility of coupled neuronal populations to in-phase synchronization. Network simulations show that increasing the soma-AIS distance shifts recurrent synaptic inputs generated by nearly synchronous spikes into a refractory or weakly responsive phase of the firing cycle, preventing recurrent excitation from reinforcing synchrony. To clarify the mechanism underlying this dual effect, we introduce an analytically tractable two-compartment model consisting of the soma and AIS. The analysis reveals that increased electrical separation between the two compartments reduces bidirectional axial currents in distinct phases of the firing cycle: reduced AIS-to-soma current during spike initiation lowers the effective somatic load on the AIS and facilitates spike generation, whereas reduced soma-to-AIS current during interspike depolarization delays subsequent spike initiation and lengthens the firing period. This phase-dependent current regulation is associated with a transient reversal of membrane potentials between the soma and AIS during spike generation. These results identify AIS plasticity as a subcellular structural mechanism that can couple homeostatic recovery of intrinsic excitability to stabilization of network dynamics. More broadly, our findings provide a theoretical framework for understanding how neuronal morphology contributes to stable network function and may also offer insight into neurological disorders characterized by abnormal synchrony.

Disclosures: K. Nishimoto: None. **H. Ito:** None. **H. Kitahata:** None. **J. Teramae:** None.

Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.21/T11

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

Support: University of Kentucky Lewis Honors College
University of Kentucky Human Health Sciences Fellowship (KN)
Gertrude Flora Ribble Fellowship (AH)
University of Kentucky Department of Biology

Title: Differential effects on synaptic transmission by serotonin and forms of LPS

Authors: *K. A. NEGLIA[1], A. HANA[1], J. BIDROS[1], E. ELLIOTT[1], R. MCINTOSH[1], M. DUNN[2], I. BAILEY[3], G. BEACHAM[4], S. BOWDEN[1], J. CALDWELL[5], T. LOCKHART[1], O. PATEL[6], L. POTTS[7], J. SCHWAMBURGER[8], E. SIDES[9], J. VARNEY[10], B. WARREN[11], J. YANG[1], M. YOUNIS[1], R. L. COOPER[12];
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Abstract: Research into Gram-negative bacterial sepsis primarily focuses on the effects of cytokines released during the immune response to bacterial lipopolysaccharide (LPS) toxins; however, it is also known that LPS can directly affect membrane potential and various ion channels, leading to altered physiological states that might affect function and efficacy of pharmacological treatments. This study investigated the direct actions of LPS from Serratia marcescens, Pseudomonas aeruginosa, and Escherichia coli on synaptic transmission and membrane potential. Also examined were the cellular responses to serotonergic modulation of synaptic transmission during LPS exposure, which were observed through electrophysiological recordings monitoring excitatory junction potential amplitude and membrane potential. Studies were conducted using the glutamatergic neuromuscular junction of the crayfish as a model, wherein it was demonstrated that synaptic transmission was enhanced by exposure to the various forms of LPS — whether largely (S. marcescens) or mildly (P. aeruginosa, E. coli) — and further increased with combined exposure to serotonin and LPS. These actions may occur through different mechanisms, leading to an accentuated final synaptic outcome; namely, LPS affects ionic driving gradients through hyperpolarization of membrane potential, while serotonin affects muscle membrane potential principally through the modulation of vesicle dynamics (and possibly cytoplasmic Ca2+ within the nerve terminal). Both LPS and serotonin influence pre- and post-synaptic cells. These results indicate that synaptic function, modulation, and pharmacological treatments may vary considerably depending on which type of LPS is present.

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Poster

PSTR006: Intrinsic Excitability: Neuromodulation, Axonal Signaling, Ion Channels, and Computational Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.22/T12

Topic: B.10. Neuro-Oncology

Title: Computational modeling of cell-type-specific cortical stimulation to suppress pyramidal output in a human layer 5 motor-cortex circuit

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Abstract: Electrical stimulation of the cortex is widely used in neurosurgery to map functional-anatomical relationships during operations, and there is growing interest in using stimulation to modulate cortical circuits for therapeutic purposes. However, the effects of cortical stimulation on individual cells, local populations, and downstream targets remain difficult to predict because neuronal recruitment depends not only on amplitude, frequency, and spatial pattern, but also on cell morphology, cell type, cortical depth, and field orientation. Layer 5 pyramidal neurons are a major output population of motor cortex, yet it remains poorly understood how stimulation differentially recruits pyramidal and inhibitory cell classes to suppress versus drive cortical output.

To address this problem, we developed a morphologically grounded computational spiking network model of human layer 5 motor cortex in NEURON. The model includes pyramidal neurons together with PV-like basket, SST-like Martinotti, and VIP-like inhibitory interneuron populations embedded in a recurrent circuit. We first used targeted intracellular current-clamp stimulation of individual cell classes to characterize class-specific dose-response relationships and determine how selective recruitment altered pyramidal output. In these simulations, stimulation was delivered as current injection to defined populations, and firing was quantified across baseline, stimulation, and post-stimulation epochs. We then extended the framework to extracellular pial-surface stimulation, in which stimulation is modeled as an imposed extracellular field constrained by morphology, cortical depth, and orientation relative to the pial surface.

Preliminary targeted-stimulation simulations showed that PV-like basket-cell recruitment produced the strongest and most consistent suppression of pyramidal firing. SST-like Martinotti-cell recruitment also reduced pyramidal firing, but more gradually, whereas VIP-like recruitment alone produced little direct suppression. In contrast, nonselective stimulation of all cell classes increased pyramidal firing overall, indicating that direct pyramidal recruitment and disinhibitory network effects can outweigh inhibition when stimulation is not selective. These findings support the hypothesis that pyramidal suppression is most effective when inhibitory recruitment, particularly PV-like basket-cell recruitment, exceeds direct pyramidal activation. Ongoing extracellular simulations are testing whether pial-surface stimulation can reproduce this suppressive effect under anatomically constrained field conditions.

Disclosures: Z.A. Li: None. **T.F. Boerger:** None.

Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.01/T13

Topic: B.07. Network Interactions

Support: NIH Grant R35 NS127119

Title: Temporal filtering in the hilar mossy cells of the dentate gyrus is regulated by an inhibitory switch

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Abstract: For encoding long term memories, the hippocampus transforms cortical inputs into stable neural representations. This begins in the dentate gyrus (DG) where the principal excitatory cells, granule cells (GCs) transform complex entorhinal input into sparse codes; while hilar mossy cells (HMCs) and different types of interneurons recurrently modulate GC output to the CA3. The DG is hypothesized to gate and decorrelate highly similar input patterns from the entorhinal cortex, performing a computation known as pattern separation. Temporal filtering by synapses contributes to pattern separation - which in turn, depends on short term dynamics of individual cells and subtypes. While much attention has been given to biophysical properties of the GCs, studying HMCs, that receive entorhinal inputs disynaptically via GCs, has been challenging in the polymorphic hilar region. Hence, the differences in the short-term plasticity between these cells in the DG have not been systematically characterized. We utilized a genetically encoded voltage sensor, hVOS (hybrid voltage sensor), targeted to the different excitatory cells in the DG from adult mice (aged 6-16 weeks) of both sexes. GCs were targeted with *Prox1-CreERT2* (n = 24 slices, 13 animals*)* and HMCs with *Calcrl-Cre* (n = 16 slices, 11 animals*)*. Pairs of stimuli at different inter-pulse intervals (IPIs) were delivered to the perforant path in 300 μm acute transverse slices. We observed moderate levels of heterogeneous facilitation in GCs with an exponential decay (Paired pulse ratio (PPR) = 1.32±0.6 at 30 ms). However, HMCs consistently showed paired pulse depression (PPR = 0.89±0.6 at 30 ms). $GABA_A$ receptor blockade eliminated this depression in HMCs, resulting in paired-pulse facilitation (PPR = 1.58±0.8 at 30 ms). Further, pharmacological blockade with Gabazine and DCG-IV in GCs indicated that feedforward inhibition and not feedback inhibition onto GCs may be responsible for this suppression. Additionally, preliminary data from stimulating the CA3 back projections to HMCs showed modest paired pulse facilitation (PPR = 1.5±0.12 at 30 ms; n=3 slices, 2 animals), indicating that suppression of facilitation is pathway-specific, and not an intrinsic property of HMCs. Our findings indicate that facilitation in disynaptic connections to HMCs from the perforant path, can be masked by integration of feedforward inhibition. Thus, HMCs may serve as a dynamic high-pass filter for GC inputs and inhibition may help restrain runaway amplification to aid pattern separation.

Disclosures: S. Sengupta: None. **M.B. Jackson:** None.

Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.02/T14

Topic: B.07. Network Interactions

Support: NIH EY014924
NIH NS116623
Ben Barres Professorship to T.M.

Title: Condition-dependent noise correlations without condition-dependent spike counts

Authors: *D. KIM[1], M. F. PANICHELLO[2], T. MOORE[3];
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Abstract: Correlations in neuronal spiking activity across trials of the same condition, or noise correlations (NCs), have been interpreted as a reflection of shared synaptic connectivity and as a contributing factor to the information capacity of neuronal populations. The impact of NCs on coding is most often considered in populations of selective neurons, i.e. neurons with condition-dependent spike counts (SCs). However, theoretical work suggests that NCs could provide information separate from neuronal selectivity. To test this hypothesis, we measured the condition dependence of NCs in neuronal populations with varying degrees of SC selectivity. Data were obtained from Neuropixels recordings from large neuronal populations (8,225 neurons across 25 sessions) in prefrontal cortex (PFC) of three male rhesus monkeys performing a spatial delayed response task with visual, memory, and motor epochs.
We first assessed the extent to which PFC neurons exhibited selectivity during the visual, memory or motor epochs of the task. SC selectivity in each epoch was assessed using linear classification. Neurons with large magnitudes of classifier weights supporting above-chance classification of visual, memory or movement location were labeled SC-selective, while the remainder were labeled SC-nonselective. Next, NC selectivity in each epoch was assessed by modeling the SCs of each neuron pair using linear regression. We compared two linear models. The base model predicted the condition-normalized SCs of one neuron from the other, capturing condition-invariant NCs. The full model included an interaction term allowing NCs to vary across conditions. Pairs with significant interaction terms were labeled NC-selective. The magnitude of NC selectivity was quantified as the proportional increase in variance explained by the full model compared to the base model.
Overall, we found that neuron pairs displaying visual, memory, and motor selectivity in their SCs often exhibited selectivity in their NCs. However, we also found that neuron pairs without SC selectivity during the different task epochs nonetheless exhibited condition-dependent NCs. Moreover, we found that the magnitude of condition-dependent NCs were largely comparable across selective and non-selective neuronal pairs. These results demonstrate that correlated variability in spiking activity can be condition-dependent even in the absence of condition-dependent SCs. Our findings suggest that NCs are not merely a byproduct of shared synaptic inputs among tuned neurons, but a robust feature of the population that can serve as a distinct channel for task-relevant information.

Disclosures: D. Kim: None. **M.F. Panichello:** None. **T. Moore:** None.

Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.03/T15

Topic: B.07. Network Interactions

Title: Morphometric identification of predictors of the neuronal structure in chronic cerebral hypoperfusion

Authors: *V. AKULININ[1], S. STEPANOV[1], D. AVDEEV[1], I. TSUSKMAN[1], D. AKULININ[2], A. SHORONOVA[1], K. TAGAKOV[1], V. SERGEEV[1];
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Abstract: Chronic cerebral hypoperfusion, modeled by bilateral ligation of the common carotid arteries in rats, induces prolonged remodeling of neuronal populations in the sensorimotor cortex (SMC). Traditional univariate morphometric analysis is unable to reveal hidden multivariate patterns, discrete neuronal states, and their trajectories. We developed an algorithm combining principal component analysis (PCA), metric multidimensional scaling (MDS), K-means clustering, ‘Random Forest’ with Shannon entropy calculation, partial correlation networks, LASSO regression, and syndrome dynamics analysis. Layers III and V of the SMC were examined in 72 Wistar rats in the control and at 30, 90, 150, 210, and 270 days after surgery. Neurons and glial cells were detected using H&E and Nissl staining, and NeuN, MAP-2, GFAP, and Iba-1. Six morphometric parameters were measured per 0.2 mm² for each observation: total neuronal density (TND), density of hyperchromic shrunken (HCS), hyperchromic non-shrunken swollen (HCNS), hypochromic (HCN) neurons, ghost cells (GC), and neuroglial index (NGI). PCA identified a major axis of PC1 degeneration, explaining 51.6% of the total variance, with the largest contributions from HCN (25.8%), GC (25.2%), and HCNS (20.9%). MDS followed by K-means clustering with an optimal k = 10 (maximum mean silhouette coefficient of 0.387) identified 10 discrete morphometric syndromes of neuronal states. The ‘Random Forest’ model classified the syndromes with an out-of-bag error of 1.39% (71 out of 72 correct). Ranking of predictors revealed the dominance of the density of the HCNS (41.4) and the NGI (40.5). Shannon entropy analysis revealed a pronounced peak at 90 days in layer III (0.35–0.50), interpreted as a critical period of uncertainty – the therapeutic window. LASSO regression revealed a switch in the predictor formulas for the NGI between layers: in layer III – HCNS (β=+0.077) and GC (β=-0.061), in layer V – HCN (β=-0.088) and GC (β=+0.061) when the HCNS was set to zero. Partial correlation networks demonstrated architectural plasticity of layer V (rarefaction of the pathological node by day 270) and rigidity of layer III (preservation of connections). Centroid trajectory analysis revealed a relapsing course in layer III (1/9→3→6→8→2→8) with a return to an intermediate syndrome and stable remodeling in layer V (7→5→4→4→10→10) with the achievement of a stable syndrome 10 (low TND, high NGI 1.53). The paradigm formalizes the concept of "neuronal structure" in the form of reproducible quantitative syndromes, layer-specific predictors, and architectural plasticity – aspects inaccessible with traditional analysis.

Disclosures: V. Akulinin: None. **S. Stepanov:** None. **D. Avdeev:** None. **I. Tsuskman:** None. **D. Akulinin:** None. **A. Shoronova:** None. **K. Tagakov:** None. **V. Sergeev:** None.

Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.04/T16

Topic: B.07. Network Interactions

Support: Anid Exploracion 13240026
CENIA FB210017
AFOSRFA8655-25-1-8026

Title: Metabolic Constraints on Neural Dynamics: Testing the Energy Homeostasis Principle in Cortical Cultures

Authors: *P. E. MALDONADO[1], J. SIERRALTA[1], R. C. VERGARA[3], S. MADARIAGA[4], M. PEDRAZA[1], R. HERRERA-MOLINA[5], B. CARRASCO[2];
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Abstract: The Energy Homeostasis Principle (EHP) posits that biological systems organize their internal states and behaviors to minimize metabolic energy expenditure while maintaining physiological stability and functional integrity. To investigate the EHP in neural circuits, we conducted a series of experiments exploring the energy dependence of primary neuronal cultures grown on standard substrates and multi-electrode arrays (MEAs). We analyzed the dynamics of gene expression, synaptic connectivity, and electrophysiological firing patterns under varying glucose concentrations, comparing high-glucose (25 mM) conditions to lower, more physiologically relevant levels (10 mM).Our results indicate that while cell viability was maintained in low-glucose media, key glucose and lactate transporters showed significant changes in expression. Furthermore, real-time MEA recordings during progressive glucose reduction revealed an increase in average firing rates coupled with a decrease in neuronal connectivity, as measured by cross-correlograms. These findings are consistent with the EHP; we propose that reduced energy availability impairs the efficient restoration of ionic gradients, leading to altered excitability, while the system simultaneously reduces metabolically expensive synaptic connectivity to conserve resources. This study demonstrates that metabolic constraints directly shape the functional architecture of neural networks, suggesting that energy efficiency is a fundamental driver of neural coding and circuit organization.

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Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.05/T17

Topic: B.07. Network Interactions

Support: Fitzgerald Translational Neuroscience Fund

Title: Machine learning-assisted characterization of hippocampal input-output transformations on an ex vivo three-dimensional MEA platform

Authors: *J. T. LIM[1], M. KHANTAN[1], A. NAPOLI[2], M. D. SERRUYA[3];
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Abstract: Purpose: Living neural microcircuits possess computational capabilities but deploying them as synthetic biological computing elements requires systematic characterization of their input-output transformations. We therefore developed a reproducible ex vivo approach for quantifying how organotypic hippocampal slices transform spatially localized microstimulation inputs into discriminable focal population-level field potential (LFP) responses. Methods: The hippocampal region of brain slices were interfaced with three-dimensional multi-electrode arrays (3D-MEA) for focal two-site microstimulation and multi-channel extracellular recordings of CA3 subnetwork responses. Signals within the post-stimulus window (2-5 seconds after stimulation) were bandpass-filtered (4-30Hz). Welch PSD yielded theta (4-12Hz) and beta (12-30Hz) band-limited power features used to train classifiers with stratified 5-fold cross-validation, reporting accuracy, macro-F1, recall, ROC-AUC, and significance by permutation tests. Results: Our 3D multi-electrode arrays recorded stable spontaneous LFPs within the hippocampal region of slices. CA3 microcircuits exhibited separable focal population responses to spatially distinct microstimuli, where classifier performance generally exceeded chance across datasets. Post-stimulus power frequently contributed to classifier performance and permutation tests confirmed significance of above-chance classification. Conclusion: This study provides a quantitative framework for assessing spatially dependent focal population responses in hippocampal microcircuits. These findings show that band-limited LFP features can serve as stable readouts for decoding stimulation location and provide an initial operational estimate of the slice's input-output transfer function. This reproducible *ex vivo* framework establishes a foundational module for future efforts to systematically expand and standardize how living neural tissue can be written to and read from as a biological computing element.

Disclosures: J.T. Lim: None. **M. Khantan:** None. **A. Napoli:** None. **M.D. Serruya:** None.

Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

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Program #/Poster #: PSTR007.07/T19

Topic: B.07. Network Interactions

Support: MH130862
25AARF-1376894

Title: Chronic Mild Stress impairs hippocampal myelination through SOX6-dependent dysfunction of Oligodendrocyte lineage cells

Authors: *C. A. MARTIN[1], A. BOMBIN[2], S. YAN[3], Y. GONZALEZ-GIRALDO[4], E. DEW[6], K. JIAO[5], Q. WANG[7], F. ZHOU[3];
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Abstract: Chronic stress is linked to progressive white matter abnormalities, increasing susceptibility to major depressive disorder and other mental illnesses. Myelination deficits are a key pathological feature of stress-related disorders, yet the molecular mechanisms by which chronic stress drives oligodendrocyte lineage dysfunction remain unclear. Using single-nucleus multiome sequencing in a mouse model of chronic unpredictable mild stress (CUMS), which simulates the heterogeneous stressors of human daily life, we profiled paired gene expression and chromatin accessibility across hippocampal cell populations. The results showed that CUMS triggered extensive transcriptional and epigenomic reprogramming, with stress-responsive networks selectively enriched for depression-associated genes. The oligodendrocyte lineage was vulnerable, particularly at immature OPC and intermediate stages, where CUMS disrupted migratory capacity, OPC-to-ODC progression, intercellular signaling, and myelination. Integrated multiomic analysis identified stage-specific cis-regulatory elements and gene regulatory networks converging on SOXD family transcription factors. SOX5 and SOX6 emerged as central nodes in OPC dysfunction. SOX6 ChIP-seq confirmed direct SOX6 binding at regulatory elements associated with genes controlling OPC morphogenesis, migration, and glutamatergic signaling. CUMS reduced SOX6 protein levels and activity of the SOX6-associated regulatory network in OPCs, whereas OPC-specific enhancer-driven restoration of SOX6 rescued stress-induced defects in OPC migration and myelination. These results establish a stress-sensitive SOX6 regulatory axis as a mechanistic link between chronic stress and oligodendrocyte dysfunction and myelination deficits, positioning SOX6 as a functional regulatory node with therapeutic potential for stress-related brain pathology.

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Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

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Program #/Poster #: PSTR007.08/T20

Topic: B.07. Network Interactions

Support: 1.NIH DIRP ZIAMH002797
2.BRAIN initiative U19 NS107464-01

Title: Decodable, amplified, critically-scaling responses to holographic perturbation in the visual cortex of awake mice

Authors: *T. L. RIBEIRO[1], R. SIDDIQUI[2], S. PAJEVIC[3], D. PLENZ[4];
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Abstract: A core computational principle of brain function involves detecting unexpected, salient events and efficiently broadcasting this information across neural circuits to guide adaptive behavior. Theoretical frameworks of critical brain dynamics propose that systems operating near a second-order phase transition exhibit non-linear, scale-invariant responses to perturbations. To investigate how locally initiated activity propagates through cortical networks and to decode information about perturbed neurons from network-wide responses, we employed targeted two-photon (2P) optogenetic stimulation combined with population calcium imaging in awake mice. Using a low-repetition-rate, high-power laser system (Carbide/Orpheus; LightConversion) paired with a high-resolution spatial light modulator (MeadowLark), we achieved precise 2P activation of individual ChrimsonR-expressing neurons. Concurrently, we monitored population activity via GCaMP8s imaging in layer II/III pyramidal neurons of primary visual cortex (V1), identified through widefield mapping. We recorded approximately 150-300 neurons within a 450×450 μm field of view (depth: 100-200 μm) at 45 Hz while holographically photostimulating (100 ms duration; <10 mW per target) 32 pyramidal neurons co-expressing the opsin across 100 trials per configuration. Target neurons were organized into hierarchically structured groups (1, 2, 4, 8 and 16) based on spatial proximity and stimulated sequentially across recording sessions. Machine-learning-based denoising was applied to calcium imaging data, followed by deconvolution to extract spike timing information. Photostimulation evoked significant responses in a subset of non-targeted neurons (>92% above baseline firing), without preferential recruitment of cells sharing similar orientation tuning with stimulated targets. Critically, population responses scaled non-linearly with the number of stimulated neurons as well as total spike count from target cells. Analysis of network activity patterns enabled decoding of information about which neurons were perturbed, revealing structured propagation of evoked activity. To contextualize these findings, we simulated 2D sparse cellular automaton networks tunable across criticality regimes. Virtual stimulation experiments applying identical analytical pipelines reproduced experimental observations exclusively at the critical point, providing evidence that cortical networks operate near criticality and that this regime optimizes information propagation and decoding of perturbation identity.

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Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

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Program #/Poster #: PSTR007.09/T21

Topic: B.07. Network Interactions

Support: NRF Grant RS-2024-00415957
NRF Grant RS-2024-00402116

Title: MEA-Based 4-Quadrant Modular Neural Network Platform for Associative Plasticity Analysis

Authors: *D. KIM[1], S. HWANG[1], S. JUN[1,2,3];
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Abstract: The brain comprises functionally distinct modules that enable efficient information processing. However, conventional in vitro cultures on microelectrode arrays (MEAs) lack this structural organization. Here, we developed a four-quadrant modular neural network platform using a window-type PDMS mask on MEAs to mimic the brain's compartmentalized architecture. Primary hippocampal neurons were cultured in separated compartments, and the mask was removed at DIV 10 to allow controlled inter-module neurite outgrowth. Optical imaging confirmed that somatic organization within each quadrant was preserved, while neurites established structural connections across compartment boundaries by DIV 21. Electrophysiological recordings revealed distinct maturation trajectories between modular and non-modular control networks. In modular networks, mask removal at DIV 10 triggered a transient hyper-excitable state at DIV 11, characterized by elevated mean firing rates (MFRs) and high burst percentages, likely due to rapid axogenesis. By DIV 15-18, while control networks showed a progressive decline in modularity, modular networks maintained high modularity ($Q \approx 0.6$), confirming the preservation of compartmental identity. Concurrently, the burst percentage in modular networks decreased with maturation, indicating a shift from stochastic single-electrode firing, while network burst frequency continued to rise, reflecting the emergence of strong inter-module synchronization. To isolate baseline functional connectivity from network burst-driven coactivation, the spike time tiling coefficient (STTC) was computed exclusively during inter-burst intervals (IBIs). At DIV 15, modular networks showed a higher proportion of strong intra-compartment connections relative to inter-compartment connections, whereas control networks exhibited homogeneous connectivity, consistent with preserved functional segregation. By DIV 18, inter-module connectivity strengthened in modular networks, suggesting progressive integration while structural modularity was maintained. As a proof-of-concept, paired-compartment sequential stimulation (20 ms inter-compartment interval, 0.2 Hz,

10 min) was applied at DIV 23. Probe stimulation of the directly stimulated compartment before and 5 min after the conditioning session revealed increased evoked firing rates and reduced response latencies in non-stimulated compartments, suggesting activity-dependent inter-module plasticity. Stimulation parameters are currently being optimized for systematic investigation of spike-timing-dependent plasticity in this compartmentalized architecture.

Disclosures: D. Kim: None. **S. Hwang:** None. **S. Jun:** None.

Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

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Program #/Poster #: PSTR007.10/T22

Topic: B.07. Network Interactions

Title: Bridging rodent and human biology with an optimized iPSC triculture HD-MEA model to interrogate network excitability alterations in neuropsychiatric disorders

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Abstract: Dysregulated network excitability is implicated in neuropsychiatric disorders, including schizophrenia and bipolar disorder, yet scalable human assays that capture circuit-level phenotypes remain limited. To address this, we established an iPSC-derived triculture containing glutamatergic neurons, GABAergic neurons, and astrocytes. Initial characterization using immunocytochemistry, RNA-seq, and high-density microelectrode arrays recordings confirmed functional neurotransmission through progressive increases in synaptic markers and organized burst activity sensitive to GABAergic and glutamatergic pharmacological modulation. To enhance scalability, we optimized astrocyte seeding density and coating conditions; specifically, using polyglycerol amine significantly accelerated functional maturation and network synchronization compared to standard poly-D-lysine.
In parallel, we established cross-species validation paradigms using rodent systems to define manipulable network excitability phenotypes and mechanistic anchors for perturbation studies in the hiPSC platform. To benchmark immune-driven circuit remodeling, we evaluated complement pathway activation in primary rodent cultures. Complement activation markedly reduced inhibitory synapse density, an effect rescued by depleting upstream pathways, supporting a role for this pathway in modulating network excitability. Furthermore, to evaluate the system's sensitivity to genetic and pharmacological modulation of network excitability, we characterized functional network dynamics in a GRIN2A-deficient model. Ex vivo slice patch-clamp electrophysiology demonstrated a baseline hyperexcitable phenotype that was successfully normalized using a NMDA receptor modulator. This pharmacological intervention restored spontaneous inhibitory postsynaptic currents, correcting the aberrant hyperexcitable network phenotype.

Together, these validated perturbation approaches position the optimized hiPSC triculture as a scalable, mechanistically informed platform for quantifying network excitability and advancing translational strategies for neuropsychiatric disorders.

Disclosures: C. Ho: A. Employment/Salary (full or part-time):; Johnson & Johnson. **V. Zell:** A. Employment/Salary (full or part-time):; Johnson & Johnson. **W. Mao:** A. Employment/Salary (full or part-time):; Johnson & Johnson. **B. Balana:** A. Employment/Salary (full or part-time):; Johnson & Johnson. **L. Fourgeaud:** A. Employment/Salary (full or part-time):; Johnson & Johnson. **P. Bonaventure:** A. Employment/Salary (full or part-time):; Johnson & Johnson.

Poster

PSTR007: Network Interactions: Other

Location: WCC Halls A-C

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Topic: B.07. Network Interactions

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Title: ASAP2s Voltage Imaging Reveals Strong Inhibitory Potentials in ChAT-positive Neurons of the Septal Nucleus

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Abstract: Acetylcholine (ACh), released by neurons of the basal forebrain and septal nuclei, plays critical roles in attention, learning, and affective regulation. To investigate how cholinergic circuits process synaptic inputs, we used the genetically encoded voltage indicator (GEVI) ASAP2s to monitor membrane potential dynamics in choline acetyltransferase (ChAT)-expressing neurons. Selective expression of ASAP2s was achieved by crossing TIGRE2-ASAP2s (Ai169) mice with ChAT-Cre mice, resulting in stable, brain-wide expression of the voltage indicator in ChAT-positive neurons. In acute coronal brain slices, weak ASAP2s fluorescence was observed in the neocortex, reflecting the sparse distribution of cholinergic axons, whereas strong fluorescence was detected in the septal nuclei. Electrical stimulation of either region evoked detectable optical responses. Interestingly, stimulation of the medial prefrontal cortex (mPFC) produced hyperpolarizing responses in the ChAT-labeled population of the lateral septum (LS). Blockade of GABA-A receptors with gabazine (4 μM) converted these hyperpolarizations into depolarizing responses, suggesting an underlying PFC excitatory drive to LS that is normally masked by strong local inhibition. These findings raise the hypothesis that excitatory inputs to ChAT-expressing LS neurons are tightly regulated by local GABAergic

circuitry, consistent with the predominantly inhibitory composition of the LS. To test this hypothesis, we investigated the nature of functional segregation within the LS by simultaneous whole-cell recordings and GEVI imaging. Strikingly, in response to the same afferent stimulation, non-ChAT neurons exhibited excitatory postsynaptic potentials (EPSPs), whereas neighboring ChAT-expressing neurons displayed inhibitory postsynaptic potentials (IPSPs). During EPSPs recorded from individual non-ChAT neurons, the surrounding ChAT-labeled population undergoes synchronized hyperpolarization. These results demonstrate that voltage imaging can resolve circuit-level inhibitory dynamics (hyperpolarizations) that are inaccessible to calcium imaging. Our findings provide fresh insights into information processing in lateral septal circuits and highlight the unique value of GEVIs for dissecting excitation-inhibition interactions in neuromodulatory networks.

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Poster

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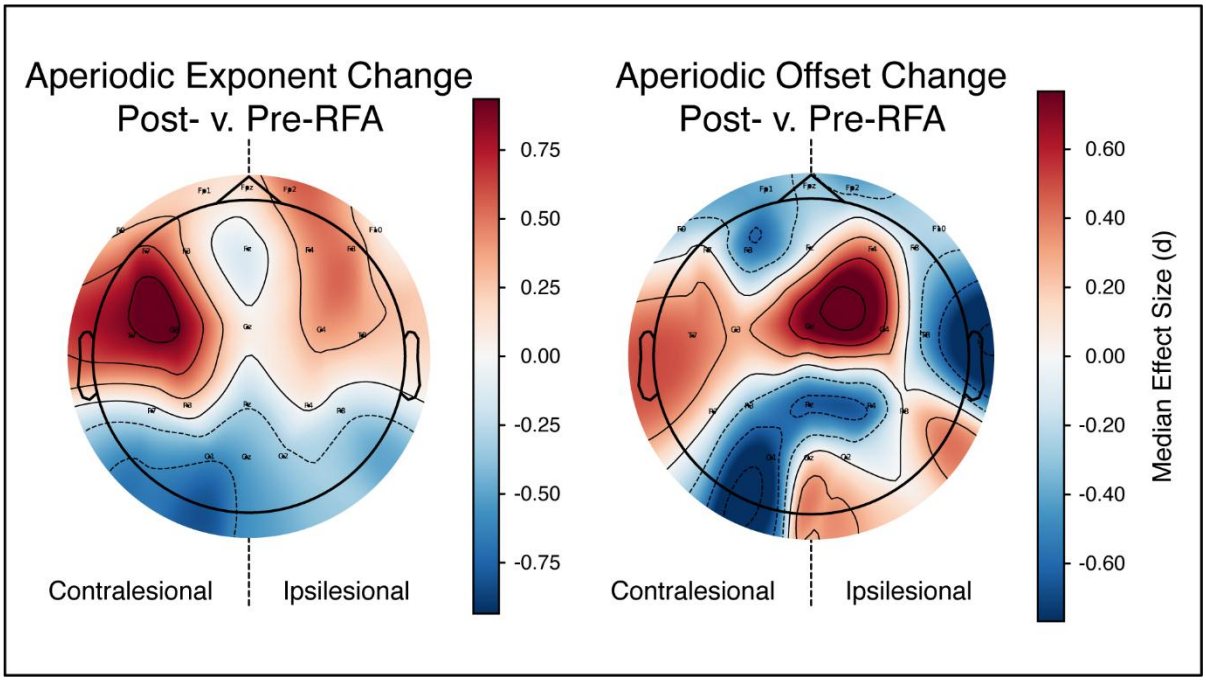
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Title: Focal Amygdala Ablation Induces Distributed, Hemisphere-Specific Shifts in Aperiodic Brain Activity

Authors: *N. K. BRYSON[1,3], H. PARK[2], P. BRUNNER[4], J. T. WILLIE[3];
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Abstract: Radiofrequency ablation (RFA) is an increasingly utilized minimally invasive treatment for intractable epilepsy that enables focal destruction of epileptogenic tissue. Despite increasing clinical adoption, the acute network-level consequences of focal tissue ablation remain poorly understood. Previous studies have identified the emergence of slow, sleep-like activity following RFA, but have largely focused on low-frequency oscillations. Here, we investigated distributed cortical reorganization immediately following ablation using aperiodic features derived from scalp EEG. Six patients with medically refractory epilepsy underwent clinically indicated amygdala RFA (3R/3L). Scalp EEG was recorded before and after ablation. To facilitate group-level comparisons, recordings were reflected into a common lesion hemisphere such that right-sided electrodes were treated as ipsilateral to the lesion. Power spectra were computed across electrodes and parameterized to quantify changes in aperiodic exponent and offset following ablation. Following amygdala RFA, scalp EEG exhibited marked hemispheric asymmetries in aperiodic activity. Aperiodic exponent increased most prominently in the contralesional hemisphere, with maximal effects observed over frontotemporal and central electrodes (F7, T7, and C3). In contrast, increases in exponent in the ipsilesional hemisphere were smaller and largely confined to frontal regions. Aperiodic offset exhibited the opposite hemispheric distribution, with the largest increases localized to the ipsilateral hemisphere and centered over frontocentral electrodes (F4, C4, and Cz). Together, these findings reveal hemispheric-specific alterations in aperiodic activity following focal amygdala ablation. A highly localized lesion produced spatially organized changes in large-scale neural dynamics detectable by scalp EEG. Quantifying these aperiodic signatures may provide a scalable biomarker for measuring network reorganization following focal brain lesions and other causal perturbations of the human brain.



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Poster

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Topic: B.07. Network Interactions

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Title: A hierarchical spiking circuit as a tunable reservoir for computation

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Abstract: How can a recurrent circuit generate a rich, controllable repertoire of activity patterns that downstream neurons can read out to drive behavior? We address this question using a network of pulse-coupled neurons wired by the constraints of the Sudoku puzzle. Placing one neuron in each cell of a 9x9 grid and coupling neurons that share a row, column, or block by reciprocal inhibition, with complementary excitation, yields a network whose stable rhythmic firing patterns map one-to-one onto Sudoku solutions. Because this network admits on the order of 10^9 distinct solutions, our 81-neuron network supports an enormous repertoire of periodic attractor states. We found that excitation-inhibition balance maximizes the number of accessible attractors, network symmetry governs their abundance and stability, and that a common sub-threshold oscillation combined with targeted depolarizing biases can select and stabilize any chosen pattern through a phase-of-firing code, much as shared oscillations organize activity in hippocampus and olfactory cortex. Here we ask whether sequencing these patterns enables computation. We introduce a hierarchical network in which a small master layer of Nm neurons, arranged in a ring with global inhibition and slow spike-frequency adaptation, sequentially imposes structured biases on the Sudoku network. Adaptation destabilizes the active master neuron while asymmetric inhibition releases the next, sweeping the Sudoku layer through long, non-repeating sequences of solutions. The resulting 81 spike trains form a high-dimensional reservoir. We found that we could fit a single linear readout to reconstruct arbitrary non-rhythmic targets without training any recurrent weights. Critically, we could tune the complexity of the generated dynamics through both Nm, the number of master neurons, and the adaptation strength. While Nm determines the number of distinct Sudoku states available to the dynamics, adaptation controls the dwell time within each state and thus the timescale of sequential switching. Small Nm or weak adaptation produces short, repetitive itineraries, whereas larger Nm and stronger adaptation generate richer, less periodic trajectories that explore a larger portion of the attractor landscape. As complexity increases, reconstruction error falls sharply and then saturates, revealing a regime beyond which added complexity yields diminishing returns. These results show that a compact, biologically motivated recurrent circuit can act as a tunable reservoir, and they provide a systematic handle for relating the complexity of internally generated neural activity to computational capacity.

Disclosures: G. Halder: None. **C.G. Assisi:** None.

Poster

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Topic: B.07. Network Interactions

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RF1MH128969
UM1NS132358
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Title: A quantitative whole-brain atlas of cell-type density signatures and spatial organizational domains

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Abstract: The mammalian brain's structural and functional organization relies on the highly coordinated architecture of diverse cell types. Disruptions in this cellular architecture are increasingly recognized as contributing factors in both neurodevelopmental and neurodegenerative disorders. To investigate how cell-type composition shapes brain regionalization and disease vulnerability, we mapped the whole-brain distribution of 30 Cre-line-defined neuronal and glial populations at single-cell resolution. Using serial two-photon tomography and registration to the Common Coordinate Framework (CCF), we generated a comprehensive quantitative atlas of cellular densities across both male and female mice. Our analyses revealed that major anatomical divisions and functionally related regions, such as distinct cortical territories, striatal input domains, and thalamic nuclei, share characteristic cell-density signatures. By applying density-based spatial clustering (DBSCAN), we demonstrated that precise anatomical boundaries naturally emerge from the local density gradients of individual molecular markers. To determine the minimal molecular complexity required for this spatial organization, we performed an exhaustive combinatorial search. We found that broad cortical arealization can be perfectly reproduced by a compact subset of just six markers, with the required complexity varying significantly by cortical depth. Furthermore, region-wise comparisons uncovered robust, sex-associated differences in populations with developmental expression histories, suggesting sex-dimorphic variation in developmental cell lineages. Importantly, we applied these computational parcellation tools alongside whole-brain clearing and immunolabeling techniques to examine patterns of cellular organization and activity in circuits implicated in neurodevelopmental and neurodegenerative disorders. This integrated approach revealed region-specific alterations in cellular architecture and activity, consistent with early pathological processes and atypical circuit development observed in conditions such as Alzheimer’s disease and autism spectrum disorder.

Disclosures: R. Muñoz Castañeda: None.

Poster

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Topic: B.07. Network Interactions

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Title: Excitatory and inhibitory circuits orchestrate signal integration in the insular cortex

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Abstract: The insular cortex (IC) is an evolutionarily ancient associative cortex that processes both exteroception and interoception to maintain homeostasis and drive diverse behavioral outcomes. Its functions are conventionally attributed to subregions along the anterior-posterior axis, where the anterior IC primarily mediates cognitive functions, while the posterior IC primarily processes sensory signals. In parallel, the IC comprises three anatomical subregions roughly along its dorsal-ventral axis, the agranular, dysgranular, and granular IC (AI, DI, and GI), defined by the absence, emergence, and full presence of Layer IV, respectively. This unique anatomical organization and functional diversity distinguish the IC from primary sensory cortices and pique interest in whether it employs distinct mechanisms for signal processing. As specialized neuronal types and excitatory-inhibitory (E-I) balance have been proven critical for primary cortex functions, a deeper understanding of the IC cellular and circuit organization is much needed to establish the foundation of its structure-function relationship.
To address this knowledge gap, we generated a comprehensive atlas of mouse IC pyramidal cell types, based on their anatomical locations, projection targets, dendritic morphologies, intrinsic properties, and local connectivity. Combining ex vivo whole cell recordings with morphological reconstruction of over 1,000 neurons, we identified cell types that preferentially localize to anatomically and functionally distinct subregions, project to specific targets, and receive unique local inputs. In particular, certain cell types receive excitatory intra-insular inputs that are distinct

from canonical cortical microcircuits, and may underlie long-sought connections linking sensory information to valence.
Synergistic with the excitatory pyramidal neurons, IC inhibitory neurons also play pivotal roles in circuit integration. Interestingly, parvalbumin (PV) neurons, typically the most abundant inhibitory cells in neocortices, are much sparser in the AI than in the DI/GI, raising the question of whether the AI and DI/GI achieve the E-I balance through distinct mechanisms. To address this question, we combined electrophysiology with either laser-scanning photostimulation or targeted expression of channelrhodopsin to uncover differences in E-I responses induced by local versus long-range circuits.
Together, our work defines the cell types and E-I circuit motifs of the IC, which provides mechanistic insights on how this evolutionarily distinct associative cortex orchestrates signal integration to support diverse functions.

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Poster

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Program #/Poster #: PSTR007.16/T28

Topic: B.07. Network Interactions

Title: Local and input-driven contributions to cortical intrinsic timescales

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Abstract: Cognitive processes that give rise to behavior require the brain to operate across different timescales: sensory processing requires rapid information transmission, whereas working memory and decision-making require sustained activity over longer periods of time. Consistent with this, previous work has established an intrinsic timescale hierarchy across the cortex, quantified by fitting exponential decays to the autocorrelation of neural activity, in which primary sensory regions exhibit faster timescales than frontal and association areas. This organization is conserved across species and recording modalities; however, the mechanisms that give rise to it remain largely unexplored. Biophysical properties of single neurons, local network connectivity, and external inputs such as motor or neuromodulatory signals have all been proposed to contribute to the timescale gradient, but these hypotheses have primarily been explored through theoretical and computational models rather than direct experimental testing. Here, we combined mesoscale imaging, optogenetics, and high-density electrophysiology to test whether intrinsic timescales arise from local circuit dynamics or are shaped by the inputs those circuits receive. In a first set of experiments, we used widefield calcium imaging to record activity while optogenetically activating cortical inhibitory neurons at dorsal cortical sites ranging from frontal to primary visual cortex. While transiently suppressing local activity, we

quantified the timescale of recovery. Surprisingly, frontal regions recovered more quickly from suppression than sensory areas, suggesting that local circuit properties alone do not account for the timescale gradient. Next, we tested an input-driven framework by combining neuromodulator imaging and electrophysiological recordings to measure cholinergic release and motor-related signals alongside neural activity. By regressing these signals from the recorded activity and recomputing autocorrelation-derived timescales, we found that motor-related inputs influence timescales broadly across dorsal cortical regions, while cholinergic signals preferentially shape the dynamics of frontal areas. Together, these results suggest that the cortical timescale hierarchy does not exclusively arise from local circuit dynamics but is actively shaped by the inputs those circuits receive.

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Poster

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Topic: B.07. Network Interactions

Support: NIH R00 NS112575

Title: Measuring directed information flow across cortical regions in freely behaving mice

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Abstract: Large-scale human neuroimaging studies have used directed information flow metrics to characterize communication among distributed cortical networks, but whether similar patterns can be robustly measured in freely moving animals remains unclear. To address this gap, we developed a multi-region fiber photometry platform to quantify directed interactions among anterior cingulate (ACAv), anterior insula (AIV), retrosplenial (RSPv), and auditory (AUDp) cortices in freely behaving mice. These regions were selected based on our secondary analyses of human connectome project (HCP) and awake mouse fMRI data, implicating frontal, insular and posterior-midline in integrative functions, and sensory cortical systems as drivers of directed information flow. Adult mice received AAV-CaMKIIα-GCaMP8m injections and optical fiber implants targeting ACAv, AIV, RSPv, and AUDp. Simultaneous calcium activity and wireless inertial movements were recorded during open-field exploration, auditory stimulation, social-approach, novel object location, and operant reinforcement paradigms. Directed interactions were estimated using normalized directed transfer entropy (NDTE) applied to preprocessed

multi-region calcium signals, including isosbestic-based motion corrections. To evaluate whether observed directional structure exceeded chance levels, NDTE estimates were compared against surrogate-null datasets generated using temporal shuffling procedures designed to disrupt directionality while preserving key statistical properties of the original signals.Preliminary analyses revealed structured directional interactions among cortical regions that consistently exceeded surrogate-null distributions, supporting the feasibility of estimating directed information flow from simultaneously recorded cortical calcium dynamics in freely moving mice. Initial observations further suggest behavioral-context-dependent variation in regional sender-receiver relationships across recording conditions. Ongoing analyses are evaluating the robustness of these patterns across animals, behavioral paradigms, and experimental sessions. Together, these findings establish a framework for measuring directed cortical communication in freely behaving animals and provide a foundation for future studies examining behavioral modulation, neurodevelopmental risk models, and causal perturbations of cortical information flow.

Disclosures: I.V. Olivarez: None. **G. Deco:** None. **C. Tang:** None. **D.T. Page:** None. **K. Espinoza:** None.

Poster

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.18/T30

Topic: B.07. Network Interactions

Title: Mild Blast Traumatic Brain Injury Reshapes Functional Organization, Recruitment, and Synchronization of Spontaneous Rhythmic Activity from In Vitro Neuronal Networks

Authors: *J. MARTINEZ[1], C. ADAM[2], S. MUFTI[3], N. KRISHNAN[4], R. SHI[5];
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Abstract: Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide, with no established treatment. Common in war zones, blast induced TBI (bTBI) presents a significant clinical challenge, as most bTBIs are mild (mbTBI), and therefore difficult to detect. Furthermore, the mechanisms of how mbTBI affects neuronal firing remain unclear, rendering treatment difficult. In particular, it is unclear how injury affects the organization of synchronous network activity and bursting dynamics necessary for behavioral responses. To fill this knowledge gap, properties of synchronous neuronal activity were quantified from microelectrode array recordings of primary mouse cortical neuronal cultures subject to mbTBI. While mbTBI did not abolish coordinated population activity (bursts), analyses with greater temporal and cellular resolution revealed substantial changes in network organization that were not apparent from burst occurrence alone. Following injury, fewer neurons participated in each burst and

individual bursts contained markedly fewer spikes, indicating reduced propagation of activity across the network. Synchronization analyses demonstrated less-consistent cell participation in bursts and less-consistent firing behavior relative to bursts. However, the extent of these changes varied between cultures, revealing that burst dynamics in different cell populations can exhibit differential vulnerability to injury. The first or last cell to fire in a burst (burst starter or ender, respectively) was not random before or after injury. However, injury altered the probability that cells behaved as burst starters or enders. Cells that exhibited lower, but nonrandom, probability of being burst starters or enders before injury exhibited higher probability of starting or ending a burst after injury, suggesting that mbTBI amplifies preexisting organizational tendencies and increases functional specialization within the networks. Together, these findings demonstrate that mbTBI induces a substantial reorganization of synchronized neuronal network dynamics characterized by reduced cell participation, diminished burst spike count, altered synchronization, less-consistent firing behavior relative to bursts, and the concentration of functional roles into specific neuronal subpopulations. These results highlight that rhythmic activity is altered in a consistent manner after mbTBI, opening avenues for future mechanistic investigation and potential therapeutic targeting to mitigate pathology after mbTBI.

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Poster

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Topic: B.07. Network Interactions

Title: 3D Neuronal Network Formation, Axonal Connectivity, and Calcium Wave Propagation Using Xeno-Free VitroGel NEURON hydrogel and VitroPrime™ 3D Culture and Imaging Plate System

Authors: *R. I COHEN[1], J. HUANG[2];
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Abstract: Understanding long-range neuronal connectivity and signal propagation requires culture systems that support spatially extended axonal growth and dendritic arborization in a physiologically relevant 3D microenvironment. Brain organoids, while informative for studying developmental events, grow as enclosed spheroidal masses in which neurons are radially confined, preventing organized projections to external targets and limiting network connectivity to the spheroid interior. These geometric constraints preclude the study of long-range signal transduction and coordinated network activity across biologically meaningful distances. To address these limitations, we utilized the VitroPrime™ 3D Culture and Imaging Plate system in 96-well, 24-well, and 6-well formats to culture human iPSC-derived neurons embedded in xeno-

free VitroGel® NEURON hydrogel within an open 3D matrix. The VitroPrime™ platform's proprietary sample-anchoring design eliminates gel floating, rotation, and displacement during routine media exchange, while a lateral side channel permits 100% media change without direct contact with the 3D sample, preserving gel integrity and fixed spatial coordinates across weeks of culture. This zero-disruption workflow enabled repeated longitudinal imaging of identical neuronal fields using the #1.5 glass-bottom surface, compatible with confocal microscopy, widefield fluorescence, and automated high-content screening platforms. Neuronal cultures in the 24-well format developed axonal tracts and dendritic processes traversing several millimeters within the hydrogel matrix. Unlike organoid systems where calcium signaling is restricted to the spheroid interior, this open-matrix architecture permitted real-time imaging of calcium wave propagation across the full extent of these millimeter-scale networks using genetically encoded Ca^{2+} indicators and calcium-sensitive dyes, revealing coordinated activity patterns consistent with functional synaptic connectivity. The 96-well format extended these capabilities to compound screening and automated multi-parametric imaging, while the 6-well format supported bulk neural tissue production for transcriptomic profiling and biochemical analyses. Together, these data demonstrate that the VitroPrime™ system provides a scalable, imaging-compatible platform for studying neuronal network formation, long-range axonal connectivity, and signal transduction in 3D—capabilities not achievable with conventional 2D culture or brain organoid approaches.

Disclosures: R. I Cohen: None. **J. Huang:** None.

Poster

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Topic: B.07. Network Interactions

Support: NINDS 5R01NS131858-03
Whitehall Foundation
Simons Foundation

Title: Reciprocal interactions between CA1 pyramidal and axo-axonic cells control sharp wave-ripple events

Authors: *A. J. HUTCHINSON[1], E. T. GILBERT[2], C. M. BUHLER[7], L. M. KLAVER[3], K. C. ARNDT[2], J. KIM[4], X. JIA[5], J. C. BASSO[6], S. A. MCKENZIE[9], D. F. ENGLISH[8];
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Abstract: Inhibitory circuits are necessary to modulate neuronal activity and control the timing of cell assembly spiking across multiple timescales. Specifically, in the hippocampal CA1 region, there are over 20 types of GABA-ergic interneurons that help organize the spiking of pyramidal cells (PYR) during network events like sharp wave-ripples (SPW-R). SPW-Rs are required for memory consolidation and depend on the interplay between excitation and inhibition of CA1 cell assemblies. While PYR activity during SPW-Rs is well-characterized, inhibitory mechanisms remain unclear. One type of interneuron, called axo-axonic cells (AACs) are particularly interesting in that they exclusively target the axon initial segment of PYRs which enables them to powerfully control spike output. The role of AACs in SPW-Rs has been debated, largely because these cells are difficult to target and identify. To address this gap, we used optogenetic tagging of AACs along with silicon probe recordings of awake, behaving mice to monitor and manipulate AAC activity. We observed wide variability in AAC characteristics as well as in their responses during SPW-Rs. This contrasts with the consistent responses shown by typical parvalbumin-positive interneurons. Additionally, we found that AAC-PYR connectivity modulated AAC ripple involvement. Finally, optogenetic silencing of AACs led to altered SPW-R structure and PYR recruitment. These results suggest that AACs play a role in organizing cell assembly activity during SPW-Rs.

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Poster

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Topic: B.07. Network Interactions

Support: U24MH137478

Title: Characterizing the Specificity and Regulatory Activity of Layer-Specific Enhancers in Mouse Brain

Authors: *D. OGBEH[1], W. R. STAUFFER[4], V. HSIA[2], A. OFOSU[2], A. VENTRONE[3], J. AI[2]; [1]Dept. of Pharmaceut. Sci., [2]Univ. of Maryland Eastern Shore, Princess Anne, MD; [3]Univ. of Maryland Eastern Shore, Salisbury, MD; [4]Neurobio., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Deciphering complex brain functions requires a precise understanding of neural circuits at the cell-type level. However, discovering cell-type-specific enhancers remains challenging. In this study, we evaluated Adeno-associated virus (AAV) vectors engineered with machine learning-designed enhancers, originally identified via ATAC-seq from non-human primate tissue, to characterize their expression patterns in mice. Here, we packaged a layer 5-specific pyramidal neuron enhancer into AAV.PHP.eB capsids to generate a versatile delivery

library. We subsequently performed systemic injections of this enhancer-driven AAV and a control AAV - which contained the pan-neuron hSyn promoter - into separate cohorts of wild-type mice. Histological analysis demonstrated targeted neuronal labeling within the cortex and some off-target expression in other structures. Despite the off-target expression, we sought to quantify the performance in layer 5, relative to the control. This quantification revealed that the control AAV labeled 13% of layer 5 neurons, whereas the layer 5-specific enhancer L5E1 significantly enriched targeting, driving GFP expression in 29% of layer 5 neurons in the primary motor area and 50% in the primary somatosensory area. These results demonstrated that the machine learning-guided enhancer successfully enriched transgene expression within cortical layer 5. Future work will use spatial transcriptomics to identify gene expression profiles in off-target cells and use this information to refine future enhancer constructs to improve layer-specific targeting. Our goal is to validate a suite of enhancers capable at directing optogenetic construct expression to various cortical cell types and furthering cell-type- and circuit-specific neuroscience studies.

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Poster

PSTR007: Network Interactions: Other

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

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Topic: B.07. Network Interactions

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Title: Volume EM analysis of area 9 microcircuits receiving corticocortical inputs from area 10 in the marmoset prefrontal cortex

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Abstract: The prefrontal cortex (PFC), which has expanded dramatically in primates, is fundamental to higher cognitive functions. A recent mesoscale study in marmosets (Watakabe et al., 2023) reported the presence of columnar structures and their reciprocal interconnections.

However, the synaptic-level connection patterns underlying these circuits remain unexplored. To address this knowledge gap, we utilized ATUM-Blade-TEM, a large-volume electron microscopy (vEM) system, and acquired high-resolution (2.4 nm/pixel) images over a large area (1.1 × 1.7 mm²) encompassing multiple cortical columns.We aimed to visualize the synaptic connectivity between area 10 (A10; frontopolar cortex) and area 9 (A9; part of the dorsolateral prefrontal cortex) of the PFC by co-injecting anterograde and retrograde viral tracers into A10. Using Correlated Light and Electron Microscopy (CLEM), we focused our investigation on layers 2/3 (L2/3) of A9. We found that A10-originated axons directly formed synapses onto the dendrites of A9 neurons that project back to A10, providing direct synaptic-level evidence for reciprocal connectivity between these prefrontal areas.Quantitative analysis of A10-to-A9 projection targets in L2/3 revealed that approximately 90% were the spiny dendrites of pyramidal cells (comprising both apical and basal dendrites), while 10% were the aspiny dendrites of putative fast spiking basket cells (FSBCs; a specific type of inhibitory local interneuron). The FSBCs in A9 that received A10 inputs exhibited highly specific targeting locally within L2/3, with 96% of their output synapses directed onto pyramidal cells and the remaining 4% onto FSBCs (including self-connections). Furthermore, we analyzed the local axonal collaterals of the projection neurons located in L2/3 of A9 that were retrogradely labeled from A10. Their synaptic targets included pyramidal cell dendrites (63%, both apical and basal dendrites), FSBCs (35%), and putative double bouquet cells (2%), another type of inhibitory interneuron.These findings demonstrate an intricate synaptic organization where interareal inputs, local axonal collaterals, and inhibitory microcircuits are coordinated. This study provides novel insights into the structural organization of cortico-cortical communication in the primate brain. Moreover, although the current analysis was focused on L2/3, our acquired high-resolution dataset also encompasses layer 5. Future analysis of this deeper layer will help elucidate layer-specific differences in A10-to-A9 connectivity and the laminar organization of these prefrontal circuits.

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Poster

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Topic: B.07. Network Interactions

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Title: Circuit modelling of volume electron microscopy derived marmoset prefrontal cortico-cortical projections in working memory

Authors: *C. S. SOZUER[1], T. MIYAZAKI[2,3], E. TÓTH[2], N. L. KAMIJI[4,2,3], S. UPRETI[2], M. SUGA[5,3], A. WATAKABE[3], Y. KAWAGUCHI[6], R. SASAKI[2,7], V. PANDEY[8], Y. KUBOTA[2,3,4], K. SEMBA[1];
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Abstract: In the prefrontal cortex (PFC), microcircuit organization must support flexible cognition, including working memory, which is often linked to persistent firing supported by recurrent excitation. However, the cortico-cortical projections that most strongly regulate working-memory-relevant dynamics remain unclear. Using volume electron microscopy, we identified a set of bidirectional projections between Brodmann areas 10 (BA10) and 9 (BA9). These BA10-BA9 projections show highly preferential targeting by presynaptic cell type and postsynaptic compartment at the level of individual synaptic contacts. The cell type and compartment specificity of the BA10-BA9 projections suggest a specialized role rather than incidental connectivity. The functional consequences of these projections are not predictable by inspection and the targeted experimental perturbation of the connectivity of these projections is infeasible. Therefore, we use in silico circuit modeling to investigate the functional implications of the BA10-BA9 projections. Our circuit model contains reduced cortical columns representing those in BA10 and BA9 wired to support the maintenance of spatial information during delays and selectively gate different sources of information. We compare a baseline connectome that includes these projections with perturbed control connectomes that preserve overall coupling strength while changing target cell classes, dendritic compartments, reciprocity, or replacing the projections with generic interareal connectivity. For each network variant, we quantify working-memory-relevant regime properties including the ability to maintain stimulus selective activity over delays, stability, the number of simultaneously stored items, and robustness to distractor like perturbations. Together, these comparisons provide a mechanistic, testable link between interareal microcircuit structure and the circuit operations that implement working memory.

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Poster

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Topic: B.07. Network Interactions

Support: NSF Expeditions in Computing `Mind in Vitro' 2123781
NSF EFRI BEGIN OI 2515342

Title: Living Neurosheets: Engineering Readily Deployable Neural Architectures

Authors: *G. UPADHYAY[1], K. KAZEMI[2], S. KIM[4], X. ZHANG[3], H. YUAN[5], Z. DOU[6], S. KANG[2], T. SAIF[7], H. KONG[8], J. M. BEGGS[9], H. GRITTON[10], M. GAZZOLA[3];
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Abstract: Scalable engineering of neural tissues with durable, application-specific architectural control and multimodal interrogation capabilities has not been achieved. We present Living Neurosheets: practical, malleable, and modular platforms for realizing living neural architectures, bio-inspired or beyond evolutionary precedent. By innervating porous sheets, we integrate neural function into these versatile materials, leveraging their pre-programmed porosity to anchor deposited neurons for robust spatial control. Cutting, folding, and stacking allow intuitive design, modular composition, and batch fabrication (by the hundreds) of complex motifs that preserve functionality for months. Reversible integration enables sample reuse across hardware or hardware multiplexing across samples, supporting high-throughput, multimodal investigations. We demonstrate these aspects across planar topologies, gyri-inspired manifolds, and laminar cortical mimics, attaining control over fundamental dynamical features such as wave propagation, suppression, and augmentation. Utilizing portability across instruments, we tracked network maturation using high-resolution electrophysiology and spatial transcriptomics within the same tissue, linking coordinated gene programs to emergent neural behavior.

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Poster

PSTR007: Network Interactions: Other

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Program #/Poster #: PSTR007.25/U5

Topic: B.07. Network Interactions

Title: Sevoflurane Anesthesia Alters REM Sleep-Related Transcriptional Signatures in the Brainstem

Authors: N. ATLURI, D. CLARK, J. WOOTERS, **S. GANGAR**, H. OSURU, *N. LUNARDI; Anesthesiol., UNIVERSITY OF VIRGINIA, Charlottesville, VA

Abstract: Problem statement: General anesthetics are thought to reversibly induce unconsciousness, at least in part, by modulating endogenous sleep-wake circuits. Preclinical studies suggest that the anesthetic gas sevoflurane suppresses Rapid Eye Movement (REM) sleep, resulting in REM sleep debt. Consistent with this concept, our group recently demonstrated REM sleep rebound following emergence from sevoflurane anesthesia, accompanied by increased c-Fos activation in the sublaterodorsal nucleus (SLD), a brainstem region essential for REM sleep generation. Recent studies have identified the muscarinic acetylcholine receptor genes *Chrm1* and *Chrm3* as critical for REM sleep, as REM sleep is nearly abolished in mice lacking both genes. We therefore investigated the effects of sevoflurane anesthesia on REM-related transcriptional signatures within brainstem REM regulatory regions of aged mice. We hypothesized that expression of *Chrm1* and *Chrm3* would be suppressed during sevoflurane anesthesia and increased following emergence, consistent with inhibition of REM-generating circuits during anesthesia and REM rebound during recovery. **Methods:** Aged male C57BL/6J mice (17-18 months) were exposed to surgical concentrations of sevoflurane (2.8%-3.2% in 100% O_2) for 3 hours. Brains were harvested either immediately before the end of anesthesia (0 h) or 5 hours after emergence. Animals were perfused with 4% paraformaldehyde, and brains were cryoprotected in 30% sucrose before cryosectioning into 10-µm slices. Spatial transcriptomics analysis was performed using the 10x Genomics Visium HD platform. Expression of *Chrm1* and *Chrm3* within the SLD was quantified using Loupe Browser 9 software. Data are presented as Log_2 fold change relative to total gene expression within the same region of interest. **Results:** Expression of both *Chrm1* and *Chrm3* within the SLD was reduced during sevoflurane anesthesia (Log_2 value: *Chrm1* = 0.070 and *Chrm3* = -0.010*)* and increased 5 hours after emergence in aged mice (Log_2 value: *Chrm1* = 1.579 and *Chrm3* = 1.329). **Conclusions:** Two genes essential for REM sleep generation, *Chrm1* and *Chrm3*, are dynamically regulated by sevoflurane anesthesia. Their suppression during anesthesia and increased expression following emergence support the hypothesis that sevoflurane inhibits REM-generating circuits within the SLD, leading to REM sleep debt during anesthesia and compensatory activation of REM sleep pathways during recovery. These findings provide molecular evidence linking sevoflurane anesthesia to modulation of brainstem REM sleep regulatory networks.

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Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.01/U6

Topic: B.09. Glial Mechanisms

Support: NIH Grant F31NS139646

Title: Differential development of cortical astrocyte lineages

Authors: *K. MARKEY[1], A. GARCIA[2];
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Abstract: Astrocytes, a major glial cell class, are vital for central nervous system (CNS) function. They serve many roles like supporting synapse formation and function. Despite their critical role, astrocyte development following specification remains poorly understood. Our lab has shown a subpopulation of astrocyte progenitor cells (APCs) in the cortex respond to Sonic Hedgehog (Shh) signaling and express Gli1, a readout of active Shh signaling. Astrocytes derived from these progenitors are referred to as the Gli1 lineage. Gli1 lineage astrocytes makeup 50-60% of cortical astrocyte population, suggesting the cortex harbors two populations of astrocytes derived from molecularly distinct progenitor populations. Whether these two populations exhibit differential development is unknown. In order to distinguish between lineages, we used genetic fate mapping to trace Gli1 lineage astrocytes using the Gli1CreER/+;Ai14 mouse line and immunostaining with astrocyte markers like glutamine synthetase and Sox9 to label all astrocytes. We assessed whether proliferation varies between lineages. To do this we injected mice with BrdU at P0 and examined the number of marked cells within each lineage. Throughout the first postnatal week, we observed a smaller fraction of Gli1 lineage astrocytes labeled with BrdU compared to the non-Gli1 lineage. Consistent with this, fewer astrocytes within the Gli1 lineage were Ki67+. Together these data demonstrate that fewer astrocytes within the Gli1 lineage proliferate during the first postnatal week compared to the non-Gli1 lineage cells. We next examined morphology of cells at P7. Preliminary findings show Gli1 lineage astrocytes are larger and more complex than non-Gli1 lineage astrocytes, suggesting they are more mature than non-Gli1 lineage cells. Another way developing tissues achieve their mature populations is through use of developmental elimination, in the developing cortex both immature oligodendrocytes and neurons undergo apoptosis. Whether astrocytes in the cortex are eliminated is not well understood. Examination of apoptosis with cleaved caspase 3 revealed little evidence of astrocytes undergoing apoptosis during the first two postnatal weeks. Instead, we observed that at P7 microglia were engulfing astrocytes, consistent with studies in the retina. Interestingly, we observed both lineages interact with microglia, but non-Gli1 lineage astrocytes were preferentially eliminated. Together these data demonstrate the cortex harbors two astrocyte lineages that show differential developmental trajectories. Ongoing work is investigating whether manipulation of the Shh pathway disrupts lineage development.

Disclosures: K. Markey: None. **A. Garcia:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.02/U7

Topic: B.09. Glial Mechanisms

Support: 4RF1MH106490-09

Title: MicroRNA-mediated regulation of astrocyte postnatal maturation and function

Authors: ***J. HU**[1], M. BERTOLIO[2], J. M. YELICK[2], K. E. REYNOLDS[3], Y. YANG[4]; [1]Tufts Univ., boston, MA; [2]Tufts Univ., Boston, MA; [3]Neurosci., [4]Neurosciences, Tufts Univ. Sch. of Med., Boston, MA

Abstract: Astrocytes undergo a prolonged molecular and morphological maturation during postnatal development toacquire specialized functions essential for central nervous system (CNS) homeostasis. MicroRNAs(miRNAs) are key post-transcriptional regulators of gene expression and play critical roles in cellulardifferentiation and functional specialization. However, their roles in astrocyte maturation remain poorlyunderstood. We hypothesize that miRNAs, in particular miR-124-3p, regulate astrocyte maturation andfunction by coordinating developmental gene expression programs during postnatal development. Toidentify miRNAs involved in astrocyte maturation, we profiled miRNA expression in cortical astrocytesisolated from immature (postnatal 1 week) and mature mice (postnatal 5 week) using NanoString andMicroarray platforms. We identified 23 candidate developmentally regulated miRNAs. To identifydevelopmentally changed astrocytic genes that maybe be regulated by these candidate miRNAs, weperformed integrative bioinformatic analyses using transcriptomic data from published studies *(Lattke, M.,& Guillemot, F. (2022)* and our own developmental RNA-sequencing dataset. We identified genes thatcontain predicted 3'UTR binding sites for each of our 23 candidate miRNAs. Specifically, this analysisrevealed inverse relationships between miRNAs and gene expression, such that miRNAs upregulatedduring maturation were predicted to target genes normally repressed during development and vice-versa.Among these candidates, miR-124-3p emerged as a key putative regulator of astrocyte development due toits significant induction during development, predicted targeting to numerous genes that involved inastrocyte development. To explore the function of miR-124-3p in astrocyte maturation, we developed aunique astrocyte-specific, Cre-dependent miR-124-3p sponge mouse model to inhibit miR-124-3p inastrocyte by reducing glutamate transporter GLT-1 expression levels, which was previously shown can beupregulated by miR-124-3p. Validation studies confirmed efficient and astrocyte-specific spongeexpression and demonstrated reduced glutamate transporter GLT-1 expression levels. To further investigatehow miR-124-3p regulates astrocyte development, ongoing studies will utilize bulk RNAseq andproteomics studies in combination with this mouse model to identify novel astrocyte molecular pathwaysregulated by miR-124-3p. These findings identify miR-124-3p as a candidate regulator of astrocytematuration. This work establishes a framework for understanding miRNA-mediated regulation of astrocytedevelopment.

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Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

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Topic: B.09. Glial Mechanisms

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HHMI Emerging Pathogens Initiative
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Cure Alzheimer's Fund
MD Anderson Belfer Neurodegeneration Consortium

Title: Gene regulatory determinants of regional and reactive astrocyte diversity

Authors: *M. R. O'DEA, J. STEPHENS, S. A. LIDDELOW;
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Abstract: Astrocytes are molecularly heterogeneous - particularly across neuroanatomical regions in the healthy nervous system and across various reactive subpopulations in infection, injury, and disease. However, the gene regulatory mechanisms underlying this regional and reactive diversity remain poorly understood. To investigate these mechanisms, we applied paired single-nucleus RNA- and ATAC-sequencing to astrocytes from the mouse forebrain and midbrain in both healthy control animals and at multiple time points following an acute inflammatory challenge. We constructed a deep generative model of astrocyte gene expression and chromatin accessibility which disentangles homeostatic variation and reactivity-related variation into distinct latent representations. Through integration with multiple spatial transcriptomics datasets, we confirm that the predominant variation among astrocytes in healthy control animals is driven by brain region, while reactive variation in this model largely consists of a common transcriptomic and epigenomic remodeling shared across regional subtypes, with select subtype-specific differences. Using deep learning DNA sequence models of chromatin accessibility and regression models linking enhancer accessibility to gene expression, we constructed a lexicon of transcription factors and cis-regulatory elements associated with regional subtype identity and inflammation-induced reactivity. We identify modules of both shared and region-specific gene regulatory networks across astrocyte subpopulations, suggesting functional divergence may arise from combinatorial molecular programs. Together, this work enhances our understanding of the gene regulatory mechanisms underlying astrocyte regional heterogeneity, which may enable functional specialization to different anatomical niches, and further describes how transcription factors dynamically regulate reactive gene expression changes across the onset of neuroinflammation.

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Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.04/U9

Topic: B.09. Glial Mechanisms

Support: Kaufman New Initiative Research Grant KA2025-151544

Title: Differential Expression of Synapse-Specificity Gene By Drosophila Astrocytes

Authors: *S. I. LAKE[1], J. SAUNDERS[4], A. GARCIA[2], C. R. VON REYN[3];
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Abstract: Astrocytes are essential for brain development and function, with key roles in synaptic formation and refinement; however, how astrocytes shape circuit development remains poorly understood. To address this, we investigated astrocyte-like glia (ALG) in the developing visual system of *Drosophila melanogaster*, a model with developmental stages comparable to vertebrates. We completed a careful morphological analysis, making 3D reconstructions of individual ALG at 12-hour increments during mid to late pupal stages - an active window of synaptogenesis and refinement. We found that ALG begin to invade the synapse-rich neuropils at approximately 60 hours after pupal formation (h APF) and adopt distinct morphologies depending on the region they infiltrate, consistent with prior literature. Despite these morphological differences, the field largely regards optic lobe ALG as homogeneous, as no protein-level markers distinguishing them have been established. Using a recently published RNA-sequencing dataset of the developing optic lobe, we identified two clusters that highly express ALG canonical markers (e.g., *Eaat1*) while lacking markers of other glial or neuronal subtypes. The two ALG clusters show differential expression of several genes across these early invasion stages. One such gene, *dpr10*, encodes a cell adhesion molecule with well-defined roles in neuronal synaptic partner matching, but not previously described in glia. Optic lobe ALG show Dpr10 expression as early as 48h APF, with expression peaking between 72-96h APF, coinciding with ALG expansion into the neuropil and synaptic refinement. Notably, Dpr10 expression is concentrated in medulla ALG, with minimal expression in lobula complex ALG. From this, we conclude that *Drosophila* optic lobe ALG comprise spatially separable subpopulations invading distinct neuropil, labeled by Dpr10 expression. Dpr10 expression in medulla ALG suggests these cells may contribute to neuronal partner matching, and its absence in lobula complex ALG implies this role is circuit-specific. Future work will determine the function of Dpr10 in Dpr10-expressing ALG and whether it contributes to synaptogenesis and refinement during peak *dpr10* expression.

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Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.05/U10

Topic: B.09. Glial Mechanisms

Support: NIH K08NS102526
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CNCDPK12

Title: Astrocyte species identity alters neuronal network maturation

Authors: *S. ODDOYE[1], H. CHEN[1], J. GROSSMAN[2], K. MUELLER[2], N. J. MARAGAKIS[3], C. W. HABELA[2];
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Abstract: Astrocytes influence neuronal development, synaptogenesis, and network excitability. There are species-specific differences between human and rodent neuronal network development. However, the extent to which astrocytes drive the species-specific differences in neuronal maturation and network organization remains unclear. In this study, we used a multielectrode array (MEA) co-culture system to assess the species-specific role of astrocytes in network maturation. We compared the electrophysiologic maturation of rat hippocampal neuronal cultures grown in the absence of additional astrocytes or with either human induced pluripotent stem cell (iPSC)-derived astrocytes or cultured rat hippocampal astrocytes. Longitudinal extracellular recordings were acquired, and twenty-two standard spike, burst, and synchrony metrics were tracked over time. A multivariate network state was summarized using principal component analysis (PCA). PC-space trajectories were used to visualize condition-specific maturation. Euclidean distances and cumulative movement through PC-space were used to quantify network reorganization over time. Rat neurons alone showed an early shift away from a high-activity network state and progressive loss of analyzable wells over time, suggesting reduced long-term maintenance of robust electrophysiological activity. In contrast, rat neurons co-cultured with astrocytes maintained more organized developmental trajectories in PCA space. Rat astrocyte co-culture supported stronger early and mid-development activity-related signatures, whereas human astrocyte co-culture followed a distinct trajectory characterized by more sustained network organization, synchrony-related features, and improved long-term retention of electrophysiologically active wells. Multivariate statistical testing confirmed that astrocyte composition, developmental time, and interaction significantly shaped PCA-space organization. This study indicates that astrocyte identity alters both network state and developmental trajectory in a species-specific manner and suggests that differences between human and rodent neuronal development are at least in part driven by astrocyte influences on neuronal and network maturation.

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Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

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Program #/Poster #: PSTR008.06/U11

Topic: B.09. Glial Mechanisms

Support: NIH NINDS R01 NS134491-01
NIH NIGMS
DE INBRE

Title: Astrocyte Genetic Background Shapes Neuronal Network Activity: Implications for Epilepsy

Authors: *V. A. TALABATTULA[1], M. KHALIFE[2], M. MAHONEY[3], R. SCOTT[1], A. E. HERNAN[4];
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Abstract: The emergence of synchronized neuronal network activity is a key feature of brain development and underpins complex behaviors. Although neuronal interactions are typically considered the primary drivers of this process, astrocytes are now recognized as active regulators of synaptic connections. Our current study used a "common garden" approach to determine whether the genetic background of astrocytes can change the functional output of identical neurons. We cultured C57BL/6 (B6) neurons on monolayers of astrocytes derived from four different mouse strains: B6, WSB, 129S, and CAST. We evaluated functional maturation using multi-electrode array (MEA) recordings at three important developmental stages: DIV 7, 14, and 21. Our results show that the astrocyte’s genotype controls the major aspects of neuronal network synchronization, including frequency, intensity, and spatial recruitment of population burst activity. B6 astrocytes drive the development of population bursts that increase in frequency over days in vitro and are supported by a network that is driven by hub neuronal firing and high functional efficiency. CAST-derived astrocytes acted as "Master Synchronizers," supporting higher burst frequencies and greater spatial recruitment across the array. These networks also displayed longer burst durations, indicating a highly connected synaptic architecture. WSB astrocytes resulted in a fragmented network with localized synchronization, whereas 129S backgrounds failed to support significant maturation. The differences in these functional profiles were most pronounced between DIV14 and DIV21, highlighting a critical window for astrocyte-driven network activity. These variations likely stem from strain-specific differences in astrocytic potassium buffering, glutamate transport, and secretion of synaptogenic factors. Such insights offer a new molecular framework for understanding neurodevelopmental disorders like epilepsy and autism, where network synchrony is often disrupted. In the end, this research shows that astrocytes are not just supportive cells but are key architects of the brain's functional development.

Disclosures: V.A. Talabattula: None. **M. Khalife:** None. **M. Mahoney:** None. **R. Scott:** None. **A.E. Hernan:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.08/U13

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01NS12650

Title: Sphingosine-1-Phosphate Receptor 1 Regulates Competition Dependent Astrocyte Morphogenesis and Tiling in Murine Cortex

Authors: *J. GONZALES;
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Abstract: Astrocytes are highly abundant in the mammalian brain and coordinate with neurons and other glial cells to regulate the organization and function of neural circuits, synaptic function, blood-brain barrier integrity, and many other processes to maintain proper brain homeostasis. Astrocytes perform most of these functions owing to their highly complex morphologies and hundreds of thousands of fine processes that are important in contacting neuronal synapses and other glial cells. In fact, the morphological complexity of astrocytes is regulated by the presence and activity of neurons and helps establish astrocyte territory/tiling in a non-overlapping pattern; however, the mechanisms of astrocyte tiling are not well characterized. Using a human astrocyte-mouse neuron coculture system, we previously showed that sphingosine-1-phosphate receptor 1 (S1PR1) regulates astrocyte morphogenesis in a neuronal contact dependent manner. In this study, we find that S1PR1 regulates astrocyte morphogenesis in vivo. Using astrocyte-specific S1PR1 knockout mouse models and adeno-associated viral labeling methods, we show that S1PR1 is crucial in establishing competition driven astrocyte tiling and morphogenesis in the developing brain. Furthermore, we show that JAK-STAT3 signaling regulates neuronal contact induced expression of S1PR1 in co-cultured astrocytes. These studies therefore uncover a lipid signaling receptor as a major regulator of astrocyte morphogenesis and tiling within the murine cortical layers.

Disclosures: J. Gonzales: None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

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Topic: B.09. Glial Mechanisms

Support: Aligning Science Across Parkinson's (ASAP-020607)
HHMI Investigator funding to C.E.
NIH T32 HD040372

Title: Retromer protein Vps35 controls astrocyte morphogenesis through regulation of Nlgn2 surface localization

Authors: *N. BROSE[1], K. SAKERS[2], R. BAUMERT[2], J. SKINNER[2], C. EROGLU[2];
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Abstract: Astrocytes, the most abundant glial cells in the brain, directly contact and regulate synapses through specialized structures known as perisynaptic astrocyte processes (PAPs). These PAPs enable bidirectional signaling between astrocytes and neurons via cell-adhesion proteins, which tightly regulate both neuronal and astrocyte development. Despite its critical function in membrane protein recycling, the role of the retromer complex in astrocyte morphogenesis in response to neuronal contact remains unknown. Here, we identify Vps35, the core cargo-recognition component of the retromer, as a critical regulator of astrocyte morphogenesis by regulating neuroligin-2 (Nlgn2) localization.
Using postnatal astrocyte labeling by electroporation in the developing cortex, we found that Vps35 depletion significantly reduced astrocyte complexity, as assessed by 3D Sholl analysis. This phenotype was recapitulated in a simplified primary astrocyte-neuron coculture system, indicating the necessity of Vps35 for neuron-contact-induced astrocyte morphogenesis. Genetic interaction experiments in co-culture demonstrated non-additive effects with Nlgn2 depletion, suggesting that the two proteins may operate within a shared pathway. Supporting this model, co-immunoprecipitation in a heterologous cell system revealed an interaction between Vps35 and Nlgn2. Furthermore, using a combination of molecular modeling and biochemical approaches, we found that this interaction was strengthened by the E3 ubiquitin ligase Nedd4l, a protein that is essential for proper astrocyte morphogenesis and Nlgn2 stability. Loss of Vps35 and Nedd4l in co-culture also produced a non-additive morphogenesis phenotype, placing Vps35 within the Nedd4l-Nlgn2 morphogenesis pathway. Finally, surface-biotinylation experiments in N2A cells demonstrated that Vps35 loss severely reduced surface-localized Nlgn2, indicating that Vps35 controls Nlgn2 availability at the cell surface.
Together, these findings establish Vps35 as a critical regulator of astrocyte morphogenesis and support a model in which Vps35 regulates Nedd4l-linked trafficking of Nlgn2 during astrocyte-neuron interactions.

Disclosures: N. Brose: None. **K. Sakers:** None. **R. Baumert:** None. **J. Skinner:** None. **C. Eroglu:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

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Topic: B.09. Glial Mechanisms

Support: NIH DP2NS136873
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UNC Neuroscience Center T32
NIH 1F31NS145447-01A1

Title: Astrocyte-specific Ptprz1 deletion impairs perineuronal net structural development in the mouse cortex

Authors: *H. E. SPENCE-OSORIO[1], S. RHOADS[3], G. G. GOLE[2], K. T. BALDWIN[4]; [1]Neurosci. Ctr., [2]The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Univ. of North Carolina Chapel Hill, Chapel Hill, NC, ; [4]Cell Biol. and Physiol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Perineuronal nets (PNNs) are highly specialized extracellular matrix structures associated with critical period closure in the cortex. PNNs are primarily comprised of secreted chondroitin sulfate proteoglycans (CSPGs) bound to a hyaluronan backbone. Astrocytes secrete many of these CSPGs, produce enzymes important for PNN remodeling, form tripartite synapses within the PNN matrix, and directly facilitate closure of the visual critical period by promoting PNN maturation. Despite these known roles for astrocytes in PNN development, the molecular mechanisms regulating direct interactions between astrocytes and PNNs remain critically understudied. To address this knowledge gap, we used our recently developed, astrocyte-specific *Ptprz1* conditional knockout (cKO) mouse model to investigate the role of astrocytic protein tyrosine phosphatase receptor Z 1 (PTPRZ1) in PNN development. The secreted isoform of PTPRZ1, phosphacan, is a critical PNN component and more abundantly produced by astrocytes than any other brain cell type. We conducted a detailed structural analysis of PNNs in sex-matched pairs of male and female *Ptprz1* WT and cKO mice at postnatal day 56 (P56) using super-resolution 3D stimulated emission depletion (STED) microscopy and our custom, open-source multivariate image analysis pipeline. We identified significant structural differences in *Ptprz1* cKO PNNs compared to control mice across cortical regions and in the hippocampus at P56, indicating astrocytic PTPRZ1/phosphacan is broadly required for PNN maturation. We also found decreased astrocyte-PNN association in *Ptprz1* cKO mice, indicating PTPRZ1 is required for direct astrocyte-PNN interactions. To characterize the time course of the observed phenotype, we examined PNN structure at the earliest developmental timepoints where nascent PNN structures are identifiable. Intriguingly, we found significant structural differences in *Ptprz1* cKO PNNs at these timepoints, along with increased intensity of the PNN marker WFA. Collectively, these results characterize PNN structural phenotypes following ablation of *Ptprz1* in astrocytes, the significant source of PTPRZ1/phosphacan in the developing brain. We present PTPRZ1 as a molecular regulator of astrocyte-PNN interactions with a potential role for regulating critical period closure by controlling the time course of PNN development. Ongoing work aims to identify the molecular mechanisms governing astrocytic PTPRZ1 regulation of PNN development and determine whether the visual critical period remains open into adulthood in *Ptpz1* cKO mice.

Disclosures: H.E. Spence-Osorio: None. **S. Rhoads:** None. **G.G. Gole:** None. **K.T. Baldwin:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

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Support: NIH NIMH R01 grant (R01 MH132556)
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Brain Research Foundation grant to X.Y.

Title: Cell-specific proximity proteomics reveals astrocyte-intrinsic and astrocyte-neuron interface mechanisms in the medial prefrontal cortex

Authors: *H. DU[1], Y. TAN[2], E. KIM[3], J. V. SWEEDLER[4], X. YU[5];
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Abstract: Astrocytes are among the most abundant resident glial cells in the central nervous system (CNS) and establish intimate, highly organized interactions with neurons throughout the brain. In the mature brain, astrocytes express numerous transporters, ion channels, and receptors that are essential to monitor, integrate, and regulate neuronal activity. Astrocyte dysfunction has been implicated in a wide range of CNS disorders, yet the molecular mechanisms underlying astrocyte signaling and astrocyte-neuron interactions remain incompletely understood. Defining the protein components that support astrocyte cell-autonomous functions and astrocyte-neuron communication is therefore essential for understanding both normal CNS physiology and disease mechanisms. Here, we developed two cell-type-specific proteomic strategies based on TurboID-mediated proximity biotinylation to profile protein composition within astrocytes and at the astrocyte-neuron interface. Using these approaches, we characterized astrocyte cytosolic proteomes and astrocyte-neuron interface proteomes in the medial prefrontal cortex (mPFC). Our proteomic analyses revealed cell-specific changes in protein expression within mPFC astrocytes and at astrocyte-neuron contact sites following suppression of astrocyte calcium activity. Proteins related to neurotransmitter regulation, vesicular transport and core astrocyte functions were detected in astrocyte cytosolic proteome. Excitatory neuron proteins and inhibitory neuron proteins were identified in astrocyte-neuron interface proteome and exhibited heterogeneous alteration. We also identified many disease-associated proteins and genetic risk factors in our proteomics analysis. Together, these findings establish proximity labeling-based proteomic

approaches for dissecting astrocyte-intrinsic and astrocyte-neuron interface molecular landscapes *in vivo*. Our data provide new insight into the molecular mechanisms by which astrocytes regulate neuronal activity through both cell-autonomous and non-cell-autonomous pathways.

Disclosures: H. Du: None. **Y. Tan:** None. **E. Kim:** None. **J.V. Sweedler:** None. **X. Yu:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.12/U17

Topic: B.09. Glial Mechanisms

Title: Neuronal activity regulates expression of astrocytic AMPA receptors

Authors: *J. KOVALSKI[1], A. CARPER[1], A. GARCIA[2];
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Abstract: Astrocytes are an important glial cell type in the brain that are intimately associated with synapses and shape synaptic communication. How neural activity influences this interaction is not well understood. In neurons, AMPARs facilitate rapid excitatory synaptic transmission and are dynamically regulated in response to activity, resulting in a stronger synapse. Interestingly, AMPAR are also found on astrocytes. Whether astrocyte AMPAR (aAMPAR) expression is modified by activity is unknown. In this study, we investigated the role of experience in aAMPAR expression in cortical astrocytes and the underlying molecular mechanisms. We first investigated subunit expression in cortical astrocytes using RNAScope. We found expression of *Gria1* and *2*, but not *Gria3*. To understand if aAMPAR expression changes after experience, mice were exposed to 4 days of whisker stimulation (WS). We found an increase in *Gria2*, but not *Gria1*, suggesting astrocytes can dynamically alter their AMPAR expression in response to activity, in a subunit specific manner. To investigate the mechanism underlying activity-dependent regulation of aAMPAR, we investigated a novel gene, *Luzp2*, encoding a leucine zipper protein of unknown function. We examined LUZP2 expression in the adult cortex by immunostaining and RNAScope and found that its expression is astrocyte specific. Interestingly, we found that cortical astrocytes significantly upregulate *Luzp2* expression after 2 hours of enriched environment (EE) exposure, demonstrating rapid upregulation in response to neuronal activity, but returns to baseline by 4 days. We injected virus carrying shRNA against *Luzp2* with a GFP reporter under control of the GFAP promoter into the lateral ventricles of mice at postnatal day 0 (P0). We performed 3D reconstruction of individual GFP-labeled cells with Imaris and evaluated immunostaining for aAMPARs in the somatosensory cortex. We found an increase in GluA2, but not GluA1, in cortical astrocytes, suggesting *Luzp2* negatively regulates aAMPARs, in a subunit-specific manner. Interestingly, *Luzp2* harbors the GLI consensus sequence, suggesting direct regulation by the molecular signaling pathway, Sonic hedgehog (SHH). Consistent with this, we observed an increase in astrocytic LUZP2 at both the RNA and protein level, suggesting that SHH signaling negatively regulates its expression. Taken together,

these data demonstrate that cortical astrocytes express AMPARs characterized primarily by GluA1 and GluA2 subunits that are selectively regulated by experience. Ongoing work is examining the role of Shh signaling and Luzp2 in regulation of aAMPARs at baseline and after experience.

Disclosures: J. Kovalski: None. **A. Carper:** None. **A. Garcia:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

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Topic: B.09. Glial Mechanisms

Support: Department of Veterans Affairs Merit Award: BX005403 (MLR)
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Title: Quantifying astrocyte-synaptic coupling in STED super-resolution tripartite synapse images: a comparison of methods

Authors: *Y. HUANG[1], O. COULTER[2], A. WALLS[3], M. JONES[3], N. KUMAR[3], W. C. RISHER[4], M.-L. RISHER[5];
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Abstract: Synaptic structural dynamics are an important indicator of cognitive function, maturation, and health. In a tripartite synapse, a peripheral astrocyte process (PAP) ensheathes the pre- and post-synaptic neuron terminals (e.g., axons and dendrites, respectively), an arrangement critical for synaptic maintenance and efficient astrocyte-neuron communication. Studying this astrocyte-synaptic coupling is therefore essential for understanding synaptic function, but a consistent method to reliably quantify these occurrences is still lacking. In standard confocal images, the overlap between fluorescently labeled synaptic components is commonly quantified, but it is a result of the limited resolution of traditional light microscopy rather than true colocalization, and thus does not accurately represent the proximity between PAP and synaptic terminals. Moreover, this method is no longer suitable for images taken with super-resolution techniques, such as stimulated emission depletion (STED) microscopy, since there is often no overlap due to the improved resolution. Here, we used two methods to quantify a set of 3-channel fluorescent STED images of tripartite synapses in the ventral and lateral OFC of mouse brain sections. One is a manual quantification method, and the other is a batch-processing ("batch") method based on SynBot (Savage et al., 2024), a machine learning-based ImageJ macro for quantifying synaptic colocalization. In the images, pre-synapses, post-

synapses, and PAPs are fluorescently labeled (tagging Bassoon, PSD-95, and Ezrin, respectively). In the manual method, the analyst locates a trio of PAP, pre-, and post-synaptic puncta within a 1 μm diameter range. Linear ROIs are drawn to measure the distances from the center of the PAP to both the pre- and post-synapses, which are averaged as a measurement of proximity. In the batch method, puncta are detected automatically by SynBot, and their XY coordinates on the raw image are extracted. A batch-processing script uses the coordinates to find the closest neighboring post-synapse and PAP around each pre-synapse within a 1 μm diameter range. Proximity is calculated using the coordinates similarly to the manual approach, processing the entire image dataset at once. Though validation of the batch method is still ongoing, preliminary results support this approach as a high-throughput, unbiased method for quantifying astrocyte-synaptic coupling in 3-channel STED images. This work is supported by the National Science Foundation under Cooperative Agreement No. OIA-2242771.

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Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.14/U19

Topic: B.09. Glial Mechanisms

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NKFIH EXCELLENCE program 151377

Title: STORM super-resolution imaging of monoacylglycerol lipase in ultrathin astrocytic processes

Authors: M. ZÖLDI[1], ***I. KATONA**[2];
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Abstract: Astrocytes influence neural circuit function through molecular mechanisms that operate across highly specialized subcellular domains. Yet, these mechanisms remain far less accessible than those of neurons because much of astrocytic signaling occurs in extremely fine processes, often only ~10-100 nm wide, that are intricately interdigitated with synapses and other cellular elements. This structural complexity has limited the ability to assign molecular signals to defined astrocytic compartments and to quantify them at the scale at which many signaling events are organized. To address this limitation, we developed a single-molecule localization microscopy workflow for nanoscale molecular imaging of individual astrocytes in intact hippocampal circuits. Using postnatal electroporation to sparsely tag the plasma membrane, we achieved selective labeling of hippocampal astrocytes in mice and visualized their complete arborization with nanoscale precision by stochastic optical reconstruction microscopy (STORM).

We combined this labeling strategy with practical analytical pipelines for segmentation, compartmental measurement, quantitative analysis, and visualization of molecular distributions within astrocytic territories. We validated the approach by dual-color STORM imaging, demonstrating that molecular signals associated with astrocytic processes can be distinguished from neighboring synaptic proteins despite the dense organization of the neuropil. We then applied the workflow to monoacylglycerol lipase (MAGL), a lipid-metabolizing enzyme that regulates synaptic plasticity in neurons and links endocannabinoid signaling to prostaglandin-mediated inflammatory pathways in astrocytes. This analysis revealed cell-type-specific differences in MAGL distribution and provided evidence for a synapse-independent nanoscale organization of the astrocytic MAGL pool. Together, these results establish a robust and accessible strategy for quantitative molecular mapping within ultrathin astrocytic processes. More broadly, they provide a framework for investigating how nanoscale molecular architecture in astrocytes contributes to circuit function, lipid signaling, and neuroinflammatory regulation.

Disclosures: M. Zöldi: None. **I. Katona:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

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Program #/Poster #: PSTR008.15/U20

Topic: B.09. Glial Mechanisms

Support: P01 AG078116

Title: Promoters and payload affect astrocyte specific targeting using AAV vectors

Authors: *K. S. ZULUAGA OSORIO[1], E. B. RUCKER, III[2], C. B. ROGERS[3], C. M. NORRIS[3];
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Abstract: Astrocytes are commonly manipulated in vivo using adeno-associated viral vectors (AAVs) combined with astrocyte-enriched promoters. Because AAV tropism alone does not ensure astrocyte-selective expression, the field frequently relies on regulatory elements derived from the glial fibrillary acidic protein (GFAP) gene, including the widely used Gfa2 and Gfa104 promoter variants. However, promoter activity may be influenced by vector backbone, transgene payload, regulatory context, and interactions between co-delivered AAV constructs, raising the possibility that GFAP-based promoters alone may not reliably ensure astrocyte-specific expression. In our initial validation studies, intrahippocampal delivery of AAV-Gfa2-eGFP produced predominantly astrocytic reporter expression, consistent with the expected activity of GFAP-derived promoters. However, when the reporter payload was replaced with Cre recombinase, both AAV-Gfa2-Cre and AAV-Gfa104-Cre showed Cre expression in astrocytes and neurons. These findings suggested that off-target neuronal expression may reflect a payload-

dependent effect associated with Cre expression. To directly evaluate whether miRNA-based detargeting could improve astrocyte-enriched expression in this context, adult wild-type mice received intrahippocampal co-injections of AAV-Gfa2-eGFP together with either AAV-Gfa2-Cre or AAV-Gfa104-Cre-4x6T which is a miRNA detargeting cassette. When cloned into the 3′ UTR of the transgene, the cassette is designed to target viral mRNA transcripts for degradation in neurons and endothelial cells, thereby enriching transgene expression in astrocytes. In the co-injection experiments, eGFP-positive cells were detected in both astrocytes and neurons when AAV-Gfa2-eGFP was combined with AAV-Gfa2-Cre, suggesting that cells co-transduced by the Cre-expressing vector can include neuronal populations when the 4x6T cassette is absent. In contrast, co-injection of AAV-Gfa2-eGFP with AAV-Gfa104-Cre-4x6T resulted in predominantly astrocytic eGFP expression, consistent with reduced off-target expression in neurons and endothelial cells through miRNA-mediated degradation of viral transcripts. Together, these findings demonstrate that astrocyte specificity is not determined solely by promoter identity and can be substantially influenced by transgene payload. Our results emphasize the need for empirical validation of newly generated AAV reagents and support previous work (Gleichman et al, 2023) showing that the combination of GFAP-derived promoters with miRNA detargeting enhances astrocyte-enriched expression in vivo.

Disclosures: K.S. Zuluaga Osorio: None. **E.B. Rucker:** None. **C.B. Rogers:** None. **C.M. Norris:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

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Topic: B.09. Glial Mechanisms

Support: NIH AG027297
NIH AG078116

Title: Astro^{On} and Astro^{Off}: Novel doxycycline-based knock-in mouse lines for astrocyte specific gene induction and knockout studies

Authors: *E. B. RUCKER[1], K. S. ZULUAGA OSORIO[1], C. B. ROGERS[2], S. D. KRANER[1], B. E. WEISS[3], J. L. GOLLIHUE[3], C. M. NORRIS[2];
[2]Sanders-Brown Ctr. on Aging, [3]Sanders Brown Ctr. on Aging, [1]Univ. of Kentucky, Lexington, KY

Abstract: To adequately interrogate established mouse models for neurological diseases and disorders, there is an unmet need to have an inducible system for performing either transgene overexpression or gene knockouts *in vivo* within distinct cell populations in these models. Astrocytes are structural and foundational cornerstones of the central nervous system, essential for maintaining synaptic connections, the blood-brain barrier, and metabolic homeostasis.

However, most astrocyte-specific transgenic lines are based on random integration events of the transgene cassette, which traditionally exhibit position-dependent effects and unanticipated expression in ectopic tissues. Moreover, use of promoters, like Aldh1l1, may be well suited for targeting all astrocytes, but less suitable when research questions involve reactive, $GFAP^{+}$-astrocytes specifically. To circumvent these issues and develop cell- and temporal-specific genetic models, we have generated a suite of transgenic lines called "$Astro^{On}$" and "$Astro^{Off}$" mice, based on the $GfaABC_1D$ promoter and third generation Tet-On3G system. The CRISPR-Cas9 system was used to knock-in transgenic cassettes into the *Col1a1* safe-harbor locus at an intergenic region on mouse chromosome 11. Nine distinct knock-in lines were made built on the third-generation tetracycline-system (i.e. reverse tetracycline transactivator rtTA or "TetOn3G"; tetracycline responsive element "TRE3G") for astrocyte-specific overexpression in $Astro^{On}$ mice or gene deletion in $Astro^{Off}$ mice. The *Col1a1-GfaABC$_1$D-TetOn3G-4x6T miR* line contains a glial fibrillary acidic protein (GFAP) promoter paired with a miRNA cassette in the 3' UTR of the rtTA transcript to detarget expression in neurons and endothelia. The $Astro^{On}$ model couples the TetOn3G and a novel TRE3G-GOI (gene of interest) line, while the $Astro^{Off}$ uses the TetOn3G and novel TRE3G-Cre bred into a loxP 'floxed' line. Doxycycline administration in either model induces expression of the TRE3G-based transgene. $Astro^{Off}$ mice were bred into the Ai9 reporter line containing a CMV promoter-loxP-STOP-loxP-dtTomato and treated with doxycycline water (2 mg/ml; 5% sucrose) for two weeks. Analysis of brains from $Astro^{Off}$; $Ai9^{+}$ mice showed widely distributed astrocyte-specific tdTomato expression in cortex that co-localized with GFAP expressing cells. Moreover, tdTomato expression was not found in neurons as determined by NeuN staining. These results demonstrate that these lines can be used to genetically manipulate astrocytes to understand their roles in normal biological contexts as well as disease states.

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Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

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Program #/Poster #: PSTR008.17/U22

Topic: B.09. Glial Mechanisms

Support: NIH R61 AG094651
NIH R01 NS129888

Title: Characterization of a magnetogenetic approach for control of astrocyte calcium signaling

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Abstract: Although growing evidence indicates that astrocytes modulate synaptic function via calcium-dependent transmitter release (e.g., ATP, glutamate, GABA), a causal link between astrocytic calcium elevations, gliotransmission, and synaptic activity remains missing. This gap is largely due to the inability to precisely manipulate astrocyte calcium signaling in freely moving animals. Here, we characterized the use of FeRIC, a wireless and noninvasive approach to control astrocytic calcium signaling using radiofrequency (RF) magnetic fields. In FeRIC, recombinant calcium-permeable TRPV4 channels are coupled with endogenous ferritin, enabling their activation with RF. We characterized the RF-induced calcium responses in cultured hippocampal astrocytes expressing $TRPV4^{FeRIC}$ using GCaMP6 variants targeted to the cytosol (cyt-GCaMP6), the plasma membrane (Lck-GCaMP6), and the endoplasmic reticulum (ER-GCaMP6). RF induced astrocytic calcium increases in all examined subcellular locations with variations in the kinetics and patterns across the distinct GCaMP6 variants. Cyt-GCaMP6 resolved prominent responses at the soma, whereas Lck-GCaMP6 did not capture somatic elevations. The amplitude of astrocytic calcium responses depends on the RF duration and strength, with longer RF exposure or larger RF amplitude yielding larger calcium elevations. Moreover, RF-induced calcium responses require calcium influx through TRPV4 channels, as a TRPV4 antagonist and removal of extracellular calcium blocks the RF effects. Additionally, these calcium increases are amplified by ER calcium release, as depleting ER calcium stores with thapsigargin or blocking ryanodine receptors reduced the amplitude of RF-induced responses. In conclusion, our results demonstrate that magnetogenetic activation of TRPV4FeRIC-expressing astrocytes provides efficient control over astrocytic calcium signaling. The noninvasive nature of RF stimulation, combined with its ability to penetrate deep tissues and be applied in freely moving animals, makes this approach well-suited for investigating the role of astrocytic calcium signaling in the regulation of synaptic activity.

Disclosures: E. Stauffenberg: None. **M. Hernandez-morales:** None. **C. Liu:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.18/U23

Topic: B.09. Glial Mechanisms

Support: NIH 5R01NS118747-05

Title: In vivo approaches to study astrocyte exosome signaling and proteomics in the CNS

Authors: *M. BERTOLIO[1], Y. YANG[2];
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Abstract: Astrocytes regulate central nervous system (CNS) development, homeostasis, and pathology, partly via extracellular vesicle (EV) signaling such as exosomes, a small EV type (50-200 nm diameter) of endosomal origin. However, current in vitro models lack the complex

physiological morphology of mature astroglia, leaving in vivo dynamics of astrocytic exosome biogenesis poorly understood. Furthermore, profiling cell-type-specific EV protein cargoes in vivo is highly challenging due to CNS cellular heterogeneity. To address these limitations, we developed tools for visual mapping of the astrocytic endolysosomal network (ELN) and proteomic profiling of astrocyte-derived EVs directly from brain tissue. To visualize ELN distribution in vivo, we designed AAV5-GfaABC1D-DIO-hRab5smFP-Myc, AAV5-GfaABC1D-DIO-hRab7smFP-FLAG, and AAV5-GfaABC1D-DIO-hLamp1smFP-V5 constructs, fusing human early endosome (hRab5), MVB (hRab7), and lysosome (hLamp1) markers with epitope-tagged "spaghetti monster" fluorescent proteins (smFPs). Stereotaxic injection into the motor cortex of Aldh1l1-CreER+ mice followed by immunostaining and confocal microscopy revealed that hRab5smFP-myc is restricted to the soma and major processes, whereas hRab7smFP-FLAG and hLAMP1smFP-V5 show widespread distribution. We also generated PHP.eB-GfaABC1D-DIO-hRab7smFP-FLAG, demonstrating efficient delivery into the CNS via retro-orbital injection in Slc1a3-CreER+hCD63-GFPf/+ exosome reporter mice. Moreover, STED microscopy found close proximity (< 200 nm) between hCD63-GFP+ intraluminal vesicles and hRab7-FLAG+ signals, indicating the detection of MVBs. In parallel, to circumvent cell-type-specific EV isolation hurdles from complex tissues, we integrated an astroglia-specific TurboID proximity-labeling platform using Aldh1l1-CreER+TurboIDf/+ mice. Following tamoxifen and biotin administration, brain-derived EVs (BDEVs) were isolated via differential centrifugation and size-exclusion chromatography. Nanoparticle Tracking Analysis (NTA) showed a size distribution of 80-200 nm with a mean diameter of 130 nm, indicating the isolation of small EVs. Furthermore, Western blot confirmed the presence of the EV marker CD81 and the absence of the Golgi marker Golga5, demonstrating high EV purity. Finally, total BDEVs underwent streptavidin pull-down, successfully capturing biotinylated EV protein cargoes as shown by Western blot. Together, this combinatorial strategy provides a robust framework to investigate astrocytic ELN distribution and EV composition in vivo without the requirement for cell-type-specific marker isolation.

Disclosures: M. Bertolio: None. **Y. Yang:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.19/U24

Topic: B.09. Glial Mechanisms

Title: Visualizing Chronological Age of Mitochondria in Astrocytes

Authors: *F. Y. TOMANENG KIM, P. J. YAO, D. KAPOGIANNIS;
Lab. of Clin. Investigation, Natl. Inst. on Aging, Baltimore, MD

Abstract: Mitochondria are dynamic organelles that are crucial for energy production and play diverse roles in health and disease. An emerging and understudied dimension of mitochondrial

biology is mitochondrial age. Prior studies have revealed that mitochondrial age influences oxidative phosphorylation and fission-fusion balance. However, prior studies primarily focused on stem cells rather than neurons or glia, which are highly sensitive to dysfunctional mitochondria. In astrocytes, mitochondrial dynamics have been shown to control morphogenesis and neuronal support; however, mitochondrial age has never been investigated. To address this gap, we used a pulse-chase strategy for mitochondrial proteins (i.e., TOM20 and OMP25) to visualize mitochondria of two ages in primary rat astrocytes. Specifically, we labeled mitochondrial proteins present at baseline or following new protein synthesis after 24 hours. We used super-resolution confocal microscopy and quantified fluorescent signals of old and new mitochondrial proteins, normalized to the total mitochondrial signal. We identified distinct astrocyte subpopulations: most astrocytes contained mitochondria carrying a heterogeneous mixture of young and old protein, whereas a minority contained either primarily young or primarily old mitochondrial protein. This suggests different astrocytes may employ variable rates of mitochondrial biogenesis or quality control. Among astrocytes carrying mixed age mitochondrial proteins, older proteins were diffused along the mitochondrial network, whereas younger proteins localized in discrete puncta. Furthermore, we found that this spatial distribution remained consistent across astrocytic sub compartments, including the cell body and branches. Finally, we showed that astrocytic tunneling nanotubules contain a mixture of young and old mitochondria. These findings suggest astrocyte mitochondrial protein turnover is a regulated process, involving individual mitochondria rather than across the entire network. Moreover, these findings underscore the importance of investigating mitochondrial age in the context of brain cells, unlocking a new dimension of astrocyte biology. In the future, we will study potential implications for organismal aging and brain disease.
This research was supported by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH authors are considered Works of the United States Government. The findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

Disclosures: F.Y. Tomaneng Kim: None. **P.J. Yao:** None. **D. Kapogiannis:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.20/U25

Topic: B.09. Glial Mechanisms

Support: Research Council of Finland, Nos. 330776, 355256, 358049, and 373683
Pirkanmaa Regional Fund of the Finnish Cultural Foundation

Title: Cerebellar astroglial calcium signaling across scales: modeling Bergmann glial nanostructure and whole-cell dynamics

Authors: *L. KETO, T. MANNINEN;
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Abstract: Astrocytes respond to neuronal activity through calcium signals that are shaped by both nanoscale geometry and whole-cell morphology. This structure-function relationship is especially relevant in Bergmann glia (BG), specialized cerebellar astroglia whose radial stem trees and dense lateral processes constrain diffusion, buffering, and biochemical signaling. Using our CellRemorph toolkit (Keto & Manninen, 2023), NEURON (Carnevale & Hines, 2006), and ASTRO (Savtchenko et al., 2018), we constructed multiscale BG models linking nanogeometry to whole-cell calcium signaling. Developmentally distinct whole-cell BG stem trees were reconstructed from structural studies (Grosche et al., 1999; Lippman et al., 2008) and populated with two electron microscopy (EM) -derived nanogeometries based on Grosche et al. (1999) and Nguyen et al. (2023). To resolve local effects, we performed subcellular simulations across four lateral process types: stubby, thin, branching and bulbous (Lippman et al., 2008). For each process type and nanogeometry, we compared calcium diffusion and calcium-calmodulin (CaM) reaction-diffusion dynamics following focal calcium input near putative synaptic sites. At the whole-cell scale, models incorporated radial and longitudinal calcium diffusion, cytosolic buffering, membrane calcium fluxes and calcium release and uptake from endoplasmic reticulum. Results indicate that BG calcium dynamics are shaped by developmental stage, EM-derived nanogeometry, and lateral process morphology. Earlier postnatal models generated larger and more sustained transients in main and branching domains, whereas later postnatal models showed stronger peaks in bulbous microdomains. The two EM-derived nanogeometries produced distinct spatial signatures, with one accentuating calcium peaks in bulbous lateral processes and the other producing more uniform peaks across lateral process types. Subcellular simulations further indicate that lateral process geometry shapes local calcium spread and calcium-calmodulin signaling, with complex branching and bulbous morphologies producing more spatially constrained Ca4CaM patterns than simpler processes. Together, these results show how astroglial nanostructure can tune local biochemical signaling and cell-wide calcium dynamics. This framework links nanoscale cerebellar astroglial architecture to emergent BG signaling properties and enables testing how developmental remodeling shapes cerebellar information processing.

Disclosures: L. Keto: None. **T. Manninen:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.21/U26

Topic: B.09. Glial Mechanisms

Title: Activity-dependent mitochondrial dynamics in astrocytes mediated by lipid metabolism gene, Etnppl

Authors: *A. CARPER[1], A. LE[2], J. SAUNDERS[1], G. JOHN[4], S. HILL[2], E. ZEGAROWICZ[1], J. G. JACKSON[5], A. GARCIA[3];
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Abstract: Astrocytes respond to neuronal activity by changing their gene expression to regulate formation, elimination, and plasticity of synapses. Our lab has identified Sonic Hedgehog (SHH) signaling as a key mediator of activity-dependent gene expression. The SHH ligand is produced by neurons and transduced by a subset of cortical astrocytes, activating Shh-dependent gene expression. Neuronal activity increases SHH signaling, upregulating expression of synapse modifying cues, including Hevin and Sparc, and promoting synaptic plasticity. To identify novel SHH-dependent genes in astrocytes regulating synaptic function and plasticity, we performed bulk RNA sequencing between SHH-dependent cortical astrocytes actively transducing SHH and all cortical astrocytes. We identified over 500 genes that are enriched in SHH-dependent cortical astrocytes. Among these is *Etnppl*, encoding ethanolamine-phosphate phospholyase, and is involved in phosphatidylethanolamine (PE) synthesis, a phospholipid that is enriched in the inner leaflet of the mitochondrial membrane. *Etnppl* was the second most abundant gene enriched in SHH-dependent astrocytes. Previous studies have found that nuclear ETNPPL is developmentally regulated and is only present in mature cortical astrocytes. However, when we examined ETNPPL expression in the cortex we observed punctate ETNPPL. Additionally, when using a viral construct to label cortical astrocyte mitochondria, we observed close association between punctate ETNPPL localization and mitochondria. When mitochondrial function was tested in vitro by virally knocking down ETNPPL using a seahorse-based assay, there was a significant reduction in the amount of ATP produced. Astrocytic mitochondria rapidly and dynamically respond to neuronal activity by changing their subcellular localization and morphology to provide energetic support. Whether *Etnppl* plays a role in activity-dependent mitochondrial dynamics is not understood. To investigate this, we utilized viral constructs to knock down *Etnppl* and fluorescently label mitochondria in cortical astrocytes before exposing mice for two days to whisker stimulation (WS). Following WS, we found that there is a shift in the localization of the mitochondria to the distal astrocyte processes, as well as a decrease in mitochondrial volume compared to unstimulated (US) control mice. Knock down of *Etnppl* blocks the activity-dependent morphological and localization changes observed following WS. These results demonstrate that activity-dependent mitochondrial dynamics in cortical astrocytes requires SHH-dependent lipid metabolism.

Disclosures: A. Carper: None. **A. Le:** None. **J. Saunders:** None. **G. John:** None. **S. Hill:** None. **E. Zegarowicz:** None. **J.G. Jackson:** None. **A. Garcia:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.22/U27

Topic: B.09. Glial Mechanisms

Support: NIH grant R01AG081379

Title: Ttyh1 regulates glycolytic flux via organellar distribution of Hexokinase 2

Authors: *A. KENNY[1], J. BHUPANA[2,1], C. WONG[1];
[1]Rutgers University, Newark, Newark, NJ; [2]Pharmacology,Physiology and Neurosci., Rutgers, NJMS, Newark, NJ

Abstract: Tweety Homolog 1 (TTYH1) is a transmembrane protein significantly downregulated in the hippocampi of Alzheimer's Disease patients. *TTYH1* is highly expressed in brain astrocytes, a glial cell type that provides metabolic support to neurons. Little is known about TTYH1, with the United States National Institute of Health classifying it as an understudied protein. We recently demonstrated that TTYH1 mediates endolysosomal clearance of sphingolipids and facilitates macroautophagy. In *Drosophila* glia, loss of *tty,* the *Drosophila* ortholog of TTYH, promotes a shift towards glycolysis for ATP production, suggesting a potential role for TTYH1 in regulating glucose metabolism. Here, we investigate the mechanism of how TTYH1 regulates glycolysis in immortalized rat astrocytes. We found that rat Ttyh1 modulates both the expression and localization of hexokinase 2 (Hk2), the first rate-limiting glycolytic enzyme. Hk2 proteins were found to be reciprocally distributed between mitochondria and endolysosomes. Crucially, such organellar localization correlated with glycolytic activity and depended on Ttyh1 expression. Thus, glycolysis-dependent astrocytic functions were altered in the absence of Ttyh1. Our findings implicate an interplay between endolysosomal lipid processing and glucose metabolism in astrocytes.

Disclosures: A. Kenny: None. **J. Bhupana:** None. **C. Wong:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.23/U28

Topic: B.09. Glial Mechanisms

Title: A quantitative framework for visualizing glycogen distribution and mitochondrial organization in the central nervous system

Authors: *M. F. VELOZ CASTILLO[1], R. SICAT[2], C. GENOUD[3], P. J. MAGISTRETTI[1], C. CALI[4];
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Abstract: Understanding brain energy metabolism at the ultrastructural level is essential for identifying mechanisms and therapeutic targets associated with metabolic dysfunction and brain injury. Glycogen granules and mitochondria represent key morphological indicators of cellular

energy status; however, conventional tissue processing and image analysis approaches often compromise glycogen preservation and limit accurate ultrastructural characterization. Here, we present an integrated workflow encompassing tissue fixation, volume electron microscopy, and semi-automated image analysis for the study of glycogen distribution and mitochondrial organization in the brain. We evaluated focused-beam microwave (FBMW) fixation against conventional chemical fixation using volume electron microscopy datasets and quantitatively assessed ultrastructural preservation across three FBMW fixation conditions. To enable efficient nanoscale analysis, we developed a no-code segmentation workflow combining minimal manual annotation, conditional fine-tuning of publicly available deep-learning models, and targeted proofreading. This approach enabled reliable 3D reconstruction of mitochondria, glycogen granules, and myelin. FBMW fixation markedly improved glycogen preservation, detectability, and segmentation performance compared with conventional chemical fixation while maintaining good ultrastructural contrast. Among the tested conditions, FBMW fixation at 5 kW for 600 ms provided the most robust results for semi-automated segmentation and 3D reconstruction. For deep-learning assisted segmentation, the fine-tuned MitoNet model achieved the highest accuracy for mitochondrial segmentation, whereas the fine-tuned DeepLab model produced the strongest performance for glycogen and myelin segmentation. Together, these findings establish a robust workflow for integrated ultrastructural and metabolic analyses of brain tissue, enabling reliable visualization, quantification, and three-dimensional reconstruction of key energy-related cellular components.

Disclosures: M.F. Veloz Castillo: None. **R. Sicat:** None. **C. Genoud:** None. **P.J. Magistretti:** None. **C. Cali:** None.

Poster

PSTR008: Astrocytes: Development, Diversity, Structure, and Molecular Organization

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.24/U29

Topic: B.09. Glial Mechanisms

Support: NIH Intramural Research Program
NINDS
Brown University Neuroscience Graduate Program

Title: Proteomics analysis of the glial stress response in Drosophila

Authors: *A. DERMADY[1,2], J. YIN[1], Q. TIAN[1], C. LONG[1], Q. YUAN[1];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; [2]Brown Univ., Providence, RI

Abstract: Glia are important for maintaining nervous system function and homeostasis, particularly during physiological stress in both healthy and diseased states. While alterations in glial lipid metabolism are well-documented in response to stress, the cellular mechanisms mediating stress-induced lipid metabolic flux are incompletely understood. Here, we take a

proximity labeling proteomics approach to understand how the glial stress response is coordinated. We began by examining the cytoplasmic proteome of astrocyte-like glia under normal conditions, which revealed enrichment of cytoskeletal, cell signaling, and redox-related proteins, among others. About 35% of these proteins are shared with mouse astrocytes, highlighting the functional conservation between fly and mammalian glia. Further experiments will analyze the proteomes of individual organelles across various conditions to investigate how glia respond to stressors on a cellular level. To assess glial types that show a clear cellular response to metabolic stress conditions, we tested diet supplements, such as oleic acid (OA), which increases the number of lipid droplets (LDs) in the *Drosophila* larval brain. Preliminary data further suggests that astrocytes specifically form more LDs in larvae grown on OA-supplemented food, indicating a glia-type-specific response to altered dietary lipid content. Future proximity labeling experiments may reveal the protein signature of the glial stress response.

Disclosures: A. Dermady: None. **J. Yin:** None. **Q. Tian:** None. **C. Long:** None. **Q. Yuan:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.01/U30

Topic: C.01. Brain Wellness and Aging

Title: Regulation of mitochondrial activity via Hif1alpha in microglial functions during brain development

Authors: *A. CAMPOS SALAZAR[1], B. HORVATH[2], S. KUMAR[1], D. M. NGUYEN[5], Y. MARTINEZ CASTILLO[3], B. DEVLIN[2], J. DZIABIS[4], E. A. BORDT[6], C. EROGLU[7], C. S. EVANS[4], S. D. BILBO[2];
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Abstract: Systemic inflammation during critical windows of brain development can drive behavioral abnormalities. As the brain resident macrophage, microglia respond against inflammatory challenges through changes in cytokine production or synaptic pruning. In development, microglial synaptic pruning is responsible for synaptic maturation, which in turn allows to develop adequate behavior. Recently, it has been shown that impairment of mitochondria function leads to reduction in microglial phagocytosis. Following inflammation, however, both microglial synaptic pruning and mitochondria respiration in microglia are impaired. Whether mitochondrial function regulates developmental microglial synaptic refinement of circuitry responsible for adult behavior remains unknown. My data has shown that

lipopolysaccharide (LPS, 10 mg/kg i.p.) injection at postnatal day 9 leads to increase in ultrasonic vocalization at postnatal day 12 and impaired mitochondria function in cortical microglia. We hypothesize that during early development impaired mitochondrial function under inflammation impacts microglial synaptic pruning, which ultimately sculpts neuronal circuitry for proper behavior. Because changes in behavior can suggest impaired neuronal connectivity, we quantified neuronal activity using activity-dependent cFos+ labeling across the brain. We found that the anterior cingulate cortex (ACC) displayed the highest $cFos^+$ activity. In the ACC, we found that synaptic pruning of $Vglut2^+$ synapses was reduced and the number of excitatory synapses $Vglut2^+$ $PSD95^+$ were increased following LPS. Next, we found higher mitochondria function at the gene expression and functional level with increased mitochondria membrane potential in cortical microglia from LPS-treated mice. Finally, we are using a microglial-specific promoter to ablate the hypoxia-inducible factor 1α (*Hif1α*) gene, a transcriptional factor that coordinates mitochondrial and inflammatory responses in immune cells. Intriguingly, mice lacking *Hif1α* expression displayed worsening of ultrasonic vocalizations. Our data has also shown that *Hif1α inhibition* prevents the inflammatory and metabolic response after LPS by decreasing interleukin-1b and lactate dehydrogenase A gene expression, as well as the increased mitochondria functional respiration. The quantification of microglial synaptic pruning in the anterior cingulate cortex in *Hif1α*-deficient mice will allows to connect our behavioral and molecular data.

Disclosures: A. Campos Salazar: None. **B. Horvath:** None. **S. Kumar:** None. **D.M. Nguyen:** None. **Y. Martinez Castillo:** None. **B. Devlin:** None. **J. Dziabis:** None. **E.A. Bordt:** None. **C. Eroglu:** None. **C.S. Evans:** None. **S.D. Bilbo:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.02/U31

Topic: C.01. Brain Wellness and Aging

Title: Midbrain NAMPT drives sex-specific hyperlocomotion and cocaine sensitivity in mice

Authors: *S. J. VILCA[1], T. LINTZ[1], M. A. SHELTON[3], R. W. LOGAN[2];
[1]Univ. of Massachusetts Chan Med. Sch., Worcester, MA; [2]Psychiatry, Univ. of Massachusetts Chan Med. Sch., Hopkinton, MA; [3]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Neuronal metabolism and circadian rhythms have become active areas of research for psychiatric and substance use disorders. Indeed, many individuals with psychiatric disorders show comorbid metabolic and circadian rhythm dysfunction. Previous studies have shown that rhythmic expression of tyrosine hydroxylase (TH) is regulated by the interaction between core circadian gene *CLOCK* and the histone deacetylase Sirtuin 1 (*Sirt1*). Interestingly, SIRT1 activity requires the coenzyme, nicotinamide adenine dinucleotide (NAD), which is primarily produced through a salvage pathway dependent on nicotinamide phosphoribosyltransferase

(NAMPT). However, no study has examined the role of NAMPT in psychiatric disorders. Therefore, we sought to determine how knockdown of *Nampt* in dopaminergic neurons influence affective and drug-related behaviors. To this end, we generated DAT-Cre x Nampt-flox mice (Nampt +/-) and ran a battery behavioral tests: open field, light/dark box, elevated plus maze (EPM), sucrose preference, and cocaine locomotor sensitization. Our results indicate that hemizygous knockdown of *Nampt* increases locomotion across behavioral paradigms, primarily affecting females. Furthermore, *Nampt* knockdown heightens sensitivity to cocaine. Next, to increase specificity and examine drug reinforcement, we virally knocked down *Nampt* in midbrain dopamine neurons (MB^{DA}) using a TH-driven Cre and performed cocaine intravenous self-administration (IVSA) dose response. Viral-mediated knockdown of *Nampt* in MB^{DA} neurons increased sensitivity to cocaine and locomotor activity across all doses and regardless of sex. In conclusion, NAMPT may play a role in baseline and cocaine-induced locomotor activity, as well as sensitivity to cocaine, suggesting that neuronal metabolism contributes to homeostatic and drug-related behaviors.

Disclosures: S.J. Vilca: None. **T. Lintz:** None. **M.A. Shelton:** None. **R.W. Logan:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.03/U32

Topic: C.01. Brain Wellness and Aging

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DoD Grant W81XWH-22-1-0646

Title: Mitochondrial transfer from satellite glial cells to neurons protects against peripheral neuropathy

Authors: *J. XU[1], Y. LI[2], Z. YAN[2], S. BANG[3], A. MCGINNIS[2], S. CHANDRA[2], W. HE[5], C. EROGLU[6], D. VELMESHEV[4], R.-R. JI[7];
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Abstract: Primary sensory neurons in dorsal root ganglia (DRG) have large cell bodies and long axons and a high demand for mitochondria for maintaining membrane potential and firing action

potentials. Mitochondrial dysfunction has been implicated in peripheral neuropathy after diabetes and chemotherapy. However, the mechanisms by which primary sensory neurons maintain their mitochondrial supply remain unclear. Given the unique morphology of primary sensory neurons, we hypothesize that these sensory neurons require mitochondrial support from adjacent cells to maintain their normal neuronal functions. Satellite glial cells (SGCs) in DRG encircle sensory neurons and regulate neuronal activity and pain. Here we show that SGCs are capable of transferring mitochondria to DRG sensory neurons in vitro, ex vivo and in vivo by the formation of tunnelling nanotubes with SGC-derived myosin 10 (MYO10), an unconventional actin-based motor protein that plays a critical role in the formation and function of filopodia. Scanning and transmission electron microscopy revealed an enrichment of tunnelling nanotube-like ultrastructure between SGCs and sensory neurons in mouse and human DRG. Blockade of mitochondrial transfer in naive mice leads to nerve degeneration and neuropathic pain. Single-nucleus RNA sequencing and in situ hybridization revealed that MYO10 is highly expressed in human SGCs. Furthermore, SGCs from DRG of donors with diabetes exhibit reduced MYO10 expression and impaired mitochondrial transfer to sensory neurons. Adoptive transfer of human SGCs into the mouse DRG provides MYO10-dependent protection against peripheral neuropathy. This study uncovers a previously unrecognized role of peripheral glia and provides insights into small fiber neuropathy in diabetes, offering new therapeutic strategies for the management of neuropathic pain.
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PUBLICATIONS: 1.Xu, J. et al. Mitochondrial transfer from glia to neurons protects against peripheral neuropathy. Nature (2026).2.Marin, I. A. Satellite glia fuel up neurons. Nat Neurosci 29, 249 (2026).3.Im, G. B. & Melero-Martin, J. M. Borrowed mitochondria, spared neurons. Cell Res (2026).

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Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.04/V1

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant 1R01NS122800
NIH Grant 1R01NS140248
Sondra and Charles Gilman '52 Graduate Research Fellowship

Title: Mitochondrial phenotypes vary with axon myelination status.

Authors: *M. E. DOTY, S. C. WATSON, R. A. HILL;
Dept. of Biol. Sci., Dartmouth Col., Hanover, NH

Abstract: In Multiple Sclerosis and other demyelinating conditions, disability and cognitive decline are often associated with neuronal degeneration rather than demyelination alone. However, why neurons eventually degenerate in these conditions remains unclear. Myelin is canonically recognized as an insulator that supports action potential propagation along long-range projecting axons in white matter. Yet, myelin is also found on locally projecting axons in gray matter, where its purpose is less clear. Myelin can support axons metabolically, through the delivery of lactate and pyruvate. Once in the axon, lactate and pyruvate can be used by axonal mitochondria for energy production. Despite the seemingly complementary roles of myelin and axonal mitochondria, the dynamic relationship between these two structures is poorly understood. To explore this, we used SCoRe (Spectral Confocal Reflectance Microscopy) for label-free visualization of myelin, in combination with transgenic mouse lines that express cytoplasmic and mitochondrial reporters in defined neuronal subpopulations. Using these tools, we compared mitochondrial phenotypes along partially myelinated axons in layer I of the somatosensory cortex. In multiple neuron types, we found increased mitochondrial size and density in myelinated axon segments relative to paired unmyelinated axon segments. Additionally, we used intravital imaging to determine if the presence of myelin impacts mitochondrial motility and the extent to which axonal mitochondria rearrange during the formation of new myelin. These findings highlight myelin's role as a metabolic supporter of axons and provide further insights into the purpose of myelin on partially myelinated axons in gray matter.

Disclosures: M.E. Doty: None. **S.C. Watson:** None. **R.A. Hill:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.05/V2

Topic: C.01. Brain Wellness and Aging

Support: NIH/NIA T32AG078110

Title: Microglial HIF1a is necessary to restrict demyelination and neuroinflammatory sequelae in a mouse model of white matter degeneration

Authors: *S. DIMAS[1,2], J. M. MORGANTI[3,2];
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Abstract: White matter (WM) degeneration, though commonly affiliated with Multiple Sclerosis (MS), is also a feature of several neurodegenerative conditions, suggesting convergent mechanisms. Previous studies across different WM degenerative conditions demonstrate a

commonality- reactive microglial subsets differentially enriched for expression of HIF1α, a master regulator of cellular glycolytic metabolism. To determine if microglial HIF1α plays a direct role in response to WM pathology, we investigated it within the context of cuprizone mediated demyelination. We generated microglial-specific conditional knockouts of HIF1α via Tmem119CreERT2^{+} Hif1α$^{fl/fl}$ ('cKO') and their wildtype littermates: Tmem119CreERT2^{-} Hif1α$^{fl/fl}$ ('WT'). Following recombination, mice were subjected to demyelination and remyelination paradigms, with endpoints of histopathology, single-cell RNA sequencing, and spatial transcriptomics. Our findings demonstrate that compared to WT, cKO mice exhibited enhanced significant deficits demonstrated by MBP and Olig2 staining and increased microglial reactivity (CD68, Iba1, Clec7a, MHCII, Stat1). Myelin deficits persisted in the remyelination paradigm. scRNAseq revealed exacerbated disease-reactive subtypes of microglia in cKO mice, relative to WT. Using a novel 480 gene panel in our Xenium spatial transcriptomic workflow, we demonstrate the spatial accumulation of several subsets of microglia demonstrating varying heterogeneity across anatomical locales. Spatially, we observed significant accumulation of disease-reactive microglia subsets in response to cuprizone, wherein cKO mice demonstrated a dramatic accumulation of an interferon-responsive population, concurrent with histological findings. To further investigate the interplay between HIF1-mediated signaling and interferon response, we treated immortalized murine microglia with a pharmacological inhibitor of HIF1α in tandem with an IFN-β stimulus. In addition to potentially maladaptive functional and metabolic disturbances, these microglia exhibited exacerbated transcriptional interferon response after HIF1α inhibition. Taken together, our findings are the first to demonstrate HIF1α as a necessary restraint on microglial over-activation in response to cuprizone-mediated demyelination and loss of this transcription factor drives exacerbated outcomes during both demyelination as well as remyelination. These findings may point toward targeting glycolytic intermediates in microglia as a potential therapeutic to combat against WM degeneration.

Disclosures: S. Dimas: None. **J.M. Morganti:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.06/V3

Topic: C.01. Brain Wellness and Aging

Support: PID2024-162805OB-I00

Title: Infiltrating macrophages trigger lactate-driven glial lineage plasticity by eliciting a glycolytic surge in the injured brain

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Abstract: Although previous studies suggest that damage creates a permissive environment for glial lineage plasticity, since neuronal reprogramming is more efficient in the injured brain and invasive injuries that disrupt tissue compartmentalization enable cortical astrocytes to regain plasticity forming multipotent neurospheres in vitro, the molecular and cellular mechanisms linking injury, fate conversion, and dedifferentiation have remained elusive.
To address these questions, we first established reactive cultures derived from the injured mouse cortex that recapitulate key features of the injured brain (Maria Arzate D*, Alvaro V* et al. (2025). BioRxiv). We found that these reactive cultures promoted neurosphere formation from co-cultured uninjured adult cortical cells. By integrating this culture system with complementary myeloid cell models, including peripherally derived human macrophages, we identified infiltrating macrophages under injury-like conditions as the source of this endowing of a stem cell-like state to adult astroglia. This state enables multipotent neurosphere formation and fosters astrocyte-to-neuron reprogramming.
Mechanistically, proteomic profiling of macrophage-conditioned media identified macrophage-secreted proteins predicted to engage integrin signalling, including galectin-3, SPP1, GPNMB and SPARC as candidate mediators. Accordingly, the exposure to these proteins, either individually or in combination, was sufficient to induce neurosphere formation from uninjured cortical glia or senescent astrocytes, whereas the integrin antagonist CWHM-12 prevented it. Downstream, transcriptomic and metabolic analyses revealed that integrin signalling activation in astrocytes shifted cellular metabolism toward a more glycolytic state, leading to increased intracellular lactate levels. Consistently, constraining glycolysis by replacing glucose with galactose abolished neurosphere induction driven by integrin-activating proteins. Whereas exogenous lactate exposure of uninjured cortical astrocytes was sufficient to induce neurosphere formation and markedly enhanced neuronal conversion in vitro and following in vivo administration.
Together, these findings uncover an immunometabolic axis by which macrophage-derived signals from the injured brain environment induce de novo plasticity in adult astrocytes through integrin-dependent metabolic reprogramming toward glycolysis, with lactate acting as a key downstream effector of glia dedifferentiation.

Disclosures: V. Álvaro Sánchez: None. **D.M. Arzate:** None. **F. Ortega:** None. **M. Götz:** None. **B. Berninger:** None. **S. Gascón:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.07/V4

Topic: C.01. Brain Wellness and Aging

Support: PRESBYTERIAN HEALTH FOUNDATION
NIH GMS R35 GM137921

Title: Metabolic disruption reshapes cortical development following Ogdh and Ogdhl loss

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Abstract: Cortical development requires precise coordination of neural stem cell (NSC) proliferation, differentiation, migration, synaptogenesis, and circuit refinement mechanisms. These stages are highly energy dependent and require a metabolic transition from glycolysis in stem cells to oxidative phosphorylation (OXPHOS) in neurons. Disruption of this shift can impair neuronal maturation and contribute to neurodevelopmental disorders. Pathogenic variants in OGDH and OGDHL, rate limiting components of the tricarboxylic acid (TCA) cycle, have been identified in children with severe neurological impairment. The molecular mechanisms by which these mutations give rise to neurodevelopmental disorders remain poorly understood. We hypothesize that OGDH/L loss disrupts cortical development by impairing this metabolic transition, altering neuronal differentiation and migration. Using in utero electroporation of shRNA targeting Ogdh or Ogdhl at E15.5 in mice, we examined cortical development at E19.5 and postnatally. At E19.5, neither knockdown affected the transition from NSCs to intermediate progenitors, the stage at which the metabolic switch is required. However, both significantly disrupted neuronal migration, producing a twofold increase in mislocalized neurons within layers IV-VI compared to controls. This phenotype persisted at P21 in Ogdh knockdown brains but resolved in Ogdhl knockdown brains, indicating delayed yet eventual recovery in Ogdhl deficient neurons. Mispositioned neurons retained upper layer (II/III) molecular identity despite residing in deeper layers, demonstrating preserved cell type fate. A population of mislocalized neurons survived through P60, suggesting long term integration despite aberrant positioning. To identify underlying mechanisms, we are sorting electroporated E19.5 neurons for bulk RNA sequencing. Based on preliminary data, we expect OGDH/L loss to alter transcriptional programs regulating neurogenesis, with Ogdh loss producing a more pronounced effect consistent with its broader developmental expression and more pronounced long-term phenotype. Collectively our results demonstrate that Ogdh and Ogdhl loss disrupt cortical development primarily by impairing neuronal migration rather than early differentiation. Ogdh deficiency produces a more persistent phenotype, suggesting an essential role for Ogdh in metabolic regulation during corticogenesis. Ongoing transcriptomic analyses will clarify how TCA cycle dysfunction alters metabolic and gene regulatory pathways underlying these neurodevelopmental disorders.

Disclosures: K. Cizio: None. **T. Lewis:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.08/V5

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01MH129292
NIH Grant F31MH136717
Braude Foundation

Title: Identifying miRNA : mitochondrial RNA interactions using chimeric RNA sequencing

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Abstract: MicroRNAs (miRNAs) are small noncoding RNA molecules that are loaded onto an Argonaute (Ago) protein to function as guides for the RNA-induced silencing complex (RISC) to bind and regulate the expression of target RNAs, typically through repression of translation and target RNA degradation. Though putative miRNA binding sites can be identified bioinformatically, predictive approaches alone lack the ability to directly identify interactions in the endogenous setting. Advances in the field have expanded our toolkit to include Argonaute crosslinking and immunoprecipitation (Ago-CLIP) techniques, including our optimized approach termed CIMERAseq, that leverage UV crosslinking, Ago immunoprecipitation, and ligation of miRNA to their bound target RNA to allow for subsequent sequencing and analysis of miRNA:target RNA chimeras. We performed CIMERAseq on mouse forebrain homogenate and detected an unexpected abundance of miRNA interactions with RNA derived from the mitochondrial genome. It is currently unknown how miRNA and/or Ago enter mitochondria, although both RISC components are found in mitochondria in multiple tissues, including neurons. RISC function within mitochondria is currently under investigation, with existing work having reported both miRNA-dependent activation and repression of the translation of mitochondrial-encoded proteins in different settings. Because the stoichiometric balance of each mitochondrial-encoded protein with its nuclear-encoded binding partners is essential for efficient electron transport chain (ETC) function and ATP production, post-transcriptional regulation of mitochondrial genes is poised as a potential mechanism for nuclear-mitochondrial coordination. We focus our investigations on conserved miRNAs detected in our datasets as preferentially binding to mitochondrial transcripts relative to nuclear transcripts and pursue understanding of their impact on mitochondrial function and gene expression. Our ongoing research aims to address gaps in knowledge by furthering the fundamental understanding of miRNA:mt-RNA targeting, and downstream functional impacts in the central nervous system with implications for further understanding neurological development and disease.

Disclosures: E. Eiss: None. **M.K. Meffert:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.09/V6

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant U54AG090669
NIH Grant R01AG055909
NIH Grant K00AG079793

Title: Multi-omic profiling and prime editing in human iPSC-derived glial cells identifies molecular drivers of mitochondrial and lysosomal systems

Authors: *G. FOGO[1], F. M. AHSAN[2], C. R. BENOIT[2], A. J. CURLE[1], S. E. HEUER[1], G. TERZIOGLU[3], M. A. KEARNEY[2], T. L. YOUNG-PEARSE[1];
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Abstract: Mitochondrial and lysosomal dysfunction are shared hallmarks of neurodegenerative diseases, namely Alzheimer's disease (AD) and Parkinson's disease. Genome-wide association studies have identified numerous genetic variants linked to mitochondrial and lysosomal function that modify risk for neurodegenerative disease. An enrichment of these variants is found in genes highly or specifically expressed by glial cells. A critical need exists to understand the molecular drivers of mitochondrial and lysosomal systems in human glial cells to investigate their role in disease. To unbiasedly identify molecular patterns associated with these systems we performed RNA, protein, and metabolic profiling of human iPSC-derived astrocytes (iAs) and microglia (iMG). In parallel, we performed live cell imaging for mitochondrial and lysosomal systems. We profiled glial cells from ~100 human donors from ROSMAP, a deeply genotyped and phenotyped longitudinal cohort. Live cell readouts were combined with RNA sequencing, proteomics, and metabolomics to yield molecular patterns associated with each system. We identified a strong association between iA mitochondrial membrane potential and important lysosomal enzymes including the AD risk gene PLD3. Mitochondrial content was inversely associated with IFN-α/β signaling and positively associated with the AP2 endocytosis complex, suggesting how metabolic pathways differ based on glial cell functional priorities and cell states. Comparison of the two glial cell datasets also produced new insights into the cell-type specificity of these systems, with astrocytes and microglial having differential cathepsin usage in lysosomes. Current efforts are focused on using CRISPR prime editing to interrogate the directionality and causality of the identified relationships. For example, loss-of-function and AD risk variants in PLD3, along with mitochondrial disease mutations, are being engineered in human iPSC lines for the investigation of PLD3's relationship with mitochondrial function. These findings are supplemented by matched-donor multi-omics from cortical brain tissue. The addition of brain RNA sequencing, proteomics, metabolomics, and lipidomics from bulk tissue will greatly enhance the insights identified in the monoculture analyses. Together, we identified novel relationships of the mitochondrial and lysosomal systems in glial cells at the transcript, protein, and metabolite level. These cell type-specific approaches in tractable human cellular models inform both basic science mechanisms and the development of future therapeutic interventions.

Disclosures: G. Fogo: None. **F.M. Ahsan:** None. **C.R. Benoit:** None. **A.J. Curle:** None. **S.E. Heuer:** None. **G. Terzioglu:** None. **M.A. Kearney:** None. **T.L. Young-Pearse:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.10/V7

Topic: C.01. Brain Wellness and Aging

Support: UKY IRC 2024
NIH UL1TR001998

Title: Why Some Brain Regions Rust: Mitochondrial Respiratory Capacity Predicts Regional Brain Iron Burden in Aging

Authors: *V. ZACHARIOU[1], E. BIEBERICH[2];
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Abstract: Brain iron supports neuronal metabolism, but age-related increases in redox-active iron can promote oxidative injury and are implicated in cognitive decline and Alzheimer's disease. Brain iron accumulates unevenly with age, but why some regions become iron "hotspots" remains unclear. Inflammaging has been proposed as one contributor but shows inconsistent associations with MRI-indexed brain iron burden, prompting a search for additional contributors. Because mitochondria support heme metabolism and iron compartmentalization, age-related increases in mitochondrial stress may impair iron utilization and favor iron retention, particularly in regions with low respiratory capacity. We therefore tested an atlas-based index of regional mitochondrial respiratory capacity (TRC), and systemic mitochondrial stress as contributors to iron hotspots in aging, beyond systemic inflammation. Thirty-nine healthy older adults (ages 60-85; mean 71.1 years; 24 women) completed structural MRI, quantitative susceptibility mapping (QSM) for regional iron burden, and whole-plasma assays of the systemic mitochondrial stress markers GDF-15 and FGF-21 and the pro-inflammatory markers IL-1b, IL-6, IL-8, TNF-a, and IL-12p70, each expressed as a composite score. Normative priors from the MitoBrainMap dataset (Mosharov et al., 2025) provided TRC for 16 gray-matter regions. Linear mixed-effects models tested whether lower TRC predicted higher iron in the same regions and whether systemic mitochondrial stress moderated this association, adjusting for age, sex, physical activity, and the systemic pro-inflammatory composite. Lower regional TRC predicted higher iron burden [$R^2 = 0.45$; $b = -63.9$, $p < 0.001$]. A significant negative TRC by mitochondrial stress interaction [$b = -8.12$, 95% CI -15.6 to -0.65, $p = 0.03$] indicated that mitochondrial stress predicted iron burden more strongly in low-TRC regions. To visualize this effect, regions were median-split into low- and high-TRC categories and QSM was averaged within each. Systemic mitochondrial stress was positively associated with iron in low-TRC regions [$b = 17.35$, $R^2 = 0.43$, $p < 0.001$] but not in high-TRC regions [$b = 6.45$, $R^2 = 0.14$, $p = 0.45$]. These results suggest that low-TRC regions may experience greater age-related mitochondrial stress, increasing their vulnerability to iron retention. Pending replication with CNS-proximal mitochondrial stress markers, assessed in neuronal and astrocyte extracellular vesicles, these findings nominate regional mitochondrial respiratory phenotype as a marker of iron hotspots and mitochondrial stress as an actionable pathway for future iron-focused prevention studies.

Disclosures: V. Zachariou: None. **E. Bieberich:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.11/V8

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant OD032451
NIH Grant EY030747
NIH Grant EY31248

Title: Differentiation status and oxidative stress affect the expression of proteins involved in synaptic structure and neurotransmission in neural progenitor cells and neurons derived from neural progenitor cells

Authors: R. S. DUNCAN, S. M. RIORDAN, ***P. KOULEN**;
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Abstract: Neural progenitor cells (NPCs) and NPC-derived neurons are often used as *in vitro* model systems of neurodegeneration and neuroprotection. Oxidative stress contributes to the development of neurodegenerative diseases leading us to determine whether oxidative stress uniquely affected the expression of proteins in immature and differentiated NPCs. Undifferentiated and differentiated NPCs were exposed to tert-butyl hydroperoxide (tBHP, 10μM) for 24 hours to induce oxidative stress. Proteomics was utilized to identify differentially expressed proteins among experimental groups based on cellular differentiation status, oxidative stress, or both. Enriched biological processes related to ion and small molecule transporters, synaptic proteins, and neurotransmission were found. We generated a proteome of 7,875 proteins and found 101 proteins associated with ion and small molecule transporters synaptic proteins, and neurotransmission. Most of these proteins were differentially expressed throughout differentiation across a ten-day period. In addition, oxidative stress altered the expression levels of at least 40 of these proteins with some exhibiting differential directional (up- or down-regulation) and/or temporal (early versus late) patterns of expression. Changes in neuronal protein expression levels identified possible therapeutic targets for the prevention of neurodegenerative diseases and have potential relevance to cytotherapies.

Disclosures: R.S. Duncan: None. **S.M. Riordan:** None. **P. Koulen:** None.

Poster

PSTR009: Metabolism, Inflammation, and Brain Function

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.12/V9

Topic: C.01. Brain Wellness and Aging

Title: Medium Chain Triglycerides Attenuate LPS-Induced Delirium Like Responses and May Protect Against Long Term Cognitive Impairment and Recurrent Delirium Like Responses

Authors: *K. KOMATSU[1], T. YAMANASHI[2], M. NAKAMOTO[3], T. NISHIGUCHI[4], A. MIURA[4], N. KAJITANI[5], M. SUMINAGA[2], M. IWATA[6];
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Abstract: Background:
Delirium is associated with increased mortality, prolonged hospitalization, and long-term cognitive decline. A history of delirium has also been linked to subsequent dementia and cognitive impairment. However, whether delirium contributes to long-term cognitive dysfunction and increased vulnerability to future delirium remains unclear. Neuroinflammation is thought to play a central role in delirium pathophysiology, as systemic inflammation induces microglial activation and proinflammatory cytokine release, potentially causing persistent neuronal and synaptic dysfunction. We previously demonstrated electroencephalographic slowing and delirium-like behavioral changes in a lipopolysaccharide (LPS)-induced mouse model of delirium and showed that these abnormalities were ameliorated by medium-chain triglyceride (MCT) administration. Here, we investigated whether prior LPS-induced delirium-like states lead to long-term cognitive impairment and altered responses to a second inflammatory challenge six months later.
Methods:
Male C57BL/6 mice were implanted with head-mounted devices for electroencephalography (EEG) recording. Following oral administration of MCT oil or long-chain triglyceride (LCT) oil, mice received an intraperitoneal injection of LPS (0.5 mg/kg). EEG activity was recorded before and after LPS administration and converted to bispectral EEG (BSEEG) scores (Yamanashi et al., J Psychiatr Res. 2021) to quantify EEG slowing. Two days later, mice underwent the Y-maze spontaneous alternation test and open field test (OFT) to assess delirium-like behavior. Six months after the initial LPS challenge, cognitive function was evaluated using the Y-maze novel arm recognition test. Mice then received a second LPS injection (0.5 mg/kg), followed by EEG recording, Y-maze spontaneous alternation testing, and OFT to assess delirium-like responses.
Results:
Following the initial LPS challenge, the increase in BSEEG scores was smaller in the MCT group than in the LCT group, and MCT-treated mice showed higher spontaneous alternation rates in the Y-maze test. Six months later, the MCT group tended to spend more time in the novel arm of the Y-maze. In addition, the increase in BSEEG scores after the second LPS challenge was attenuated in the MCT group.
Conclusions:
MCT administration may attenuate acute delirium-like responses induced by systemic inflammation and provide long-term protection against cognitive impairment and increased vulnerability to subsequent delirium-like episodes.

Disclosures: K. Komatsu: None. **T. Yamanashi:** None. **M. Nakamoto:** None. **T. Nishiguchi:** None. **A. Miura:** None. **N. Kajitani:** None. **M. Suminaga:** None. **M. Iwata:** None.

Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.01/V10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA grant RF1 AG074566

Title: PLCG2 Genetic Risk Variants Differentially Regulate Extracellular Matrix Remodeling and Cerebrovascular Integrity in Alzheimer's Disease

Authors: *C. FERGUSON[1], E. MESSENGER[1], L. BEDFORD[3], D. M. WILCOCK[4], B. T. LAMB[5], S. J. BISSEL[2];
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Abstract: Immune dysregulation and blood-brain barrier (BBB) dysfunction are early, interrelated contributors to Alzheimer’s disease (AD) progression. Microglia regulate cerebrovascular stability through interactions with endothelial cells and extracellular matrix (ECM) components that maintain BBB integrity; however, AD-associated microglial states can disrupt these interactions, promote aberrant ECM remodeling, and compromise endothelial barrier function. Despite this, the molecular mechanisms linking microglial activity to cerebrovascular decline remain poorly understood. Human genetic studies strongly implicate microglial genes as central modulators of AD risk, including phospholipase C gamma 2 (PLCG2). Notably, two rare coding variants in PLCG2 exert opposing effects on AD risk: the loss-of-function M28L genetic variant exacerbates Aβ pathology, whereas the hypermorphic P522R genetic variant is protective. As PLCG2 is a critical transducer of downstream myeloid receptor signaling, altered PLCG2 activity may reshape microglia within the cerebrovascular microenvironment during AD progression. To define the mechanistic link between PLCG2 and cerebrovascular integrity, we crossed PLCG2 risk variant mice with a humanized amyloid precursor protein model harboring the Swedish, Arctic, and Austrian pathological mutations ($hAPP^{SAA}$). We selected 12- and 18-month timepoints, representing moderate and advanced disease stages. At 18 months, M28L risk variant mice exhibited significantly reduced cortical CD31+ coverage, shorter average vessel length, and increased terminal branchpoints compared to control mice, consistent with impaired vascular organization. Hippocampal proteomic weighted gene co-expression network analysis revealed that PLCG2 variants differentially regulate an ECM-vascular remodeling network across disease progression. This network includes structural basement membrane proteins, such as fibronectin, biglycan, collagens, and laminins. Consistent with enhanced ECM remodeling, ELISA analyses of 18-month cortical

homogenates show elevated levels of metalloproteinases (MMPs), including MMP-2, -3, -8, and proMMP-9 in the M28L risk variant mice. Together, these findings support a previously unrecognized role of PLCG2 in regulating microglial-vascular signaling pathways that may drive ECM remodeling and BBB dysfunction in AD.

Disclosures: C. Ferguson: None. **E. Messenger:** None. **L. Bedford:** None. **D.M. Wilcock:** None. **B.T. Lamb:** None.

Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.02/V11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH U54AG090792

Title: Integrative Analysis of Polygenic Risk in Alzheimer's Disease Using Human iPSC-Derived Neurons

Authors: *R. AFIFY[1,2], M. GOMEZ[1,2], G. CHITTUM[1,2], L. VARGHESE[1,2], C. PROSSER[1,2], A. HASKELL[1,2], J. VISWANATHAN[1,2], C. GOMES[1,2], J. S. MEYER[1,2];
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Abstract: Alzheimer’s disease (AD) is the most common cause of dementia and is influenced by the cumulative effects of genetic risk variants. While genome-wide association studies (GWAS) have identified many loci associated with AD susceptibility, how polygenic risk translates into neuronal dysfunction remains poorly understood. Human induced pluripotent stem cell (iPSC)-derived neuronal models provide a powerful platform for capturing the genetic complexity of AD pathology. In this study, we utilized an NGN2-induced differentiation protocol to generate excitatory cortical neurons from eight iPSC lines derived from donors representing the upper and lower quartiles of polygenic risk. Robust neuronal differentiation was achieved across all lines, and neuronal identity was confirmed through immunocytochemistry staining, demonstrating reproducible neuronal generation across genetically diverse backgrounds. To evaluate neuronal function, we performed longitudinal recordings using multi-electrode array (MEA) technology. Preliminary analyses revealed increased firing rates and network hyperexcitability in AD-derived neurons compared with low-PRS controls, particularly at later stages of neuronal maturation. Neuronal morphology was also assessed using neurite tracing and Sholl analysis to quantify morphological complexity. In parallel, RNA sequencing of iNeurons derived from these lines identified transcriptional signatures associated with AD and polygenic risk. These findings suggest that AD-associated genetic risk may contribute to early alterations in neuronal function and synaptic activity before the onset of overt neurodegenerative pathology. To further characterize disease-associated phenotypes, ongoing analyses are integrating molecular, morphological, and transcriptomic analyses across all cell lines, including tau pathology and

ELISA-based quantification of amyloid-beta (Aβ). By integrating electrophysiological, morphological, molecular, and transcriptomic analyses, this study aims to identify early mechanisms underlying neuronal hyperexcitability in AD and determine how polygenic risk influences disease-relevant neuronal phenotypes. These findings may uncover novel pathways of neuronal vulnerability and inform the development of targeted therapeutic strategies for AD.

Disclosures: R. Afify: None. **M. Gomez:** None. **G. Chittum:** None. **L. Varghese:** None. **C. Prosser:** None. **A. Haskell:** None. **J. Viswanathan:** None. **C. Gomes:** None. **J.S. Meyer:** None.

Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.03/V12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Robert J. and Nancy D. Carney Institute for Brain Science

Title: Atypical biomarker presentation in an Alzheimer's disease PSEN1 A246E mutation carrier

Authors: *S. I. JONES[1,2,3], J. H. MENDIOLA[1,2,3], E. N. WILSON[1,2,3];
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Abstract: Early-onset Alzheimer's Disease (EOAD) is a rare form of Alzheimer's Disease (AD) caused by dominantly inherited genetic variants. The presenilin 1 (*PSEN1*) A246E variant causes EOAD, with individuals carrying this variant showing a highly predictable age of AD symptom onset and rapid disease progression. Owing to the rarity of these mutations, published data on affected individuals remain scarce, particularly in individuals near the time of symptom onset. In the current study, we evaluated a *PSEN1* A246E mutation carrier who was at the expected age of symptom onset and compared their biomarker and clinical data to a cohort of individuals along the AD continuum, diagnosed as clinically unimpaired (CU), mild cognitive impairment (MCI), or AD. Neurological exam determined the subject to be cognitively normal, with a clinically unremarkable Montreal Cognitive Assessment score, Clinical Dementia Rating scale, and additional neuropsychological testing. No cortical atrophy or enlargement of the lateral ventricles in the structural MRI were observed. Amyloid PET scan (Florbetaben) exhibited significant widespread amyloid accumulation, with an amyloid centiloid value of 99. Tau PET scan using PI-2620 showed limited tau accumulation confined only to the right supramarginal gyrus. Blood plasma biomarkers measured using the fully-automated Lumipulse *G* 1200 platform revealed Aβ42/Aβ40, GFAP, and NfL to be consistent with amyloid negative (Aβ-) CU individuals. However, in line with neuroimaging results, plasma p-tau217 was elevated and within the abnormal range. Together, these findings represent a unique case of an individual with genetic and biomarker factors strongly indicating disease risk but with limited presentation of cognitive

symptoms at expected age of onset. Future studies of this atypical *PSEN1* A246E variant carrier may elucidate the physiological processes of EOAD and bring to light potential mechanisms of resilience.

Disclosures: S.I. Jones: None. **J.H. Mendiola:** None. **E.N. Wilson:** None.

Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.04/V13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH U54 AG054345

Title: LOAD3: Gene-by-diet effects in a novel, humanized late-onset Alzheimer's disease mouse model expressing APOEe4, amyloid-beta, and tau

Authors: *K. P. KOTREDES[1], S.-P. WILLIAMS[2], M. SASNER[1], A. OBLAK[3], G. W. CARTER[1], N. T. SEYFRIED[4], P. R. TERRITO[5], G. R. HOWELL[1], B. T. LAMB[3];
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Abstract: Human data sets indicate that the complexity and heterogeneity in late-onset Alzheimer's disease (LOAD) results from dynamic interactions between genes and environment. To better model these associations, the MODEL-AD (Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease) Consortium is creating novel platform mouse models expressing risk factors shown to increase disease severity in human patients. The IU/JAX/PITT MODEL-AD Center introduces 'LOAD3,' a C57BL/6J background mouse strain triple homozygous for humanized *APOE4*, *APP*, (amyloid beta), and *MAPT* (tau) alleles. Additionally, risk-associated high-fat (HFD) and western diet (WD) cohorts were generated for comparisons to normal mouse chow. An animal phenotyping pipeline was employed to longitudinally qualify and align with neurodegenerative disease states and phenotypes observed in human patients during the course of aging. *In vivo* MRI imaging, in addition to behavior and wellness assays, were performed, as were analyses of blood and brain tissue for risk-factor-related alterations in neuropathology, transcriptomics, metabolomics, and proteomics. Tracking individual animal readouts across 4-, 12-, and 18-month timepoints with a variety of behavioral, biometric, and imaging *in vivo* assays provided powerful insight into the biochemical changes presented by sex, genotype, diet, and age. Moreover, cross-sectional cohorts at matching timepoints allow multi-omic analyses of terminal brain tissue. LOAD3 animals on high-fat and western diets showed behavioral and biometric changes, which agree with MRI data across multiple brain regions. Analysis of transcriptomic data revealed synergistic gene-by-diet effects and alterations to neuronal and synaptic pathways that resemble those observed in human

Alzheimer's disease. Continued efforts are underway to examine the clinically-relevant effects of sex, age, genotype, and diet in animals aged to 24 months of age. The MODEL-AD consortium has established the LOAD3 mouse strain to study the effects of genetic and environmental risk factors of LOAD. This model serves as a platform for the incorporation of additional AD risk factors to more closely align phenotypes in the mouse to outcomes observed in the clinic. This new mouse model and initial phenotyping will prove valuable for mechanistic and drug testing studies.

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Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.05/V14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 5R01AG076625-04

Title: Age-dependent alterations in Thiamine homeostasis in the 3xTg mouse model of Alzheimer's disease

Authors: *S. JAHAN[1,2], B. BLACKBURN[1,2], S. BRANNEN[1,3], J. ZASTRE[1,2,3];
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Abstract: Title: Age-dependent alterations in Thiamine homeostasis in the 3xTg mouse model of Alzheimer's disease[1]**Sadia Jahan,** [1]Benjamin Blackburn, [2]Samantha Brannen, and [1,2]Jason Zastre*
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Thiamine (Vitamin B1) is a water-soluble vitamin that is essential for brain energy metabolism and to support nerve cell function. Reduced thiamine levels in the brain are associated with Alzheimer's disease (AD), and the aging brain is particularly more susceptible to thiamine deficiency. However, the impact of aging on thiamine homeostasis remains poorly understood. This study aims to investigate age-dependent alterations in thiamine homeostasis linked to AD. Transporters from the SLC membrane family are responsible for the transport of thiamine into the brain, including the thiamine transporter-1 (SLC19a2), and thiamine transporter-2 (SLC19a3), while thiamine pyrophosphokinase-1 (TPK1) converts thiamine into its biologically active form, thiamine pyrophosphate (TPP). We utilized female 3xTg-AD and genetic background controls (B6.129SF2) mice and evaluated these proteins in animals at 6, 12, and 18

months of age. This approach provides insight into the age-dependent regulation of thiamine homeostasis genes under both healthy and pathological conditions. Western blot analysis demonstrated a significant increase in TPK1, and SLC19a3 expression in 3xTg-AD mice at 18 months compared with younger age groups, whereas no significant changes were observed in genetic background control mice. These findings suggest a potential adaptive response to maintain thiamine availability and TPP synthesis during AD progression. Furthermore, the lack of alteration in control mice suggests that aging alone may not induce the homeostatic disturbances necessary to trigger this adaptive regulation. Future studies will include direct measurements of brain thiamine and TPP concentrations to evaluate whether these molecular changes translate into functional outcomes.

Disclosures: S. Jahan: None. **B. Blackburn:** None. **S. Brannen:** None. **J. Zastre:** None.

Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.06/V15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Canadian Institutes of Health Research
Natural Science and Engineering Research Council of Canada
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Title: APOEε4 accelerates APP mutation-driven pattern separation deficits before detectable amyloid pathology in humanized mice

Authors: N. YALIKUN[1], *A. A. BATALLÁN BURROWES[2], B. G. MURATORI[4], S. M. CERUTTI[5], A. ARRAR[2], W. SHLEL[2], L. M. SAKSIDA[6], T. J. BUSSEY[7], T. W. SCHMITZ[3], M. A. PRADO[8], V. F. PRADO[9];
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Abstract: Pattern separation transforms similar experiences into distinct, non-overlapping memories and depends in part on adult hippocampal neurogenesis. Because hippocampal neurogenesis is impaired in Alzheimer’s disease (AD), disruption of this process may contribute to early hippocampal vulnerability. However, the genetic and pathological factors that first compromise neurogenesis and pattern separation remain unclear. We tested whether apolipoprotein E4 (APOEε4), the strongest genetic risk factor for sporadic AD, interacts with humanized APP mutations to disrupt hippocampal function. We used triple knock-in mice

carrying humanized wild-type APP (hAPP) or familial AD-linked APP alleles ($hAPP^{NL}$ or $hAPP^{NL-F}$), humanized wild-type MAPT, and humanized APOEε3 or APOEε4. Mice were assessed at 6, 9, 12, 16, and 18 months to define age-dependent trajectories of hippocampal pathology, neurogenesis, and cognition. Pattern separation was measured with the automated touchscreen location discrimination task. Hippocampal Aβ, tau, Ki67-positive proliferating cells, and doublecortin-positive immature neurons were quantified by immunofluorescence microscopy and ELISA. hAPP and $hAPP^{NL}$ mice showed no insoluble amyloid through 18 months, whereas $hAPP^{NL-F}$ mice accumulated amyloid with age, emerging earlier in APOEε4 than APOEε3 mice (9 vs. 12 months). Ki67-positive cell number and doublecortin-positive cell volume declined from 6 to 12 months across groups, consistent with age-related reductions in neurogenesis, but were not significantly affected by sex, APP genotype, or APOE genotype. Despite this lack of genotype-dependent neurogenesis change, familial APP mutations impaired pattern separation across ages. APOEε4 accelerated deficit onset, with impairments evident by 6 months compared with 12 months in APOEε3 mice, and $hAPP^{NL-F}$/APOEε4 mice were most impaired at all ages. These findings suggest that familial APP mutations drive pattern separation deficits, while APOEε4 accelerates their onset and increases their severity. Because cognitive deficits emerged before detectable insoluble amyloid accumulation or genotype-dependent neurogenesis changes, APOEε4 may promote early hippocampal dysfunction through mechanisms beyond plaque burden or reduced neurogenic capacity.

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Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.07/V16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Canadian Institutes of Health Research
Natural Science and Engineering Research Council of Canada
BrainsCAN Canada First Research Excellence Fund Accelerator Awards and The Rodent Cognition Research and Innovation Core

Title: Lecanemab reduces hippocampal amyloid but fails to rescue pattern separation deficits in humanized APP/APOEε4 mouse models.

Authors: *W. SHLEL[1], A. A. BATALLÁN BURROWES[1], A. ARRAR[2], L. ROBAYO NOGUERA[2], N. YALIKUN[3], T. W. SCHMITZ[4], M. A. PRADO[5], T. J. BUSSEY[6], L. M. SAKSIDA[7], V. F. PRADO[8];
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Abstract: Lecanemab is an anti-amyloid monoclonal antibody that reduces Aβ plaque burden in mouse models and patients with Alzheimer's disease, yet its cognitive benefits remain modest. Why effective amyloid clearance is only weakly coupled to cognition remains unclear. Addressing this gap requires humanized preclinical models that capture age-dependent amyloid pathology and neuronal dysfunction, paired with cognition assays that translate across species. Here, we tested whether such a platform can reproduce the clinical dissociation between amyloid clearance and limited cognitive sparing in a placebo-controlled lecanemab study. We used novel triple knock-in mice carrying humanized APP alleles (wild-type hAPP, hAPPNL, or hAPPNL-F), humanized MAPT, and hAPOEε4. Mice received weekly lecanemab or vehicle injections beginning at 3 months of age. At 6 months, hippocampal-dependent pattern separation was assessed with the touchscreen location discrimination task. Hippocampal pathology, including Aβ aggregates, microglial activation, lysosomal activity, and neurogenesis, was quantified by immunofluorescence, ELISA, and fluorescence microscopy at 9 and 12 months. Hippocampal plaques were detected in hAPPNL-F mice but not in hAPP or hAPPNL mice. Lecanemab significantly reduced plaque size and density in hAPPNL-F mice. However, treatment did not alter doublecortin-positive immature neuron volume or the number of Ki67-positive proliferating cells. At 6 months, hAPPNL-F mice showed impaired location discrimination performance relative to hAPP and hAPPNL mice, and lecanemab-treated hAPPNL-F mice did not differ from vehicle-treated controls. These findings show that humanized APP/MAPT/APOEε4 mice combined with touchscreen cognitive testing recapitulate the human dissociation between robust amyloid clearance and limited cognitive benefit after lecanemab treatment. The persistence of cognitive impairment despite plaque reduction suggests that hippocampal neurogenic dysfunction, potentially driven or sustained by amyloid pathology, may better explain cognitive deficits than plaque burden alone. This platform provides a human-translatable approach for defining what lecanemab modifies, what remains resistant to treatment, and why amyloid clearance alone may be insufficient for disease modification.

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Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.08/V17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AI174108

Title: Integrative Dissection of 4 Novel Alzheimer's Disease Risk Loci

Authors: *J. M. REGAN[1], A. DIWADKAR[2], M. ENGLEBRIGHT[3], S. POCHAREDDY[3], P. BOND[1], H. MARKUS[3], H. ABDELHALIM[4], D. LIU[2], L. CARREL[1];
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a complex genetic architecture. Genome-wide association studies (GWAS) have identified numerous risk loci; yet causal variants and genes at these loci remain largely unresolved. Statistical fine-mapping has achieved limited success in addressing this challenge, underscoring the need for integrated computational and experimental approaches to identify true causal regulatory variants and elucidate disease pathophysiology. Most AD risk variants are non-coding and enriched in immune cell regulatory elements, particularly in microglia, pointing to dysregulated microglial gene expression as a central disease mechanism.To systematically identify causal regulatory variants, we developed IMAC (Integrated Meta-Analysis for Cross-trait GWAS), a novel mixed-effects meta-regression model applied to four publicly available AD GWAS summary statistics datasets, replicating 56 known loci and identifying 4 novel loci. To prioritize causal variants and target genes at these novel loci, we integrated publicly available brain expression quantitative trait loci from multiple brain tissues and cell types with publicly available ATAC-seq chromatin accessibility datasets from neural cell types. At our novel Chr5q34 locus, publicly available Hi-C chromatin conformation data converged on DOK3 and DDX41 as regulated target genes. Critically, DOK3 expression is reduced in microglia from AD patient brains (Zhou et al. single-cell dataset), and DOK3 directly interacts with SHIP1 (INPP5D), a well-established AD risk gene involved in microglial immune signaling, through conserved protein interaction domains demonstrated by co-immunoprecipitation.We then functionally screened 190 variants, including those in linkage disequilibrium (r^2>0.8) with lead SNPs, from our 4 novel loci using a massively parallel reporter assay (MPRA) in HMC3 and HEK293 cell lines, identifying 21 alleles with cell-type-specific regulatory and allelic effects of which a subset were independently validated using a qPCR-based luciferase assay. Allele-specific transcription factor (TF) binding analysis of the 21 MPRA hits revealed that risk alleles at the Chr5q34 locus disrupt predicted binding of AD-relevant TF motifs, suggesting these non-coding variants reduce enhancer activity at the DOK3 locus in microglia. These findings provide a rigorous, integrative framework linking non-coding AD risk variants to microglial gene dysregulation, implicating DOK3 as a novel microglia-relevant AD candidate gene. These findings merit future analysis of the functional effects of DOK3 expression alterations in AD.

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Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.09/V18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH-5R01AG093746-02

Title: Studying the contribution of CASP8 intronic hexamer repeat expansion to AD neuropathological changes in differentiated SH-SY5Y

Authors: *D. ROMERO[1], R. F. TOMAS[1], L. NGUYEN[2];
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Abstract: Alzheimer's disease (AD) is a rapidly growing neurodegenerative disease with ~ 7 million Americans over the age of 65 currently affected. AD is characterized by neuropathological changes (AD-NC) such as the accumulation of Aβ plaques, neurofibrillary tangles composed of phosphorylated Tau (pTau), and neuroinflammation. However, AD is a multifactorial disease with multiple contributing elements. Genetic factors, such as rare mutations in *APP, PSEN1/2* account for only ~1% of total AD cases and 80+ other genes/loci including *APOE4* alleles are associated with increased AD risk. However, the genetic causes and molecular mechanisms of AD are not fully understood. We recently showed the accumulation of polyGR+ proteins partially produced from an intronic GGGAGA repeat expansion mutation in the caspase-8 gene (*C8*-GGGAGA^{EXP}) is detected in AD autopsy brains. Cellular experiments showed the *C8*-GGGAGA^{EXP} produces mutant rGGGAGA RNA and polyGR-containing chimeric protein aggregates. Additionally, a specific sequence variant of the *C8*-GGGAGA^{EXP} is associated with increased risk to AD (*C8*-AD-R1; odds ratio 2.2, p=3.1x10-5). We generated adeno-associated viruses (AAV) expressing the expanded hexamer repeats of the *C8*-AD-R1 variant (AAV-AD-R1), the more common variant (AAV-C-Var), or a short (GGGAGA)4 stretch as a control (AAV-Cntl) to study the contribution of the repeat expansion in caspase-8 in AD. Our recent work shows that AAV-AD-R1 injected animals develop AD-related behavioral changes, repeat expansion associated pathology (e.g. accumulation of RNA and chimeric proteins), neuronal loss, neuroinflammation, and transcriptomic changes. Transcriptomics showed differentially expressed genes in AAV-AD-R1 mice with enrichment in cilia and microtubule-based biological processes. Here, we aim to understand how C*8*-AD-R1 can contribute to the formation Aβ, altered phosphorylation of tau, and if cilia function is decreased using our AAV-C8-GGGAGA^{EXP} overexpression system in differentiated SH-SY5Y neurons. We differentiated SY-SY5Y using a retinoic acid-mediated approach and transduced the neurons with either AAV-AD-R1, AAV-C-Var, or AAV-Cntl for 14 days. Immunofluorescence staining was performed to study repeat expansion related pathologies, neuronal sub-type proportions, AD-related neuropathological changes, and for cilium length. Western blot assays were also used to measure extracellular aβ oligomers and changes in APP cleavage. This work will provide understanding into the effects of the *CASP8* repeat expansion mutation on neuronal survival, *C8*-AD-R1-mediated toxicity, pathological changes associated with AD, and cilia morphology.

Disclosures: D. Romero: None. **R.F. Tomas:** Other; inventor on a patent related to mouse models expressing AD- associated repeat expansion variants. **L. Nguyen:** Other; inventors on patents related to mouse models expressing AD- associated repeat expansion variants, detection of RAN proteins, and strategies to treat repeat expansion disorders.

Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.10/V19

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BrightFocus Bold Ideas Initiatives Program CA2026005

Title: Transposable element-derived exons constitute a hidden regulatory layer in Alzheimer's disease

Authors: *Y. ZHANG, X. XIAO;
UCLA, Los Angeles, CA

Abstract: Transposable elements (TEs) comprise nearly half of the human genome and represent a pervasive source of transcriptomic innovation through their incorporation into mature mRNAs. Despite mounting evidence of widespread TE-derived exons in the human genome, their genetic architecture and contribution to Alzheimer’s disease (AD) remain largely unexplored. Here, we systematically delineate the landscape of TE-derived exons in the human brain by integrating 36 long-read RNA-seq datasets, 3,049 short-read RNA-seq datasets, and matched whole-genome sequencing data across nine brain regions from three independent AD cohorts. We show that the TE-derived exon inclusion displays pronounced inter-individual variability while remaining broadly conserved across brain regions, with distinct TE families exhibiting characteristic and directionally biased inclusion patterns. We identified hundreds of AD-associated TE exons, including events in established AD-relevant genes such as *TOMM40*, *PIN1*, and *RBCK1*. Joint modeling revealed that a substantial subset of these associations is shared across brain regions, suggesting coordinated TE-exon dysregulation in AD. Through genetic mapping of TE exon inclusion levels, we identified thousands of genetically controlled TE-derived exons. Strikingly, variants associated with TE exon inclusion captured a disproportionate share of heritability for neurodegenerative disorders, suggesting that TE-derived exons may serve as an important conduit through which genetic risk influences transcriptomic regulation. Integrative transcriptome-wide association study (TWAS) and colocalization analyses further implicated a TE exon of the AD risk gene *RBCK1* as a candidate risk-mediating event, whereby TE inclusion introduces a premature termination codon and generates a truncated isoform. Collectively, our findings establish TE exon inclusion as a genetically regulated, disease-relevant layer of transcriptomic complexity in the human brain and reveal a previously unappreciated mechanism linking TE-derived exons to AD pathogenesis.

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Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.11/V20

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R21NS130390

Title: Gene editing in rats produces a cerebral amyloid angiopathy model with distinct vascular and molecular signatures

Authors: *X. ZHU[1,2], W. E. VAN NOSTRAND[2];
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Abstract: Cerebral amyloid angiopathy (CAA) is a prevalent cerebral small vessel disease associated with Alzheimer's disease and related dementias (ADRD). However, currently available transgenic animal models that overexpress human amyloid β-protein precursor (AβPP) incompletely recapitulate human CAA pathology. To address this limitation, we generated a novel gene-edited rat model (CRAβDI) expressing human Dutch/Iowa mutant Aβ via endogenous rat AβPP using CRISPR/Cas9-mediated genome engineering. Pathological and transcriptomic analyses were performed to characterize disease-associated phenotypes. CRAβDI rats develop progressive capillary CAA type-1 and significant arteriolar CAA type-2 across multiple brain regions, accompanied by increased glial cell accumulation surrounding amyloid-laden vessels. Transcriptomic profiling revealed a relatively mild pro-inflammatory signature with prominent activation of neurovascular unit-associated cells, distinguishing CRAβDI rats from transgenic CAA models that exhibit dominant microglial activation. Pathway enrichment analyses further demonstrated attenuated inflammatory responses but enhanced vascular-associated pathway alterations compared with rTgDI rats, which showed robust inflammatory activation. Gene co-expression and clustering analyses additionally identified distinct regulatory gene modules between gene-edited and transgenic CAA models. Collectively, these findings establish CRAβDI rats as a novel preclinical model of early-stage CAA with distinct pathological and molecular features compared with late-stage transgenic models. This model provides a valuable platform for investigating early disease mechanisms and evaluating therapeutic strategies targeting vascular amyloid pathology.

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Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

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the SIAT–HKUST Joint Laboratory for Brain Science (Joint Laboratory Funding Scheme [JLFS/M-604/24])

Title: APOE-ε4-carrying haplotypes reveal distinct AD risk and microglial immune signatures

Authors: *S. LIU[1,2], H. CAO[1,2], H. UHM[1,2], A. WONG[1,2], Y. JIANG[1,2], X. ZHOU[1,2], M. CHUNG TONG VINCENT[3], T. KWOK[4], Y. CHEN[1,5,6,7], F. C. IP[1,2], D. SHOAI[8,9], K. MOK[1,2,8], J. HARDY[2,8,9], A.-Y. FU[1,2,5], N. Y. IP[1,2,5];
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Abstract: Genetic factors contribute substantially to Alzheimer's disease (AD) risk, with heritability estimated at 60-80%. *APOE*-ε4 is the strongest genetic risk factor for AD, conferring a 3- to 15-fold increased risk; however, ~50% of *APOE*-ε4 carriers do not develop the disease. Previous studies have identified non-coding variants in the *APOE* locus that contribute to AD risk independently of *APOE*-ε4, suggesting that the effect of *APOE*-ε4 on AD risk may be modified by additional genetic factors. However, how genetic variants or haplotypes interact with *APOE*-ε4 to modify AD risk and disease-related biology remains largely unclear. Here, we systematically characterized *APOE*-ε4 haplotypes using AD-associated genetic variants in the *APOE* region in European and East Asian cohorts. We identified two *APOE*-ε4 haplotypes - ε4α and ε4β - associated with distinct disease outcomes. Specifically, ε4β shows delayed disease onset and reduced tau pathology compared with ε4α, suggesting a less severe AD pathology. Bulk and single-nucleus RNA sequencing analysis further shows that these haplotypes differ in *APOE* expression level in a specific subset of microglia. Notably, compared with ε4α, ε4β is associated with decreased pro-inflammatory microglial signature, suggesting altered microglial immune activation. Together, these findings identify distinct *APOE*-ε4 haplotypes with differential associations with AD-related phenotypes and microglial immune responses, highlighting that haplotype context is an important modifier of *APOE*-ε4-associated AD risk.

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Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR010.13/V22

Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Functional analysis of late-onset Alzheimer’s disease risk genes in Caenorhabditis elegans identifies regulators of neuronal aging

Authors: *S. WAGHMARE[1], M. KRISHNA[2], A. FRANITZA[2], B. A. LINK[2], L. E[3];
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Abstract: Genome-wide studies in late-onset Alzheimer's disease (LOAD) have uncovered many risk loci, yet identifying causal genes and defining their roles in disease-relevant mechanisms remain major challenges. Using *Caenorhabditis elegans* as an *in vivo* model, we investigated 14 understudied LOAD-associated genes and their homologs: ABI3/*abi-1*, B4GALT3/*bre-4*, CCDC6/*T09B9.4*, CLPTM1 (*C36B7.6* and *R166.2*), CNN2/*cpn-2*, DMWD/*wdr-20*, ECHDC3/*ech-2*, MADD/*aex-3*, NCK2/*nck-1*, RABEP1/*rabn-5*, RIN3/*rin-1*, SLC39A13/*zipt-13*, TRAM1/*tram-1*, and USP6NL/*tbc-17*. Lifelong RNAi knockdown was used to assess lifespan, age-associated degeneration of PVD and PLM neurons, and associative learning and short-term memory. Most knockdowns did not alter lifespan, with only *nck-1* and *tbc-17* shortening lifespan. In contrast, multiple homologs modified neuronal aging in a neuron-class-specific manner. Knockdown of *aex-3*, *C36B7.6*, *cpn-2*, *ech-2*, *rabn-5*, *rin-1*, *T09B9.4*, and *zipt-13* attenuated late-life PVD degeneration, whereas *R166.2* and *tram-1* accelerated PVD aging. In PLM neurons, *R166.2* knockdown exacerbated degeneration, while *tbc-17* knockdown attenuated degeneration despite shortening lifespan. Further analysis of *tbc-17* revealed preservation of mitochondrial architecture during aging and altered heat stress-induced mitochondrial remodeling consistent with enhanced mitochondrial quality control. Behavioral assays identified *ech-2* as a modulator of neuronal function, with knockdown improving short-term memory during aging. To further assess how LOAD-linked genes interact with Aβ-driven neurodegeneration, we developed a model combining age-associated PVD degeneration with

pan-neuronal expression of human $A\beta_{1-42}$. Aβ expression accelerated PVD degeneration, whereas *ech-2* knockdown abolished this effect. Targeted qPCR analysis revealed that *ech-2* RNAi reduced expression of *gst-4, prdx-2*, *hsp-6*, and *hsp-60* in aged animals, implicating altered redox and mitochondrial stress regulation as potential contributors to the neuroprotective effects of *ech-2* reduction. Together, our results demonstrate that several understudied LOAD-associated genes causally influence neuronal aging independently of organismal lifespan and identify mitochondrial metabolic pathways as candidate mechanisms governing neuronal resilience during aging and Aβ toxicity. This work establishes a scalable *in vivo* framework for translating human genetic associations into mechanistic insights and prioritizing LOAD risk genes for cross-species validation.

Disclosures: S. Waghmare: None. **M. Krishna:** None. **A. Franitza:** None. **B.A. Link:** None. **L. E:** None.

Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.14/V23

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH-5R01AG093746-02

Title: Alzheimer's risk hexamer repeat expansion variant cause disease-related pathologies and behavioral deficits in mice

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Abstract: We showed poly-glycine-arginine containing (polyGR+) aggregates accumulate in ~60% of hippocampus (Hpc) AD brains with unknown genetic etiology. In AD brains, polyGR+ aggregate levels were associated with increased AD neuropathological changes (Aβ plaques, phosphorylated Tau, and neuritic plaques). A subset of polyGR+ proteins is produced by an intronic GGGAGA repeat expansion (RpEx) in capase-8 (*C8*-$GGGAGA^{Ex}$). We showed a variant of *C8*-$GGGGA^{Ex}$ is associated with increased AD risk (C8-AD-R1 odds ratio 2.2. p=3.1x10-5) and favor the accumulation of *CASP8* polyGR+ proteins in cell models. Here we further characterize *C8*-$GGGAGA^{Ex}$ pathology in AD Hpc and study if C8-AD-R1 drives AD-related phenotypes in mice. Locus specific HCR-FISH detects mutant rC8-$GGGAGA^{Ex}$ RNA transcripts in *C8*-$GGGAGA^{Ex}$ (+) AD hippocampi but not in C8-SVA (-) AD and controls cases. Distinct aggregation patterns of polyGR+ and polyGE+ proteins are detected in AD Hpc with no comparable staining in controls. Using locus specific C-terminal antibodies, accumulation of mutant polymeric proteins from the *C8*-$GGGAGA^{Ex}$ were detected throughout the Hpc in *C8*-$GGGAGA^{Ex}$ (+) AD brains. To study the role of *C8*-$GGGAGA^{Ex}$ in AD development, we

generated an AAV overexpression mouse model system for the expanded GGGAGA region in C8-AD-R1 (AAV-AD-R1), in a common variant of *C8*-GGGAGA^{Ex} (AAV-C-Var), and a short $(GGGAGA)_4$ stretches as a control (AAV-Cntl). At 1 month, r-GGGAGA RNA accumulates in the subregions of the hpc, retrosplenial cortex, fiber tracts, and subcortical regions of AAV-AD-R1 and AAV-C-Var mice compared to AAV-Cntl mice. Behavioral tests show increased anxiety-like phenotypes and impaired spatial working memory in AAV-AD-R1 at 6 and 9 months, respectively, compared to AAV-Cntl mice. Pathological assessment of RpEx related changes shows widespread distribution and accumulation of r-GGGAGA and polyGE+ proteins in AAV-AD-R1 and AAV-C-Var mice at 6 and 9 months. In contrast, polyGR+ aggregates were significantly higher in AAV-AD-R1 mice compared to AAV-C-Var mice at both 6 and 9 months. Decreased NeuN(+) cells in the CA3 region of the AAV-AD-R1 mice compared to AAV-Cntl mice, which is negatively proportional with polyGR+ protein levels, was present. Additionally, increased Iba1(+) processes and increased Olig2(+) cells were detected in the Hpc of AAV-AD-R1 mice compared to AAV-Cntl. AAV-AD-R1 mice showed altered gene expression with enriched in cilia and microtubule biological processes. Together, overexpression of the hexamer region in the AD-associated C8-AD-R1 RpEx variant is sufficient to drive RpEx pathology, AD-related behavioral changes and neurodegeneration.

Disclosures: R.F. Tomas: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor on a patent related to mouse models expressing AD-associated repeat expansion variants. **I.M. Gerstin:** None. **D. Romero:** None. **L. Nguyen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventors on patents related to mouse models expressing AD-associated repeat expansion variants, detection of RAN proteins, and strategies to treat repeat expansion disorders..

Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.15/V24

Topic:

Support: NIH AG076921

Title: PICALM coding mutation H458R (murine H465R) protects against amyloid pathology in mice

Authors: *K. KISLER[1], Z. DAI[5], A. P. SAGARE[2], V. CLEMENTEL[1], A. GROND[3], G. SPILLARD[2], M. ZHANG[4], M. P. COBA[1];
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Abstract: *PICALM,* phosphatidylinositol binding clathrin assembly protein, is a highly validated genetic risk factor for late-onset Alzheimer's disease (AD). PICALM acts as an adapter protein and chaperone to direct clathrin-mediated internalization and intracellular receptor-mediated protein trafficking, including amyloid-β (Aβ). At least 20 AD-related PICALM single nucleotide polymorphisms (SNPs) have been identified and correlated with differential risk of development or progression of AD, but mutations or SNPs within the coding region are exceedingly rare. Recently GWAS and meta-analyses have revealed several rare coding variants of *PICALM* associated with LOAD, including PICALM H458R. AAV expression of murine PICALM H465R, the murine equivalent to human H458R, in cultured primary mouse *Picalm*-negative neurons revealed greater protection against amyloid-beta oligomer (Aβo) toxicity than wildtype PICALM. Mice expressing PICALM H465R crossed to *5xFAD* Alzheimer's disease (AD) model mice (*Picalm*$^{R/R}$; *5XFAD*) showed improved performance on behavioral tests, and less neuron loss in cortex layer 5 compared to control *Picalm*$^{H/H}$; *5XFAD* mice at 9 months of age. Interestingly, pan-Aβ staining in cortex and hippocampus did not reveal differences in amyloid load between *Picalm*$^{R/R}$; *5XFAD* and *Picalm*$^{H/H}$; *5XFAD* mice at 9 mo, implying that *Picalm*$^{R/R}$; *5XFAD* mice were more resilient to amyloid pathology. Using *in vitro* PICALM pull-down assays and mass spectrometry, we found that PICALM H458R exhibits an increased affinity for chaperone protein interactions. Importantly, we found enhanced PICALM H458R interactions with protective unfolded protein response (UPR) pathway proteins, upregulating a pro-adaptive signaling cascade to maintain ER homeostasis and protect against Aβo toxicity. This data reveals a new role for PICALM in the UPR pathway and cellular protection.

Disclosures: K. Kisler: None. **Z. Dai:** None. **A.P. Sagare:** None. **V. Clementel:** None. **A. Grond:** None. **G. Spillard:** None. **M. Zhang:** None. **M.P. Coba:** None.

Poster

PSTR010: Alzheimer's Disease: Genetics and Preclinical Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR010.16/V25

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH AG076921

Title: Neuronal PICALM loss increases susceptibility to excitotoxicity via increased glutamate signaling proteins

Authors: *G. SPILLARD[1], V. CLEMENTEL[1], D. LAZIC[2], A. P. SAGARE[1], K. KISLER[1], M. P. COBA[1];
[1]Physiol. and Neurosci., [2]USC, Los Angeles, CA

Abstract: PICALM, phosphatidylinositol binding clathrin assembly protein, is a highly validated genetic risk factor for late-onset Alzheimer's disease (AD). PICALM acts as an adapter protein and chaperone to direct clathrin-mediated internalization and intracellular receptor-mediated

protein trafficking. In neurons, PICALM regulates axonal growth and turnover of synaptic vesicles and receptors, suggesting its role in synaptic transmission. To better understand the neuronal-specific role of PICALM, we investigated the effect of neuronal PICALM loss in adult Picalm lox/lox; Camk2a-CreER mice with inducible neuronal-specific Picalm knockout (KO) and mouse neuronal cell cultures lacking Picalm (Picalm KO). In mouse primary neuronal cultures challenged with glutamate to induce excitotoxicity, we found reduced survival of Picalm KO neurons compared to wild type (WT) neurons. Immunoblot analysis of glutamate receptor subunits indicated increased receptor subunits present in Picalm KO neurons, localized to the cell membrane, implicating disrupted receptor internalization. In mice, proteomic and phosphoproteomic analysis of neuronal post-synaptic density 95 (PSD95)-associated protein fractions isolated from Picalm lox/lox; Camk2a-CreER mice and Picalm lox/lox littermates 4 weeks after tamoxifen-induced Picalm KO revealed significant protein and phosphoprotein changes in Picalm lox/lox; Camk2a-CreER PSD95 fractions. Importantly, we found that the majority (76%) of differentially expressed proteins (DEPs) were increased in Picalm lox/lox; Camk2a-CreER mice, including the activity marker protein Arc and numerous protein phosphatases. Similarly, 64% of differentially regulated protein phosphorylation sites (DRPs) in Picalm lox/lox; Camk2a-CreER mice showed increased phosphorylation. Together these data indicate an upregulation of glutamatergic signaling and higher sensitivity to excitotoxicity upon loss of neuronal PICALM. This indicates an important protective role for neuronal PICALM.

Disclosures: G. Spillard: None. **V. Clementel:** None. **D. Lazic:** None. **A.P. Sagare:** None. **K. Kisler:** None. **M.P. Coba:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.01/V26

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NI R01 AG078297
NIH R01 AG058063
TicTwo Therapeutics

Title: Brain Penetrant Strategies for TYK2 Inhibition to Reverse Neurodegeneration

Authors: *I. PARIKH[1,2], L. E. KOENIG[3], O. MILSTEIN[4], R. MOSLIN[7], N. VEMULA[8], A. H. HELD[5], B. WAINGER[5], P. SINHA[9], M. W. ALBERS[6];
[1]Albers' Lab. - Mass Gen. Brigham, Chelmsford, MA; [2]Lab. of Systems Pharmacol. - Harvard Med. Sch., Boston, MA; [3]Harvard Med. Sch., Cambridge, MA; [4]Massachusetts Gen. Hosp., Newton, MA; [5]Neurol., Massachusetts Gen. Hosp., Charlestown, MA; [6]Neurol., Massachusetts Gen. Hosp., Boston, MA; [7]TicTwo Therapeut., Princeton, NJ; [8]Chem., Paraza Pharma, Montreal, QC, Canada; [9]Neurol., Massachusetts Gen. Hosp. and Harvard Med. Sch., Acton, MA

Abstract: Neurodegenerative diseases such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS) are characterized by protein aggregation and neuroinflammation. Cytoplasmic TDP43 inclusions, a common pathological hallmark of AD and ALS, is spatially coincident with cytoplasmic double-stranded RNA (cdsRNA), a damage associated molecular pattern (DAMP) that is endogenously expressed. The accumulation of cdsRNA triggers a sustained type-1 interferon response in neurons leading to cell death. Tyrosine Kinase 2 (TYK2), a member of the JAK kinase family, mediates this response by phosphorylating STAT proteins, which activate expression of interferon-stimulated genes, contributing to chronic inflammation in neurodegenerative disease. While TYK2 inhibition has demonstrated therapeutic efficacy in inflammatory conditions - most notably deucravacitinib, an FDA-approved allosteric TYK2 inhibitor for psoriasis - its clinical utility in neurodegeneration remains untested due to poor blood-brain barrier penetrance. CNS-targeted TYK2 inhibition remains largely unexplored. Here, we evaluate multiple modalities for achieving brain-penetrant TYK2 inhibition as a strategy to reverse neurodegeneration. First, we present evidence supporting a novel brain-penetrant small molecule inhibitor of TYK2 (TTT-159) as an effective suppressor of neuroinflammatory signaling in human cellular models of neurodegeneration. Treatment with this TYK2 inhibitor resulted in a significant dose-dependent reduction of TYK2-mediated pSTAT1 signaling (IC50 = 20.7 nM) and improved cell viability with full rescue of 14-day post-differentiation human neural progenitor cells treated with a dsRNA mimetic. In parallel, we are exploring a small panel of novel antisense oligonucleotides (ASOs), an approach previously shown to be effective in treating ALS, designed to target TYK2 mRNA to reduce TYK2 expression. Preliminary findings suggest the feasibility of this approach for improved cell viability. These brain-penetrant strategies will be evaluated in vivo mouse models and aim to develop a framework for CNS-targeted TYK2 inhibition, which is a promising avenue for the treatment of neuroinflammatory and neurodegenerative disease.

Disclosures: I. Parikh: None. **L.E. Koenig:** None. **O. Milstein:** None. **R. Moslin:** A. Employment/Salary (full or part-time):; TicTwo Therapeutics. **N. Vemula:** A. Employment/Salary (full or part-time):; Paraza Pharma. **A.H. Held:** None. **B. Wainger:** None. **P. Sinha:** None. **M.W. Albers:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.02/V27

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF Grant RS-2022-NR070151
NRF Grant RS-2024-00402116
NRF Grant RS-2024-00415957

Title: Cellular composition-dependent network responses to oligomeric amyloid-β42 in MEA based neural culture models

Authors: *H. HYEON, D. KIM, S. HWANG, S. JUN;
Ewha Womans Univ., Seoul, Korea, Republic of

Abstract: Alzheimer's disease (AD) is associated with early synaptic dysfunction and abnormal neural network activity preceding overt neuronal loss. Oligomeric amyloid-β42 (oAβ42) is considered a key contributor to these early functional alterations. Glial cells, including microglia and astrocytes, actively participate in synaptic regulation and may influence neuronal responses to amyloid pathology. In this study, we investigated how cellular composition affects electrophysiological responses to oAβ42 using microelectrode array (MEA)-based neuronal culture models. Primary hippocampal neurons and cortical microglia were isolated from postnatal day 1 mice. Three culture conditions were established on MEAs: glia proliferation-inhibited neuron cultures (N), neuron-microglia co-cultures (N-M), and neuron-microglia-astrocyte mixed cultures (N-M-A). oAβ42 oligomers were prepared from amyloid beta-42 S26C dimers and applied at 100 nM. Spontaneous neural activity was recorded before and after treatment. Network activity was assessed using multiple electrophysiological metrics, including mean firing rate, burst rate, synchrony, and functional connectivity. Parameters were normalized to baseline activity and compared with corresponding untreated controls. Preliminary analyses revealed culture-dependent response patterns following oAβ42 exposure. Mean firing rate and burst rate exhibited heterogeneous changes across culture conditions and time points. In contrast, burst-related measures showed more consistent trends. Burst percentage tended to decrease in neuron-only and neuron-microglia cultures following prolonged exposure, whereas neuron-microglia-astrocyte cultures maintained relatively stable burst activity. Synchrony and functional connectivity analyses further revealed distinct temporal trajectories among culture conditions. Neuron-only cultures generally showed declining synchrony and connectivity following oAβ42 treatment, whereas co-culture and mixed-culture models displayed distinct temporal response patterns. Although substantial variability was observed across recordings, these findings suggest that cellular composition influences network-level responses to oAβ42. Together, these results provide preliminary evidence that glial cell populations contribute to differential electrophysiological responses in AD-related neural culture models and support the need for further investigation of neuron-glia interactions in amyloid-associated network dysfunction.

Disclosures: H. Hyeon: None. **D. Kim:** None. **S. Hwang:** None. **S. Jun:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.03/V28

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Human iPSC-derived cortical neurons and co-culture as a translational platform for modelling neurodegeneration

Authors: D. WALLBANK, E. BRAVINGTON, *S. HUMPHREYS, S. VYAS;
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Abstract: The FDA Modernization Act 2.0 invites alternatives to animal testing, to improve the translational success of clinical drug candidates. Human induced pluripotent stem cell (hiPSC)-derived neurons offer a more physiologically relevant model for pre-clinical assessment. Axol have developed a quad-culture model supporting function of iPSC-derived, isogenic, cortical excitatory and inhibitory neurons, microglia and astrocytes. Spontaneous neuronal activity (SNA) was monitored using Incucyte Neuroburst (Sartorius) and markers of each cell type examined by immunocytochemistry. Microglial addition increased neuronal activity and synchronisation. As clinical trials for dementia increasingly include drugs targeting neuroinflammation, coculture of neurons and glia is a relevant model for in vitro compound screening. Additionally, iPSC-derived cortical neurons from donors affected by sporadic Alzheimer's Disease (sAD) were matured and characterized in terms of neurite outgrowth and response to stressors such as glutamate and beta amyloid. Incorporating cells derived from donors with sAD into quad culture alongside the use of physiologically relevant stressors provides a useful human cell platform to test therapies for neurodegeneration.

Disclosures: D. Wallbank: A. Employment/Salary (full or part-time):; Axol Bioscience. **E. Bravington:** A. Employment/Salary (full or part-time):; Axol Bioscience. **S. Humphreys:** A. Employment/Salary (full or part-time):; Axol Bioscience. **S. Vyas:** A. Employment/Salary (full or part-time):; Axol Bioscience.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.04/W1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: In vitro AD models for efficacy evaluation of neurotoxicity and neuroinflammation induced by Aβ oligomers

Authors: *L. CHEN[1], L. ZHU[1], J. XU[1], S. ZHANG[1], P. YE[1], R. FENG[2];
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Abstract: One core pathological hallmark of Alzheimer's disease (AD) is abnormal beta-amyloid (Aβ) aggregation, where Aβ oligomers are considered the primary neurotoxins. Traditional in vitro models often fail to simultaneously simulate early synaptic dysfunction and neuroinflammatory responses, or lack human genetic backgrounds. Therefore, constructing a multidimensional in vitro system—including primary neurons, primary microglia, and

healthy/patient-derived human induced neurons (iNs)—is crucial for elucidating early AD toxicity mechanisms and drug screening.We established three complementary in vitro models: (1) Primary hippocampal neurons to evaluate early toxicity regarding synaptic connectivity and electrophysiology at the population level, addressing limitations of cytotoxicity-only assays. (2) Primary microglia to investigate Aβ-induced neuroimmune activation and antibody-dependent cellular effects. (3) Human PSEN1-mutant basal forebrain cholinergic neurons (BFCNs) to simulate endogenous Aβ accumulation, offering high translational value.High concentrations of exogenous Aβ oligomers (≥10 μM) significantly decreased hippocampal neuron viability. However, 5 μM Aβ did not compromise viability yet increased intracellular Aβ accumulation and downregulated TUJ1 expression. Multi-well MEA recordings showed reduced spontaneous spike and burst firing, disrupting synchronized network activity, confirming the "non-lethal but dysfunction-inducing" toxicity of low-dose Aβ. Furthermore, ≥1 μM Aβ oligomers significantly activated microglia (enhanced IBA1/CD68 signals). Co-treatment with Trontinemab—an antibody that binds Aβ plaques and recruits microglial phagocytosis—increased Aβ-engulfing microglia and significantly reduced plaque size (<1000 μm²), indicating enhanced immune clearance.In human PSEN1-mutant BFCNs, intraneuronal Aβ aggregated over 3-6 weeks of culture. Lecanemab treatment—a monoclonal antibody targeting soluble Aβ protofibrils—reduced abnormal Aβ accumulation and attenuated the decline in evoked action potentials.This in vitro AD platform effectively characterizes Aβ oligomer-induced neurotoxicity and immune dysregulation beyond simple cell viability. Trontinemab and Lecanemab demonstrated therapeutic efficacy in enhancing immune clearance and inhibiting Aβ accumulation, respectively. Future studies will expand this system to test combination therapies, aiming to accelerate screening of novel disease-modifying treatments.

Disclosures: L. Chen: A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **L. Zhu:** A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **J. Xu:** A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **S. Zhang:** A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **P. Ye:** A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **R. Feng:** A. Employment/Salary (full or part-time):; ChemPartner Corporation.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.05/W2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA R03AG087482
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The Emory Center for New Medicines Therapeutic Advancement Award

Title: Targeting the p38-MK2 Complex to Suppress Neuroinflammation in Neurological Disorders

Authors: J. GRALLA[1], P. FLEMING[2], E. JIN[1], N. OWENS[1], K. NEGRÓN[1], T. BEYETT[1], J. ANDERSEN[1], J. JIANG[3], Z. WEN[4], Y. DU[1], H. FU[1], *A. A. IVANOV[1];
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Abstract: Neuroinflammation is a major contributor to the progression of various neurological disorders, including Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), making it an attractive target for therapeutic development. A central regulatory mechanism of inflammatory signaling in microglia, astrocytes, and neurons is the interaction between p38 mitogen-activated protein kinase (p38) and MAPK-activated protein kinase 2 (MK2), which controls the production of proinflammatory cytokines including TNF-α, IL-1β, and IL-6. Dysregulation of the p38/MK2 signaling axis has been implicated in multiple neurodegenerative diseases, where chronic neuroinflammation contributes to neuronal dysfunction, neurodegeneration, and disease progression. Although this pathway is well established as a driver of neuroinflammation, direct inhibitors of p38 or MK2 have not yet received FDA approval, underscoring the need for novel approaches to disrupt their functional coupling. To address this unmet need, we combined AI-based structural modeling, molecular dynamics simulations, and high-throughput biochemical screening to identify peptide and small-molecule disruptors of the p38/MK2 complex. This platform identified multiple active compounds, including the FDA-approved BCR-ABL inhibitor Nilotinib and the α_1-adrenergic receptor antagonists Doxazosin, Terazosin, and Alfuzosin, which disrupted the p38/MK2 complex and suppressed cytokine responses in microglia. Biochemical assays confirmed compound binding to p38, MK2 displacement, and attenuation of cytokine production in human microglial cells. Structure-activity relationship (SAR) analysis of Nilotinib analogs identified key aromatic moieties and hydrogen-bonding features critical for activity, informing future scaffold optimization. Together, these findings establish disruption of the p38/MK2 protein-protein interaction as a non-ATP-competitive strategy for selectively modulating neuroinflammatory signaling and demonstrate the potential of drug repurposing to accelerate the development of neuroimmune therapeutics for various neurological disorders, including AD and ALS.

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Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

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Program #/Poster #: PSTR011.06/W3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RF1AG091371

Title: Extracellular CIRP induces microglial phagocytic dysfunction via STAT3/miR-155 to promote Alzheimer's disease tauopathy

Authors: *D. AYLAR[1], D. LAPIN[1,2], A. SHARMA[1,2], P. WANG[1,2];
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Abstract: Neuroinflammation and microglial dysfunction drive the progression of tau-mediated neurodegeneration in Alzheimer's disease (AD). Extracellular cold-inducible RNA-binding protein (eCIRP), a damage-associated molecular pattern released under stress, has emerged as a potent mediator of innate immune inflammation. However, its role in microglial phagocytic dysfunction and tau clearance in AD remains elusive. We hypothesized that eCIRP induces microglial phagocytic dysfunction in tau clearance in AD via TLR4/STAT3/miR-155 pathway. Plasma samples from AD patients and age- and sex-matched healthy control subjects (n=10/group) were subjected to ELISA to quantify eCIRP and soluble triggering receptor expressed on myeloid cells 2 (sTREM2), a biomarker of microglial inflammation. Plasma levels of eCIRP (5.1-fold) and sTREM2 (2.5-fold) were significantly higher in AD patients than those in control subjects ($p<0.005$) and strongly correlated (Spearman's rho=0.82, p=0.006). To examine the effect of eCIRP on microglial phagocytosis of tau, primary mouse microglia (n=8/group) were stimulated with eCIRP for 24 h. eCIRP significantly reduced uptake of fibrillar tau, as confirmed by immunoblotting (65%), confocal imaging (42.6%), and flow cytometry (43.4%). Phagocytic receptor expression and STAT3/miR-155 axis in primary microglia were quantified by qPCR (n=11/group), immunoblotting (n=6/group), or flow cytometry (n=6/group). eCIRP markedly reduced mRNA and surface protein expression of CX3CR1, a key microglial receptor for tau internalization, and MerTK, a phagocytic receptor, in wild-type (WT) microglia, but not in TLR4-KO microglia. eCIRP induced STAT3 activation by 5.2-fold and miR-155 expression by 28.6-fold in WT microglia, whereas this response was absent in TLR4-KO microglia. Pharmacological inhibition of eCIRP-TLR4 signaling with the antagonist peptide C23 effectively inhibited eCIRP-induced STAT3 activation (32.4%) and miR-155 expression (47.3%), while restoring eCIRP-suppressed CX3CR1 expression to control levels. Collectively, our data demonstrate a strong correlation between eCIRP and microglial inflammation in AD patients, identify eCIRP as a novel mediator of microglial phagocytic dysfunction through TLR4/STAT3/miR-155 signaling, and highlight C23 peptide as a potential strategy to improve the clearance of pathological tau in AD. These findings provide novel insights into the mechanisms underlying eCIRP-induced microglial phagocytic dysfunction and support targeting the eCIRP-TLR4 axis as a potential therapeutic strategy for AD.

Disclosures: D. Aylar: None. **D. Lapin:** None. **A. Sharma:** None. **P. Wang:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.07/W4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Two Novel, Highly Characterized, Human Induced Pluripotent Stem Cell Models of Alzheimer's Disease Generate High-Purity Neurons and Secrete Increased Toxic Aβ Monomers

Authors: *J. KEIL[1], A. MOOSA[2], A. GAFFNEY[2], S. A. LOUIS[2], A. EAVES[2]; [1]STEMCELL Technologies, Inc., Oak Park, IL; [2]STEMCELL Technologies Inc, Vancouver, BC, Canada

Abstract: There is a need for human-relevant in vitro models of Alzheimer's disease (AD) to bridge the gap between positive therapeutic outcomes observed in mouse models and the lack of efficacy seen in clinical trials. To address this challenge, we have developed two genetically modified human induced pluripotent stem cell (hiPSC) lines that are isogenic using the SCTi003-A healthy control hiPSC line. The first line carries the K670N/M671L mutation in the amyloid precursor protein (APP) gene, a strong driver of familial AD. The second line is homozygous for the ε4 allele in the apolipoprotein E (APOE) gene, one of the strongest risk factors for late-onset AD. The differentiation potential of the isogenic control (SCTi003-A), APP and APOE hiPSC lines was evaluated using STEMdiff™ Forebrain Neuron Differentiation Medium, Astrocyte Differentiation Medium, and Microglia Differentiation Medium. At the endpoints of each differentiation protocol, the cells were fixed and analyzed by immunostaining or flow cytometry. Spent media from the forebrain neuron differentiation protocol were collected at days 14, 21, and 35, and used to assess Aβ38, Aβ40, and Aβ42 secretion using ELISA. Forebrain neurons were plated as monocultures or in co-culture with SCTi003-A-derived astrocytes on multielectrode array plates, and the electrical activity was measured between days 14 and 48. Both the APP and APOE hiPSC cell lines generated βIIITUB+ neurons with few to no GFAP+ astrocytes after 21 days of forebrain neuron differentiation, and GFAP+ and S100β+ astrocytes after 60 days of astrocyte differentiation respectively (N = 3). After 36 days of microglia differentiation, > 90% of cells from the APP and APOE hiPSC cell lines stained positive for CD45, CD11b, P2RY12, and TREM2 by flow cytometry (N = 3). Interestingly, the levels of the Aβ40 and Aβ42 monomers were higher in the APP and APOE media compared to SCTi003-A (N=3). Between days 16 and 37, the mean firing rate and the network burst frequency were > 2 fold higher in each of the APP and APOE neurons compared to SCTi003-A (N = 1). We conclude that the APP and APOE hiPSC lines efficiently differentiate into disease-relevant neural cell types and display hallmarks of AD underscoring their relevance for translational neuroscience studies.

Disclosures: J. Keil: A. Employment/Salary (full or part-time):; STEMCELL Technologies. **A. Moosa:** None. **A. Gaffney:** None. **S.A. Louis:** None. **A. Eaves:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.08/W5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Midwestern Alzheimer's Advisory Committee

Title: Ligand-dependent FPR2 signaling modulates microglial responses to amyloid beta: Implications for Alzheimer’s disease

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Abstract: Neuroinflammation is a core pathological feature of Alzheimer’s disease (AD). Yet, clinical strategies targeting it have largely failed, underscoring the need to better understand inflammatory resolution mechanisms. The promiscuous formyl peptide receptor 2 (FPR2) and its pro-resolving ligand Annexin A1 (AnxA1) form a key myeloid resolution axis in peripheral immunity. However, its role in microglia remains poorly understood. The additional engagement of FPR2 by amyloid beta (Aβ) highlights how distinct ligands might evoke divergent signaling outcomes, driving overall microglial responses in AD. We investigated how FPR2 signaling modulates microglial responses to Aβ. In BV2 microglia, exposure to oligomeric Aβ induced metabolic and NADPH oxidase-dependent oxidative stress in the absence of robust classical inflammatory activation, supporting non-canonical activation states. Pharmacological activation of FPR2 suppressed oxidative stress and promoted pro-resolving phenotypic markers, indicating that receptor activation can modulate Aβ-induced microglial dysfunction. To assess the contribution of endogenous resolution pathways, we evaluated Aβ-induced inflammatory activation, oxidative stress, and phagocytic function in primary microglia derived from AnxA1 knockout mice using ELISA, confocal microscopy and flow cytometry. In parallel, analysis of human post-mortem transcriptomic datasets (ROSMAP, MSBB, and MAYO) revealed increased expression of *ANXA1*, *FPR2*, and NADPH oxidase subunits in AD-vulnerable brain regions, suggesting concurrent engagement of resolution-associated and oxidative stress pathways in human disease. Together, these findings support a model in which FPR2 signaling integrates pro-resolving and Aβ-driven inputs to regulate microglial functional states.

Disclosures: E.S. Wickstead: None. **H. Kim:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.09/W6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Immunocompetent human brain organoids for modeling Alzheimer's Disease

Authors: N. COUNGERIS, V. ALSTAT, J. PERKINS, E. JOHNS, A. LACROIX, *C. M. BUTT;
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Abstract: Despite significant resources directed towards understanding the pathologies of Alzheimer's disease (AD) and AD-related dementias, progress on developing drug candidates has been slow, and there are few approved treatments providing disease modifications. Using human induced pluripotent derived stem cells (iPSC), we have developed a scalable cortical organoid model (CNS-3D) that exhibits robust, reproducible, and clinically relevant phenotypes. While standard CNS-3D expresses the primary brain cell types (neurons and glia), we improved the technology by integrating microglia to enable the neuroinflammatory component critical to modeling Alzheimer's Disease. CNS-3D Inflammatory Organoids (CND-3D IO) were generated by seeding CNS-3D with isogenic microglia at 3 weeks of age. The CNS-3D IO were then challenged with 3 different forms of amyloid-β (Aβ) and measured for functional activity (FLIPR calcium imaging) and cytokine profiling. Consistent with previous work in 2D, neuronal monocultures, Aβ oligomers were the most toxic of all Aβ forms. In CNS-3D IO, oligomers and fibrils of Aβ caused significant reductions in FLIPR peak frequency of CNS-3D IO, while Aβ monomers did not, and no form of Aβ affected this measure in standard CNS-3D. Furthermore, Aβ oligomers and fibrils reduced the amplitude and slope of FLIPR peaks, while Aβ monomers did not. Cytokine analysis demonstrated that incorporation of microglia was required for activation of IL-1β and 1L-10 by Aβ oligomers and fibrils. Utilizing AD-related insults, as well as genetic approaches, CNS-3D IO can now test many features of AD to bring promising drug candidates to the clinic faster while maintaining relevance to the human condition.

Disclosures: N. Coungeris: A. Employment/Salary (full or part-time):; 28bio, Inc. **V. Alstat:** A. Employment/Salary (full or part-time):; 28bio, Inc. **J. Perkins:** A. Employment/Salary (full or part-time):; 28bio, Inc. **E. Johns:** A. Employment/Salary (full or part-time):; 28bio, Inc. **A. LaCroix:** A. Employment/Salary (full or part-time):; 28bio, Inc. **C.M. Butt:** A. Employment/Salary (full or part-time):; 28bio.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.10/W7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH U54AG090792

Title: Integrating iPSC-Derived Microglia-Like Cells and Microphysiological Systems to Elucidate the Effects of Polygenic Risk Scores in Alzheimer's Disease

Authors: *A. HASKELL[1,2], S. GOSWAMI[2], R. AFIFY[2], M. GOMEZ[2], C. PROSSER[2], G. CHITTUM[2], J. VISWANATHAN[2], C. GOMES[2], J. S. MEYER[2];
[1]Med. Neurosci., [2]Stark Neurosciences Res. Inst., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Large genome-wide association studies have identified Alzheimer's disease (AD) as being driven by the combined effects of multiple genetic variants, and many of these risk variants are found in genes expressed by microglia. The effects of polygenic risk on the function of microglia are not well understood in AD and related dementias. Because each variant contributes only a small individual effect, capturing their combined, polygenic influence requires models that preserve the full complement of a donor's risk alleles within a human relevant context. Additionally, many transcriptional differences exist between mouse and human microglia, limiting the utility of mouse models to predict human disease mechanisms or therapeutic effects. In this study, we generate 8 lines of human induced pluripotent stem cells (iPSCs) from male and female participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) with high and low polygenic risk scores (PRS) to assess the effects of these genetic factors in a human-specific model. We differentiate these lines into microglia-like cells (MGLs) to assess functional and molecular differences across risk scores using immunofluorescence, live-cell imaging, and immunostimulation. Because of the context-dependent nature of microglia studied *in vitro*, we integrate these MGLs into 3D microphysiological systems composed of assembloid models containing astrocytes and neurons from the same PRS lines to identify molecular differences within the neural microenvironment. Within these donor-matched cultures, we evaluate microglia state to resolve how polygenic risk reshapes neuron-glia interactions that are not apparent in microglia studied in isolation. We show that this model is useful for defining the specific protein dynamics affected by polygenic risk scores. Together, these human-specific platforms offer a tractable system for dissecting how polygenic risk shapes microglial function and the broader neural microenvironment, supporting the identification of disease mechanisms and candidate therapeutic targets in Alzheimer's disease.

Disclosures: A. Haskell: None. **S. Goswami:** None. **R. Afify:** None. **M. Gomez:** None. **C. Prosser:** None. **G. Chittum:** None. **J. Viswanathan:** None. **C. Gomes:** None. **J.S. Meyer:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.11/W8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH U54AG090792

Title: Investigating Astrocyte Dysfunction Associated with Polygenic Risk in an iPSC-Derived Microphysiological System of Alzheimer's Disease

Authors: *C. PROSSER[1,2], R. AFIFY[1,2], G. CHITTUM[3,2], M. GOMEZ[1,2], A. HASKELL[2], J. VISWANATHAN[2], C. GOMES[2], J. S. MEYER[4];
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Abstract: Alzheimer's Disease (AD) is a devastating neurodegenerative disease of which the underlying biological mechanisms are not fully understood. Polygenic risk scores (PRS) provide an estimate of an individual's genetic risk for AD based on the cumulative contribution of many risk loci rather than a single gene mutation. A greater understanding of how genetic risk translates into cellular dysfunction is a critical step toward connecting genetic risk for AD with disease mechanisms. Human induced pluripotent stem cells (iPSCs) offer a physiologically relevant disease model that overcomes differences between animal and human cells. iPSC-derived neural cells retain human genetic backgrounds and allow direct analysis of disease-associated pathways in a controlled experimental setting. Further, astrocytes play essential and increasingly recognized roles in disease progression, yet the mechanisms by which astrocytes promote or exacerbate neurodegeneration remain poorly defined. Here, we utilize human iPSCs to differentiate astrocytes from individuals with varied PRS to assess disease-associated phenotypes. Astrocyte identity and morphology were confirmed by immunocytochemistry and AD-relevant functional properties of PRS-stratified astrocytes in monocultures were examined. Transcriptional profiles of astrocytes were assessed by RNA-seq. Additionally, established markers of astrocyte reactivity were assessed, and AD pathology-relevant assays including phagocytic capacity and inflammatory signaling were investigated. To investigate the effect of PRS-stratified astrocytes on neuronal health, astrocytes were cocultured with Neurogenin-2 (NGN2) induced glutamatergic neurons in a reproducible 3D assembloid model, with ongoing experiments assessing astrocyte-dependent alterations in neuronal phenotype and function. Together, these studies begin to elucidate how polygenic risk influences astrocyte behavior and astrocyte-neuron interactions in an Alzheimer's disease-relevant context, improving the physiological relevance to human disease and advancing the path towards drug testing and precision medicine.

Disclosures: C. Prosser: None. **R. Afify:** None. **G. Chittum:** None. **M. Gomez:** None. **A. Haskell:** None. **J. Viswanathan:** None. **C. Gomes:** None. **J.S. Meyer:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.12/W9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: RF1AG056998
U19AG068054

Title: INVESTIGATING THE REGULATORY EFFECTS OF CALPAIN AND RCAN1 ON CALCINEURIN IN INDIVIDUALS WITH DOWN SYNDROME AND COMORBID ALZHEIMER'S DISEASE

Authors: *K. QUAN[1], E. HEAD[2];
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Abstract: This project aims to understand the role of neuroinflammatory pathways in the pathology of Alzheimer's disease (AD) and comorbid Down syndrome and AD (DSAD) to determine if immunosuppressants are a therapeutic option for treatment. AD is a debilitating aging disease caused by the accumulation of amyloid beta (Aβ) that affects millions of people. In addition, most individuals with Down syndrome (DS) will develop AD due to an abundance of Aβ pathology stemming from the triplication of APP on chromosome 21 (Hsa21). Recently, immunosuppressants have gained traction as a therapeutic option for AD, specifically those targeting the calcineurin (CN)/NFAT pathway. CN has been observed to become dysfunctionally overexpressed in AD, but its function in individuals with Down syndrome and comorbid Alzheimer's disease (DSAD) remains severely understudied. Two regulators of CN activity, RCAN1 and DYRK1a, are encoded on Hsa21 and may alter the neuroinflammatory phenotypes of individuals with DSAD. Therefore, we used western blotting to investigate the expression of CN/NFAT pathway proteins, CN, RCAN1, and Calpains 1 & 2, in the occipital tissue of individuals from four groups: without pathology (Control), with late-onset AD (LOAD), with DS (DS), and with DS and AD (DSAD). There were no differences in the expression of these four proteins between groups. The overall findings suggest that protein expression may not be a defining factor in clinical AD pathology. Future studies should investigate protein activity relative to expression levels to better understand the potential of targeting CN for drug therapy in AD and DSAD.

Disclosures: K. Quan: None. **E. Head:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.13/W10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant U54AG090792

Title: Development of CRISPR/CAS9 Gene-Edited Microphysiological Models as Translational Tools to Model and Treat Alzheimer's Disease using Precision Medicine Approaches

Authors: *J. VISWANATHAN[1,2], C. GOMES[2,1], R. AFIFY[1,2], A. HASKELL[1], C. PROSSER[1], S. CANFIELD[3], F. GUO[4], J. S. MEYER[2,1];
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Abstract: Microphysiological system (MPS) models generated through the differentiation of human induced pluripotent stem cells (iPSCs) are multi-cellular platforms that allow for the study and analysis of complex cellular interactions for disease modeling and drug discovery. However, these models have often lacked rigor and consistency, highlighting a critical need to generate reproducible and scalable MPS models for AD/ADRD studies. The Indiana University MPS-AD center is developing reproducible, scalable, and standardized 3D MPS models that recapitulate key features of human AD/ADRD pathophysiology. CRISPR/Cas9 gene editing is leveraged to introduce AD gene variants into deeply characterized ADNI patient lines (n=4) with high or low polygenic risk score for AD, resulting in isogenic sets of cell lines. Neurons, astrocytes, microglia, and brain microvascular endothelial cells from parent lines and gene edited lines are first reproducibly differentiated from iPSCs to create tier 1 MPS models. These are deeply characterized (transcriptomics and phenotypic assays) to allow the data driven selection of models to advance to tier 2 for further development into vascularized scaffolds, drug testing, PK/PD modeling, and biomarker profiling. This is a translationally relevant framework to advance development of engineered MPS models using data-driven go/no-go checkpoints. Cell lines are shared via NCRAD, plasmids are made available via Addgene, and characterization data and protocols are shared via the AD Knowledge Portal. The IU MPS-AD models serve as precision medicine research tools to investigate the complex biology of AD/ADRD and accelerate multiple aspects of drug discovery and preclinical drug development. The resources developed from the IU MPS-AD are being made available to the research community along with the associated data, protocols, and rigor metrics to facilitate uptake and reproducible implementation. *PLCG2* was selected as the first AD gene where both the disease variant (*M28L*) and protective variant (*P522R*) are in development for the study of neuroinflammatory consequences of *PLCG2* variants on AD pathophysiology. Following *PLCG2*, cell lines and models will be developed for *INPP5D*, *ABCA7*, *MTHFR*, *COL4A1*, and other nominated AD/ADRD targets using the same framework. The structure of the consortium facilitates both internal and external collaborations to enhance relevance of these models for the research community.

Disclosures: J. Viswanathan: None. **C. Gomes:** None. **R. Afify:** None. **A. Haskell:** None. **C. Prosser:** None. **S. Canfield:** None. **F. Guo:** None. **J.S. Meyer:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.14/W11

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Accelerated Directed Differentiation of Human Induced Pluripotent Stem Cell Derived Cortical Neurons

Authors: *D. ARORA, P. WALSH, V. TRUONG;
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Abstract: Alzheimer's Disease (AD) is the leading cause of neurodegenerative cognitive decline and dementia worldwide. It is characterized by the progressive deterioration of specific cortical layers, leading to early onset symptoms such as loss of memory and spatial awareness. Despite significant investment in drug development, the high failure rate of AD clinical trials emphasizes the need for reliable human-relevant models to study disease progression and therapeutic response. TBR1+ deep-layer glutamatergic cortical neurons are among the first brain regions to degenerate in AD, making them the key target for investigating disease pathology and developing treatments. We developed a rapid, small-molecule and growth factor based directed differentiation protocol that produces high-purity TBR1+ neurons within seven days from human induced pluripotent stem cells (hiPSCs), without genetic manipulation or overexpression of transcription factors. The differentiation protocol progresses through expected neurodevelopmental stages encompassing prosencephalic (SIX3) and dorsal telencephalic patterning (PAX6/FOXG1) with few undetermined contaminants. The resulting neurons express markers including TBR1, CUX1/2, VGLUT2 and TUJ1 confirming cortical identity. To assess maturation, hiPSC-derived cortical neurons were cultured for three weeks to assess morphological, transcriptional, and functional maturation. The population exhibited high neuronal purity, with progressive increases in soma size and axonal density over time. Time course qPCR and bulk RNA sequencing confirmed cortical identity. Functional maturation was assessed via multielectrode array recordings and showed spontaneous baseline activity. Together, these data demonstrate a fast, scalable, and genetically unmodified approach for generating subtype-specific cortical neurons. The hiPSC-derived TBR1+ neurons provide a valuable human-relevant platform for studying cortical neuron biology, modeling neurological disease, and evaluating potential therapeutic interventions.

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

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.15/W12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01 NS138259-02

Title: Elovanoids target the biological clock telomerase/telomere and restore epigenomic and functional resilience in human neuronal-glial cells after damage.

Authors: *S. BHATTACHARJEE[1], S. KALA BHATTACHARJEE[2], N. G. BAZAN[3]; [1]Neurol. and Neurosci. Ctr. of Excellence, LSUHSC, New Orleans, LA; [2]Neurosci. Ctr. of Excellence, LSU Hlth., New Orleans, LA; [3]Neurosci. Ctr., Louisiana State Univ. Hlth. New Orleans, New Orleans, LA

Abstract: Telomere attrition and telomerase suppression are stress-responsive biological clock mechanisms that intersect with epigenomic drift, senescence programming, and loss of neuronal structure in neurodegenerative disease. We tested whether elovanoids (ELVs; ELV-N32 and ELV-N34), endogenous pro-homeostatic lipid mediators derived from ELOVL4-generated very-long-chain polyunsaturated fatty acids, preserve telomerase/telomere integrity and restore neuronal-glial resilience after injury. Primary human neuronal-glial (HNG) co-cultures differentiated from human neuroprogenitor cells and matured for 21 days were challenged with oligomeric amyloid-β (OAβ, 10 μM) or the ferroptosis inducer erastin (10 μM), followed by treatment with ELVs (typically 200 nM) or ELV precursors (32:6 or 34:6; 500 nM in selected experiments). Compared with unstressed controls, OAβ and erastin induced dendritic degeneration, reduced cell viability, increased senescence-associated β-galactosidase positivity, and upregulated CDKN2A/p16INK4a, CDKN1A/p21CIP1, CDKN1B/p27KIP1, and TP53/p53. Stress also disrupted epigenomic homeostasis, including altered 5-methylcytosine/5-hydroxymethylcytosine balance, dysregulated DNMT, TET, and demethylase activities, and remodeling of H3K27/H3K9 methylation and acetylation marks. Critically, OAβ shortened telomeres and suppressed telomerase reverse transcriptase (TERT) transcription, whereas ELVs preserved telomere length and restored TERT expression. Across assays, ELVs shifted epigenomic enzyme activities toward baseline, reversed stress-driven histone changes, reduced senescence burden, improved cell survival, and preserved β-III tubulin-positive dendritic architecture. Data were obtained from three or more independent experiments and analyzed by one-way ANOVA with Holm-Sidak post hoc testing. These findings identify ELVs as multi-level resilience signals in human neuronal-glial cultures that target the telomerase/telomere axis while coordinating epigenomic, senescence, and structural protection under amyloidogenic and ferroptotic stress.

Disclosures: S. Bhattacharjee: None. **S. Kala Bhattacharjee:** None. **N.G. Bazan:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.16/W13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: T32AG087922 (MT)
Emory ADRC P30AG066511 (MT)
RF1AG79199 (DW)
R01AG062581 (DW)

Title: Human Locus Coeruleus Organoids Show Regional Selective Vulnerability in Alzheimer's Disease

Authors: *M. TISH[1], Y. GAO[1], Z. OU[1], F. BIREY[1], D. WEINSHENKER[2];
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Abstract: The locus coeruleus (LC) is the earliest brain region to exhibit hyperphosphorylated tau (ptau) inclusions in Alzheimer's disease (AD) and undergoes catastrophic degeneration at later disease stages. As the brain's primary noradrenergic nucleus, the LC is the principal source of norepinephrine (NE) in the forebrain. Disruption of LC-NE signaling is associated with AD symptoms, as forebrain NE modulates attention, arousal, stress response, and learning and memory. Moreover, the LC may transmit pathogenic tau to the forebrain via its extensive projections. However, nearly all information about the LC in AD has been derived from rodent models and postmortem or human imaging studies. Consequently, how early ptau accumulation in the human LC alters neuronal function, NE transmission, and tau propagation remains unknown. To address this gap, we developed organoids that possess noradrenergic neurons and many aspects of the human LC.
Organoids containing neurons resembling the LC were generated from human induced pluripotent stem cells using growth factors that induce a hindbrain fate. Cells were taken from patients with familial AD, as well as healthy controls. These organoids were then characterized using HPLC, immunohistochemistry, RNA-scope and RNA-sequencing. Human cortical organoids were used for comparison. LC organoids exhibited significantly higher levels of NE and dopamine compared to cortical controls. They also accumulated neuromenalin-like pigment and expressed many proteins and transcriptomic characteristics of LC neurons, including tyrosine hydroxylase, dopamine beta-hydroxylase, the NE transporter, Phox2A and Phox2B. Bulk RNA sequencing further demonstrated that the transcriptomic profile of LC organoids more closely the of the human LC than did cortical organoids. Notably, transcriptomic analysis revealed that LC organoids derived from familial Alzheimer's disease (AD) patients exhibited gene expression changes consistent with AD-associated pathophysiology. In addition, AD LC organoids displayed an increased 4R:3R tau isoform ratio relative to control LC organoids. Human LC organoids contain LC-like noradrenergic neurons that show pathogenic alterations when generated from familial AD mutation carriers. Studying the structure and function of LC organoids derived from both healthy controls and AD patients may provide new insights into the role of the LC and biology of selective vulnerability in AD.

Disclosures: M. Tish: None. **Y. Gao:** None. **Z. Ou:** None. **F. Birey:** None. **D. Weinshenker:** None.

Poster

PSTR011: Alzheimer's Disease: Neuroinflammation and Immune Actions: *In Vitro* Models I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.17/W14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01NS115977
24AARG-D-1191264

Title: Vascular-Perfused Human Cortical Organoids: A Next-Generation Platform to model tau-driven neurovascular and neuroimmune pathology in Alzheimer's disease

Authors: *V. C. OGBOLU[1], Y. AGARWAL[2], B. L. WOLOZIN[4], P. J. GASKILL[3], L. QIANG[5];
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Abstract: Recent advances in human induced pluripotent stem cell (hiPSC)-derived central nervous system (CNS) organoids have transformed region-specific modeling of human neurodevelopment and neurological disease; however, conventional organoids lack integrated microvasculature and microglia, substantially limiting their physiological fidelity and their capacity to interrogate neurovascular and neuroimmune crosstalk. To overcome these constraints, we engineered syngeneic vascularized, immune-competent cortical organoids (viCOs) by incorporating endothelial, mural, and microglial lineages derived from a single hiPSC source into a unified three-dimensional cortical architecture. These next-generation constructs establish widely spread endothelial-mural networks that extend throughout the organoid core and incorporate transcriptionally defined, functionally mature microglia, as validated by flow cytometry and single-cell RNA sequencing. When challenged with AD-patient-derived tau fibrils, viCOs recapitulated core features of human tauopathy, including tau hyperphosphorylation and aggregation, synaptic degeneration, microglial activation, and amplified inflammatory signaling. Notably, the system revealed a mechanistic linkage between vascular dysfunction and neurodegeneration, wherein blood-brain-barrier (BBB) impairment disrupted vascular flow and clearance pathways, thereby accelerating tau accumulation and propagation. By integrating neuronal, vascular, and immune compartments within a human 3D microphysiological framework, viCOs transcend key limitations of existing organoid models and establish an improved platform to dissect the reciprocal interactions among tau pathology, neurovascular compromise, and inflammation, with broad implications for mechanistic discovery and therapeutic innovation in AD and AD-related dementias.

Disclosures: V.C. Ogbolu: None. **Y. Agarwal:** None. **B.L. Wolozin:** None. **P.J. Gaskill:** None. **L. Qiang:** None.

Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.01/W15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA 1R01AG092661
NINDS 1RF1NS116450

Title: Late-onset Alzheimer's Disease mice show abnormally high brain excitability after focal seizure induction

Authors: *S. GHAROONI KHORRAMI[1], H. FUKUDA[2], Y. SHEN[4], S. J. SUKOFF RIZZO[3], N. F. FITZ[5], B. IORDANOVA[1];
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Abstract: Epilepsy and Alzheimer's disease (AD) are both associated with abnormal neural network excitability, but whether AD-risk genes modify excitation-inhibition balance is still unclear. This study compared electrophysiological seizure dynamics in Late-onset Alzheimer's Disease (LOAD3) mice expressing apolipoprotein APOE4 (MODEL-AD, JAX # 037778) and control (APOE3) mice. We hypothesized that AD-risk genetic background would alter susceptibility to focal seizure induction in the retrosplenial cortex (RSC), an area central to resting state networks. Acute experiments were performed in aged male and female mice LOAD3 (14-17 months, n=3); controls (15-18 months, n=3). Mice were head-fixed and maintained under urethane. A unilateral cranial window was built over RSC. Focal seizures were induced with 4-aminopyridine (4-AP; 100mM). Local field potentials (LFP) were recorded at the 4-AP delivery site with 50 kΩ tungsten electrode using Biopac system. 4-AP delivery, seizure onset, and seizure termination were identifiedfrom 1-150 Hz filtered LFP traces. Quantified parameters included seizure onset latency, duration, maximum ictal spike peak-to-valley amplitude, root-mean-square (RMS) ictal amplitude, and seizure-baseline power spectral density (PSD). LOAD3 mice had higher LFP amplitude and shorter seizure onset latency than controls (59.2 ± 17.9 s vs. 519.6 ± 162.4 s), indicating faster seizure recruitment (Fig. 1). Seizure duration was more variable in LOAD3 mice (771.9 ± 325.9 s vs. 786.2 ± 74.8 s). Our findings reveal abnormally high network excitability in the presence of late life AD-risk genes. Future work willidentify when this abnormal excitability emerges in LOAD3 model and if it has unique LFP signatures that can serve as biomarkers and can be modified by existing epilepsy strategies.

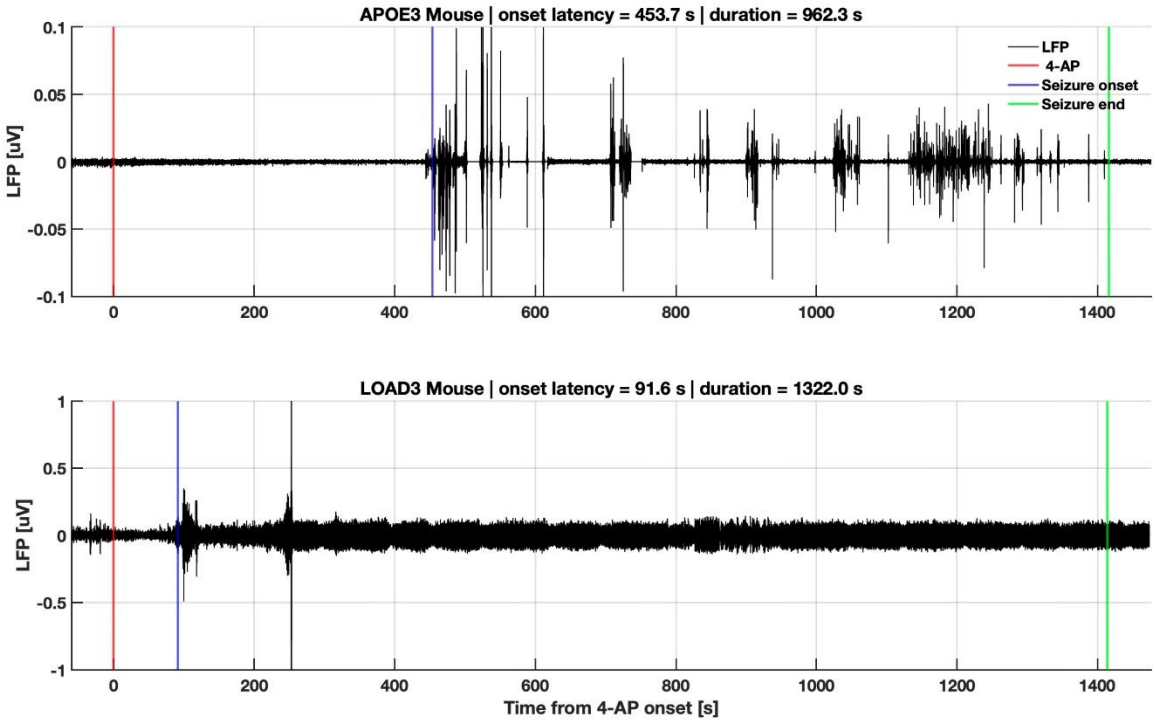


Figure 1. LOAD3 mice show faster seizure onset with higher amplitude compared to control after focal 4-AP delivery. Representative Local Field Potentials (LFP) from one control (top) and one LOAD3 mouse (bottom).

Disclosures: S. Gharooni Khorrami: None. **H. Fukuda:** None. **Y. Shen:** None. **S.J. Sukoff Rizzo:** None. **N.F. fitz:** None. **B. Iordanova:** None.

Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.02/W16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: American Academy of Neurology

Title: APOE isoform-dependent dysregulation of Golgi trafficking and glycosylation in iPSC-derived microglia

Authors: *M. RASTOGI[1], D. BRADEMAN[2], R. HUTTENHAIN[2], M. WERNIG[1]; [1]Pathology, [2]Mol. and Cell. Physiol., Stanford Univ., Stanford, CA

Abstract: The APOE4 allele is the strongest genetic risk factor for late-onset Alzheimer's disease (AD); however, the cell-type-specific mechanisms by which APOE4 disrupts cellular homeostasis remain poorly defined. Evidence points to dysfunction in endo-lysosomal and

secretory pathways, although their relevance in microglia has not been fully established. To directly compare the effects of APOE isoforms in microglia in a physiologically relevant isogenic system and to eliminate confounding factors due to interindividual genetic variation, we generated a conditional knock-in human iPSC line expressing either APOE2/3 or APOE3/4 from the endogenous locus.
Quantitative proteomics of iPSC-derived microglial monocultures identified 30 significantly upregulated and 6 significantly downregulated proteins, with 89 additional proteins detected exclusively in APOE3/4 microglia. The most strongly upregulated protein was CLEC7A (Dectin-1), a neurodegenerative microglial marker that mediates phagocytosis and innate immune activation. Several other upregulated proteins clustered around autophagy and Golgi-to-endosome trafficking, including ATG4A, which regulates autophagosome formation and is consistent with the reported impairment of autophagy in APOE4 cells; SCOC, a Golgi-resident protein essential for autophagosome formation; and AP4S1, an AP-4 adaptor complex component involved in vesicular trafficking from the trans-Golgi network and cargo sorting into the endosomal-lysosomal system. Among the downregulated proteins, the reduction in SLC35A1, a Golgi CMP-sialic acid transporter crucial for glycoprotein sialylation, is consistent with the reported reduced APOE glycosylation in human APOE4 brains, while decreased SYNGR2 (Synaptogyrin-2) points to impaired regulation of membrane trafficking. Proteins unique to APOE3/4 microglia were enriched in glycosylation (POMT2, NDST2, and MPPE1), intracellular trafficking (TMEM115, SFT2D3, VPS13B, and SNX20), and lysosomal function (PPT2, CTSK, and TMEM110).
To resolve organelle-specific alterations and vesicular trafficking, we established Lyso-IP, Endo-IP, and Golgi-IP in iPSC-derived microglial cells. Together, these findings suggest that the Golgi apparatus is a central hub of APOE4-driven proteostatic disruption in microglia, with aberrant glycosylation, impaired autophagy, and dysregulated trafficking as potential mechanisms underlying APOE4-associated microglial dysfunction in AD.

Disclosures: M. Rastogi: None. **D. Brademan:** None. **R. Huttenhain:** None. **M. Wernig:** None.

Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.03/W17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: GF005924

Title: Lipid Metabolism Drivers Of Alzheimer's Disease Risk: APOE and ABCA7

Authors: *D. A. MAY, M. N. STEWART, H. R. FERNANDEZ, S. A. FLOWERS; Neurosci., Univ. of Virginia, Charlottesville, VA

Abstract: Alzheimer's disease (AD) is a fatal neurodegenerative disorder characterized by amyloid plaques and tau tangles, resulting in memory loss and cognitive decline. Approximately 6.7 million Americans currently live with AD, a number projected to reach 13.8 million by 2060, highlighting the urgent need for effective therapies. Black and African American (B/AA) individuals are among the most at-risk US populations, with a 2–3 times higher incidence of AD than non-Hispanic Whites, underscoring the need to better understand disease mechanisms in this group.
Apolipoprotein E (APOE) is the strongest genetic risk factor for sporadic AD, with *APOE4* increasing risk compared to the most common *APOE3* and *APOE2* reducing AD risk. Notably, loss-of-function (LOF) variants in the lipid transporter gene, *ABCA7,* confer almost comparable AD risk as *APOE4* in the high-risk B/AA population. Both *APOE4* and *ABCA7* LOF disrupt lipid metabolism, yet their combined effects remain unexplored.
In the brain, astrocytes produce APOE and, along with neurons, express high levels of ABCA7. ABCA7 is a lipid floppase, transferring lipids to the outer membrane leaflet where APOE mediates lipid efflux and HDL particle formation. I hypothesize that *ABCA7* LOF, exacerbated by *APOE4*, disrupts this lipid efflux pathway, leading to lipid accumulation, impaired astrocyte metabolism, and reduced amyloid-β clearance. My work will use induced pluripotent stem cell derived astrocytes to enable the direct comparison of *ABCA7* LOF in the context of *APOE3* and *APOE4*. Brain hypometabolism precedes AD pathology by decades, while astrocytes are central to the regulation of brain metabolism. ThereforeTherefore, understanding how *ABCA7* LOF and *APOE* genotype together affect astrocyte metabolism is essential.

Disclosures: D.A. May: None. **M.N. Stewart:** None. **H.R. Fernandez:** None. **S.A. Flowers:** None.

Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.04/W18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: RCMI program grant NIMHD U54MD012392
NCCU RIPA Award
NIA R25AG086122
Duke/UNC ADRC P30AG072958
NCCU R245MH129791

Title: Cell-Type-Specific Alterations in Hippocampal Formations in APOE4 Mice

Authors: *S. DUNN[1], Q. CHENG[2], P. LI[3];
[1]North Carolina Central Univ., Raleigh, NC; [2]Biol. and Biotechnical Inst., North Carolina Central Univ., Durham, NC; [3]BRITE, Durham, NC

Abstract: Background Cholinergic deficits are a hallmark pathological feature associated with cognitive decline in Alzheimer's disease (AD). The apolipoprotein E ε4 (APOE4) allele, the strongest genetic risk factor for late-onset AD, is linked to selective vulnerability of basal forebrain cholinergic neurons. The hippocampal formation, a primary recipient of cholinergic input, exhibits pronounced synaptic loss and neuronal degeneration in AD; however, the mechanisms by which disrupted cholinergic signalling affects hippocampal circuitry remain poorly understood. This study aims to define age-dependent changes in hippocampal neuronal subpopulations and their relationship to α7 nicotinic acetylcholine receptor (α7 nAChR) expression, given the high-affinity interaction between amyloid-β and α7 nAChRs. In addition, we examine NLRP3 expression as a marker of pyroptosis to explore the intersection of cholinergic dysfunction and neuroinflammatory cell death in a late-onset AD model.**Methods**Hippocampal brain sections from APOE3 and APOE4 mice at multiple ages were analyzed using immunofluorescence staining for neuronal subtype markers, including β-calretinin and glutamate decarboxylase 67 (GAD67), as well as pathological markers such as amyloid-β and NLRP3. RNAscope in situ hybridization was used to detect nicotinic acetylcholine receptor expression. Images were acquired using a Zeiss confocal microscope and analyzed with Imaris 11.0 software for three-dimensional reconstruction, segmentation, fluorescence intensity measurement, and neuronal quantification.**Results**Preliminary findings reveal distinct expression patterns of β-calretinin and GAD67 across hippocampal subregions, including the dentate gyrus, CA1, and CA3, in APOE3 versus APOE4 mice. These observations suggest that specific neuronal subpopulations exhibit differential vulnerability to cholinergic loss. Ongoing analyses of α7 nAChR and NLRP3 expression aim to delineate the contribution of α7 nAChR to cell-type-specific neuronal vulnerability and neuroinflammatory responses.**Conclusions**This work refines the cellular characterization of cholinergic signaling within the hippocampus and provides insight into APOE4-associated neuronal vulnerability. Identification of cell-type-specific alterations may inform the development of early biomarkers and targeted neuroprotective strategies for Alzheimer's disease.

Disclosures: S. Dunn: None. **Q. Cheng:** None. **P. Li:** None.

Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.05/W19

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R21 NS140565
25AARG-NTF-1377286
NIH L32 MD016519
Burroughs Wellcome Fund Postdoctoral Diversity Enrichment Program

Title: Multimodal biomarker profiling identifies cognitive patterns of repetitive head impact exposure in former American football players

Authors: *B. SZEKELY[1,3], A. MIRMAJLESI[1,3], J. STEARNS[1,3], J. CUMMINGS[4], E. M. REIMAN[5,6,7], R. A. STERN[8,9,10], M. E. SHENTON[11,12,13], R. J. RUSHMORE, III[14,12], H. ARCINIEGA[15,3,2];
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Abstract: Former American football players with histories of repetitive head impact exposure may show persistent cognitive, clinical, neuroimaging, and fluid biomarker differences. Still, the relative contribution of these domains to distinguishing exposed athletes from the general population remains unclear. Using data from the Diagnostics, Imaging, And Genetics Network for the Objective Study and Evaluation (DIAGNOSE) Chronic Traumatic Encephalopathy (CTE) research project, we evaluated whether a global integrated model that combined clinical, cognitive, baseline demographic, genetic, blood plasma, Positron Emission Tomography (PET), structural magnetic resonance imaging (MRI), and diffusion MRI features could distinguish former American football players from asymptomatic unexposed controls. We then compared its performance with classifiers trained separately within each feature domain. We used a trained random forest model for binary classification of former players versus asymptomatic controls. The global integrated classifier outperformed all domain-specific models (area under the receiver operating characteristic curve [AUROC]: 0.952; 95%CI 0.884-0.997). Clinical measures provided the strongest standalone discrimination (AUROC 0.89; 95%CI 0.790-0.964), followed by the cognitive model (AUROC 0.760; 95%CI 0.595-0.902) and the baseline covariate model (AUROC 0.723; 95%CI 0.556-0.880). Performance was lower for structural MRI (AUROC 0.667; 95%CI 0.515-0.803) and blood biomarkers (AUROC 0.609; 95%CI 0.451-0.743), whereas diffusion MRI (AUROC 0.550; 95%CI 0.376-0.729) and PET (AUROC 0.500; 95%CI 0.500-0.500) showed little discriminative ability in isolation. Shapley analyses identified Ascertain Dementia 8 total partner score, Cognitive Change Index total score, plasma phosphorylated tau 231, Interleukin-6, and structural measures of the corpus callosum, amygdala, and sulcal morphology as key contributors to the global model's predictions. Exploratory subgroup analyses further suggested that the multimodal and clinical classifiers showed the most consistent performance across age and apolipoprotein ε4 allele stratifications. These findings suggest that although the integrated feature model provided the strongest overall discrimination between former American football players and controls, much of the signal was driven by cognitive and symptom-based measures.

Disclosures: B. Szekely: None. **A. Mirmajlesi:** None. **J. Stearns:** None. **J. Cummings:** None. **E.M. Reiman:** None. **R.A. Stern:** None. **M.E. Shenton:** None. **R.J. Rushmore:** None. **H. Arciniega:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report

that research relationship even if those funds come to an institution.; National Institutes of Health / NINDS, Alzheimer's Association, National Institutes of Health / NIMHD, Burroughs Wellcome Fund.

Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.06/W20

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Motor neurons use ApoE to regulate the activity of microglia and stability of their synapses under normal and stressed conditions

Authors: *M. C. LOPES[1], R. W. CASTRO[1], A. BARBOSA[1], G. VALDEZ[2];
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Abstract: Growing evidence suggests that ApoE plays important roles in spinal motor neurons. For instance, ApoE expression is significantly increased in injured, aging, and disease-afflicted motor neurons. Stressed motor neurons also increase the expression of various genes connected to ApoE function, many of which are involved in inflammatory responses, neuronal health, and synaptic degradation. More peripherally, *ApoE4* has been associated with motor decline in aging humans. In mice, the overexpression of human *ApoE4* in neurons causes motor deficits and muscle atrophy. Despite these data, the exact role of ApoE in motor neurons remains unknown. Here, we examined ApoE function in motor neurons using an ApoE conditional knockout (ChAT-Cre;$ApoE^{fl/fl}$;Ai14) as well as a humanized APOE4 knock-in ($APOE4^{KI}$) model. Our analyses revealed similar effects of deleting ApoE and expressing ApoE4 on motor neurons. In both mouse lines, we found otherwise healthy motor neurons surrounded by activated microglia. These microglia, however, failed to adequately clear debris following a traumatic injury to the motor neurons. This impaired debris clearance correlated with the preservation of more motor neuron synapses, which are lost following a traumatic injury in control mice. These findings suggest that a loss of ApoE function alters the communication between motor neurons and microglia that is required to maintain homeostasis and to rearrange the spinal motor circuit in response to stress. Finally, we utilized proteomics to identify promising genes and mechanisms through which mouse ApoE and human ApoE4 may act to affect motor neurons, microglia, and the motor circuitry. Overall, these data provide unique insights into the role of ApoE in motor neurons under both normal and stressed conditions.

Disclosures: M.C. Lopes: None. **R.W. Castro:** None. **A. Barbosa:** None. **G. Valdez:** None.

Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.07/W21

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG069196
R01AG074216

Title: ApoE4-associated cell-type-specific transcriptional remodeling in the olfactory bulb of PS19 tauopathy mice

Authors: S. ZAFAR, *S. LIU;
Physiol. and Pharmacol., Univ. of Georgia, Athens, GA

Abstract: Olfactory dysfunction is an early feature of neurodegenerative disorders and may reflect vulnerability of olfactory circuit components prior to the onset of widespread brain pathology. Apolipoprotein E4 (ApoE4) is the strongest genetic risk factor for late-onset Alzheimer's disease; however, whether ApoE4 contributes to age-dependent, cell-type-specific transcriptional vulnerability within the olfactory bulb (OB) during tauopathy progression remains poorly understood. To bridge this knowledge gap, we performed single-nucleus RNA sequencing to profile OB tissue from PS19 tauopathy mice carrying human ApoE3 or ApoE4 at 3 and 9 months of age. For each age group, OB nuclei were collected from PS19-ApoE3 and PS19-ApoE4 mice (n=4 mice per genotype; 2 males and 2 females). Nuclei were integrated, clustered, and annotated into major OB cell populations, followed by genotype-specific differential expression analysis within each annotated cluster.Across both age groups, nuclei exhibited comparable distribution across experimental conditions, supporting downstream cell-type-level comparisons. At 3 months, ApoE4-associated transcriptional differences were modest and primarily detected in select neuronal clusters, including interneuron-like and mitral/tufted-like neuronal populations. Exploratory pathway annotation of the differentially expressed genes suggested potential involvement of metabolic and mitochondrial RNA-related processes; however, these observations should be interpreted cautiously given the limited number of differentially expressed genes identified. At 9 months, genotype-associated transcriptional differences appeared more pronounced in specific neuronal populations. In an interneuron-like cluster, differentially expressed genes were enriched in pathways related to receptor-mediated and neurotrophic signaling. In a mitral/tufted-like neuronal cluster, differentially expressed genes were mapped to pathways involved in synaptic transmission, neurotransmitter signaling, ion channel function, and neuronal communication.Collectively, these preliminary findings suggest that ApoE4-associated transcriptional alterations in the OB are not uniformly distributed across all cell types but instead emerge in an age- and neuronal population-dependent manner in the PS19 tauopathy background, indicating selective OB neuronal populations as potential sites of early APOE4-mediated vulnerability during tauopathy progression.

Disclosures: S. Zafar: None. **S. Liu:** None.

Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.08/W22

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CIHR Grant PJT- 173540
PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research, and funding partners listed on the PPMI website

Title: Association of APOE4 with early cortical morphological changes and CSF biomarkers in Parkinson's disease: Evidence from the PPMI cohort

Authors: *A. E. ROSAL[1,2], E. TORRES CARMONA[2,1], I. BOILEAU[1,2], A. GRAFF-GUERRERO[1,2], A. P. STRAFELLA[2,1,3];
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Abstract: *Apolipoprotein E4* (*APOE4*) has been associated with cognitive impairment in Parkinson's disease (PD), although its role in this non-motor symptom remains unclear. Alterations in cortical morphology have been reported independently in both cognitively impaired PD patients and *APOE4* carriers. However, no study has comprehensively examined the relationship between *APOE4*, cortical morphology, and cognition within a PD cohort. This study aimed to determine whether *APOE4* influences cognitive performance in early-stage PD by examining its effects on the cortical morphology of regions vulnerable to PD-related cognitive impairment. Data was obtained from the Parkinson's Progression Markers Initiative (PPMI) (https://www.ppmi-info.org). Baseline T1-weighted MRI scans were analyzed from 51 PD *APOE4* carriers (58.7 ± 9.1 years; 16 females, 35 males) and 120 non-carriers (62.9 ± 9.2 years; 48 females, 72 males). Cortical morphological measures, including surface area and various folding properties (folding index and mean curvature) were extracted using FreeSurfer 7.1. Group differences were assessed using ANCOVAs controlling for age, sex, and disease duration, with estimated total intracranial volume included as a covariate for surface area analyses. Pearson correlations and regression analyses were then performed to evaluate associations between significant morphological measures and scores from domain-specific cognitive tests if needed. Secondary analyses examined relationships between significant morphological measures and cerebrospinal fluid (CSF) biomarkers associated with PD-related cognitive impairment and *APOE4*, including amyloid, tau, neurofilament light chain (NfL), α-synuclein, and glial fibrillary acidic protein (GFAP) to provide mechanistic insight. PD *APOE4* carriers exhibited increased surface area and folding index in the left angular gyrus (AnG) compared to non-carriers. Although left AnG surface area was associated with visuospatial performance, this relationship did not remain significant after covariate adjustment. Notably, both left AnG surface area and folding index were positively correlated with CSF NfL levels in PD *APOE4* carriers. No significant associations were observed with the other CSF biomarkers. These findings suggest that *APOE4* may be associated with specific cortical morphological alterations in early PD and that these structural differences may reflect underlying neurodegenerative processes related to

axonal damage. Longitudinal studies are needed to validate these findings and overall determine whether these cortical alterations predict future cognitive decline in PD.

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Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.09/W23

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Maryland Stem Cell Research Fund
Lieber Institute for Brain Development
Carol and Gene Ludwig Award

Title: Induced pluripotent stem cell models of Alzheimer’s Disease genetic risk in the locus coeruleus

Authors: *H. A. ALGRAIN[1], Y. WANG[1], A. MCCORD[1], S. JOSHY[1], B. MULVEY[1,2], H. DIVECHA[1,3], S. V. BACH[1,2], I. DEL ROSARIO[1], S. E. MAGUIRE[1], R. A. MILLER[1], J. E. KLEINMAN[1,2], L. COLLADO TORRES[1,6,7], T. M. HYDE[1,2,4], S. HAN[1,2,5], S. C. HICKS[6,7,8,9,10], D. R. WEINBERGER[1,2,3,4,5], K. R. MAYNARD[1,2,3], K. MARTINOWICH[1,2,3,10], T. SAWADA[1,4], S. C. PAGE[1,2];
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Abstract: The locus coeruleus (LC), the brain's primary source of norepinephrine (NE), is amongst the earliest sites of Alzheimer's disease (AD) pathology, marked with hyperphosphorylated tau (pTau) accumulation and loss of neuromelanin (NM) pigmentation. NM accumulates with age and is hypothesized to contribute to LC neuron vulnerability in AD. NM's metal ions are detectable via MRI, and NM-sensitive MRI is emerging as a promising early biomarker, offering potential for preventative intervention before LC degeneration and symptom onset for at-risk individuals. AD risk is disproportionately elevated in women and individuals of African ancestry (AA) compared to European ancestry (EA). Additionally, the strongest genetic contributor to AD risk is allelic variation at the apolipoprotein E (APOE) locus,

with the APOE4 allele increasing risk and APOE2 providing protection in an ancestry-dependent manner. The mechanisms by which these factors drive pathology remain poorly understood. We applied spatially-resolved transcriptomics (SRT) and NM imaging to postmortem LC tissue from neurotypical adults with varying AD risk to better understand the contributions of these risk factors prior to disease onset. We identified reduced astrocytic gene expression proximal to LC neurons in *APOE4* carriers, ancestry-dependent (AA vs EA) differences in LC gene expression, higher APOE gene expression correlates with reduced NM content, and NM-associated genes are enriched for aging-related pathways. To mechanistically interrogate these findings, we developed an iPSC-based cellular model of the LC (iPSC-LC) by differentiating human iPSCs into NE-expressing neurons and hindbrain astrocytes, with fate specification confirmed by qPCR and immunocytochemistry (ICC). We verified the expression of noradrenergic fate-specifying transcription factors (PHOX2A and PHOX2B) and markers related to NE synthesis, release, and transport (*TH, DBH and SLC6A2*). For iPSC-astrocytes, we verified the expression of canonical markers including S100B and GFAP. We then assessed the effects of a cellular aging protocol on differentiation efficiency, NM accumulation, and cellular viability using qPCR, ICC, H&E staining, and cellular activity measures. Together, these multi-modal, human-derived datasets position us to dissect the cellular and molecular mechanisms linking genetic risk factors to early noradrenergic neurodegeneration in AD.

Disclosures: H.A. AlGrain: None. **Y. Wang:** None. **A. McCord:** None. **S. Joshy:** None. **B. Mulvey:** None. **H. Divecha:** None. **S.V. Bach:** None. **I. Del Rosario:** None. **S.E. Maguire:** None. **R.A. Miller:** None. **J.E. Kleinman:** None. **L. Collado Torres:** None. **T.M. Hyde:** None. **S. Han:** None. **S.C. Hicks:** None. **D.R. Weinberger:** None. **K.R. Maynard:** None. **K. Martinowich:** None. **T. Sawada:** None. **S.C. Page:** None.

Poster

PSTR012: Alzheimer's Disease: APOE and Associated Pathways

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.10/W24

Topic: I.06. Social Cognition

Title: ApoE module expression in the MTG shows no consistent trend across Braak stage in the SEA-AD cohort

Authors: *J. VERGIS[1], D. DATTA[2], R. E. MCCULLUMSMITH[1];
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Abstract: Among the several dysregulated proteins in Alzheimer’s Disease (AD), Apolipoprotein E (ApoE) represents a metabolic network hub. However, whether ApoE-associated genes show monotonic trends at the gene expression level over Braak stage remains uncharacterized. Owing to its centrality in AD, we hypothesized that by examining an scRNA-seq dataset of the MTG from SEA-AD that we would be able to see a monotonic increase in the

expression of ApoE-related genes. To test this, we used a list of 10 high-confidence interactors in Homo sapiens of ApoE including ApoE itself for a total of 11 genes (APOE, APOC1, APOC2, APOC3, APOA1, APOA2, APOB, LRP1, LRP8, APP, and CLU) as a "module" of ApoE and defined the "ApoE module score" as the mean expression of those genes. Further, we accessed the SEA-AD's scRNA-seq data from the MTG split by sex (N_female=53, N_male=36). We then examined the variability of ApoE module scores across Braak stage across 3 cell types: astrocytes, microglia, and neurons. We observed no monotonic trend in ApoE module score across Braak stages across astrocytes ($p < 1e-4$), microglia ($p < 1e-3$), or neurons ($p < 1e-3$) by TOST on Spearman's p to test for equivalence of the means and relative invariance between the sexes. This suggests that ApoE-related genes are not globally dysregulated to the extent that was originally hypothesized. However, this does not exclude the possibility that subpopulations within astrocytes, microglia, or neurons have a trend of ApoE score across Braak stages. It also does not prove that ApoE is homeostatically regulated across AD progression. Despite these limitations, this study provides evidence against broad, global changes in ApoE transcriptomic signaling in the MTG. Future studies should aim to increase the granularity of the study by calculating individual scores for cell subclasses to verify the stability of the ApoE module.

Disclosures: J. Vergis: None. **D. Datta:** None. **R.E. McCullumsmith:** None.

Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.01/W25

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Institutes of Health 1R01AG089175-01
National Science foundation Career Award 2419849
Pittsburgh Pepper Center P30AG024827
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Title: Locomotor Learning and Dual-Task Gait in Mild Cognitive Impairment: Implications for Early ADRD Detection

Authors: *J. CHOI[1], S. LIU[2], A. M. WEINSTEIN[3], H. T. KARIM[3], G. TORRES-OVIEDO[4]; [1]Bioengineering, Univ. of Pittsburgh, PITTSBURGH, PA; [2]Bioengineering, [4]Dept. of Bioengineering, [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Alzheimer's disease and related dementias (ADRD) represent a growing public health crisis, and early non-invasive detection is widely recognized as critical to enabling timely intervention. This study focuses on the ability to learn new walking patterns and retrieving the learned walking pattern (locomotor learning capacity) and the ability to walk while performing a cognitive task at the same time (dual-task gait behavior). We examined these abilities in

individuals with mild cognitive impairment (MCI), who are more prone to developing ADRD, compared to healthy controls, with the long-term goal of determining whether gait-based parameters can serve as early, non-invasive diagnostic indicators of ADRD. Participants (n=36) completed a four-visit protocol that included a specialized treadmill designed to challenge and assess locomotor learning capacity and a dual-task gait paradigm pairing walking task with a cognitive task. Locomotor learning was quantified using one's ability to retrieve a previously learned walking pattern (locomotor learning index), while dual-task performance was characterized by capturing how much mental effort and attention participants needed to dedicate to walking while simultaneously performing a cognitive task (Attentional Gait Index (AGI)). Preliminary findings reveal that individuals with MCI (n = 22, 0.459±0.053) demonstrated a lower locomotor learning index than controls (n = 14, 0.593±0.068) suggesting a reduced capacity to consolidate and retrieve learned motor patterns. Furthermore, individuals with MCI showed increased AGI (15.865±1.225) than controls (14.436±1.439). Group differences in AGI were more subtle than anticipated; this may reflect the early stage of data collection rather than a true absence of effect, and we expect this difference to sharpen as the control cohort grows. Formal statistical comparisons between the two groups will be conducted upon completion of control data collection to ensure sufficient statistical power. Taken together, these preliminary findings support the potential of gait-based parameters as sensitive, non-invasive tools for the early identification of ADRD risk.

Disclosures: J. Choi: None. **S. Liu:** None. **A.M. Weinstein:** None. **H.T. Karim:** None. **G. Torres-Oviedo:** None.

Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.02/W26

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Kiwanis Neuroscience Research Foundation
Alzheimer’s Association Discovery Grant
RNID DRG25\22_Llano

Title: Measurement of auditory phenotypes in a novel hearing-corrected APOE4 mouse model of genetic risk for Alzheimer's Disease

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Abstract: Epidemiological studies link age-related hearing loss (ARHL) to cognitive decline, making it the largest potentially modifiable midlife risk factor for late-onset Alzheimer’s disease

(AD). However, the causal mechanism remains unclear. Apolipoprotein ε4 (APOE4) is the strongest genetic risk factor for late-onset AD. Here, we utilized APOE3-KI::Cdh^{WT} and APOE4-KI::Cdh^{WT} mouse models to test whether genetic predisposition to AD accelerates central auditory dysfunction. Crucially, these mice express human APOE while carrying a corrected cadherin allele (Cdh^{WT}) to preserve pure-tone thresholds, ensuring observations reflect aging-related hearing loss rather than strain-related premature decline. We characterized the peripheral and central auditory phenotypes of 6-month-old (young) and 12-month-old (aged) mice using Distortion Product Otoacoustic Emissions (DPOAEs), Auditory Brainstem Responses (ABRs), and Envelope-Following Responses (EFRs). No significant differences in ABR or DPOAE thresholds were found between genotypes or age groups across tested frequencies (4-32 kHz), indicating intact peripheral hearing for both groups. However, APOE4 mice showed central auditory deficits. Aged APOE4 mice showed lower overall ABR wave amplitudes at high frequency (32 kHz) across multiple sound intensities (20-70 dB SPL). Furthermore, at suprathreshold levels (above 80 dB SPL), both young and aged APOE4 mice showed significantly reduced amplitudes for later ABR waves (waves III, IV, and V) alongside prolonged wave I latencies at lower frequencies (4 kHz and 8 kHz). Additionally, aged APOE4 mice showed significantly impaired EFRs across multiple modulation frequencies (16, 32, 64, and 512 Hz) using a 16 kHz carrier, indicating a deficit in temporal coding within the central auditory system. Together, these findings indicate that the APOE4/4 genotype selectively impairs central auditory processing in aged mice, suggesting that central auditory processing degradation might serve as an early, quantifiable physiological biomarker for the central neural changes associated with late-onset AD pathology.

Disclosures: Y. Cai: None. **D.A. Llano:** None.

Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.03/W27

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Rapid progressors of Alzheimer's Disease: Differences in cognitive domain decline

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Abstract: One of the most pressing challenges in Alzheimer’s disease (AD) research is the unpredictable variability in disease progression between patients. This heterogeneity can obscure the efficacy of new treatments in clinical trials, resulting in skewed outcomes and trial failures. Rapid progressors (RPs) represent a poorly understood AD subgroup whose accelerated decline remains only symptomatically characterized. We **hypothesize** that RPs represent a distinct

clinical phenotype that can be identified and predicted by early, domain-specific cognitive and functional decline. This study explores whether changes in these cognitive domains, and early change trajectories, can differentiate RPs from non-RPs. De-identified placebo-arm data from three large randomized clinical trials (EXPEDITION 1-3, n = 1603) was used to predict RPs based on clinical and pathological metrics. First, we built deep neural network classifiers using data from weeks 4-28 weeks after baseline to predict RPs. Next, we trained deep survival models to predict probability of RP status at endpoint. Model performance was assessed with Brier score, AUROC, and AUPRC. Feature importance was used to identify cognitive domains contributing significantly to risk discrimination. Consistent with our prior work demonstrating a distinct subgroup of rapidly declining patients, RPs were defined as the 10% of participants showing the greatest deterioration on the Clinical Dementia Rating Scale - Sum of Boxes over an 80-week period (n = 150/1603, 9.4%; F = 82, 54.7%). Models incorporating data through week 28 achieved the highest performance in early identification of RPs with internal/external AUROCs = 0.81 and 0.76. Deep survival models consistently stratified RP risk over time (AUROC range: 0.93-0.94). Early decline in social cognition at 12 weeks and executive function at 28 weeks significantly (all $p < 0.01$) and most strongly differentiated RPs from non-RPs on a clinically-relevant timescale for intervention. Early (12-28 week) changes in specific cognitive domains carry substantial predictive value for rapid progression. Both deep learning and survival models accurately identified patients at risk of rapid progression and stratified their risk over time. These findings support our hypothesis that RPs can be identified as a distinct clinical phenotype represented by domain-specific cognitive changes. Identifying RPs as quickly and accurately as possible will improve clinical trial stratification, prevent treatment effect dilution, and identify targetable biological components that will enable the development of therapies for this important and overlooked subset of patients.

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Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.04/Web Only

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: University of Guanajuato 180-2025
Conahcyt ApoyosLNC-2023

Title: Retinal ganglion cell layer thinning is associated with cognitive decline, impaired delayed recall and altered nutritional status and anthropometric parameters in women with sporadic Alzheimers disease

Authors: *M. SOLIS-ORTIZ[1], N. HERNÁNDEZ SEBASTIÁN[4], B. BARRIENTOS[4], M. G. GUERRERO VILLALPANDO[2], G. BASURTO-ISLAS[5], C. MARIN ARANDA[3], M. CARDONA ALVARADO[1];
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Abstract: Alzheimers disease AD is a progressive neurodegenerative disorder characterized by cognitive decline, particularly affecting episodic memory. The retinal ganglion cell layer GCL has emerged as a potential biomarker of AD due to its direct connection with the brain. Nutrition and anthropometric factors have also been linked to cognitive impairment. However, the associations among GCL thickness, cognitive decline, episodic memory, nutritional status and anthropometric measures in AD remains insufficiently explored. **This study aimed to examine the associations of GCL thickness with delayed recall, global cognitive performance, nutritional status, and anthropometric measures in women with sporadic AD.** Seventy seven elderly women were categorized based on their global cognitive performance scores, comprising 28 women with mild, 32 with moderate, and 17 with severe cognitive impairment. **Global cognition, delayed recall, nutritional status, and anthropometric measures were evaluated and correlated with GCL thickness. Women with severe cognitive impairment exhibited bilateral GCL thinning, poorer delayed recall performance, worse nutritional status, and overweight. Reduced GCL thickness was correlated with greater global cognitive impairment, poorer delayed recall memory performance, and worse nutritional status, while showing inverse associations with body mass index and waist to height ratio. Additionally, age, height, and waist to hip ratio were significant predictors of GCL thinning. These findings suggest that body composition may contribute to GCL degeneration and support its potential role as a marker of disease progression in AD.**

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Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.05/W28

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG087945
NIH Grant AG067419
K01 AG072615
UM1TR004402

Title: Observations of Aging and Neurodegenerative Pathologies in the Anterior Cingulate Cortex of Elephant Brains

Authors: *A. M. ZARZIS[1], M. E. HILLEGAS[2], D. E. CHUSYD[3], S. P. RAO[2], M. K. EDLER[4], P. R. HOF[5], C. C. SHERWOOD[2];
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Abstract: Elephants and humans share many complex cognitive skills, including long-term memory and theory of mind. Like humans, elephants have large brains and long lifespans. While observational evidence suggests cognitive resilience with age, whether elephants develop human-like neurodegenerative pathology remains unclear. To begin to address this, we examined the anterior cingulate cortex (ACC) of male and female adult elephants (five African savanna elephants [ages 44 to 47 years] and three Asian elephants [ages 62 to 71 years]). Sections were Nissl-stained and immunohistochemically labeled for hyperphosphorylated tau protein (AT8, pS202/pT205) and microglia (IBA1). Tau-positive neurons were sparse in all 5 of the AT8-stained elephants, although they were even more rare in the youngest of the individuals (46 and 47 years). Neurofibrillary tangle and pretangle-like lesions (NFTs) were observed in the oldest elephants, although tau burden (percent of total tau-positive neurons relative to total neurons) was not more than 0.1%, significantly lower than reported in elderly human brains in the absence of Alzheimer's disease. Overall neuron density did not significantly vary with age in the sample ($R^2 = 0.09$, $p = 0.49$), which contrasts with the age-related shrinkage of dendritic and other neuropil components reported in regions of the human cerebral cortex. IBA1 was predominantly expressed in intermediate microglia across ages, suggesting limited changes in microglia activation. The youngest IBA1-stained elephants (46 and 47 years) presented the highest amount of microglia in the reactive amoeboid state. These preliminary findings suggest changes in the ACC consistent with normal aging and possible early neurodegeneration, although at substantially lower levels than found in humans. These data suggest elephants may develop some neuropathology, but also resilience, with age. Future work will include Thioflavin-S staining to confirm the presence of NFTs, quantification of Aβ40 and Aβ42 plaque volume, and other pathology markers. In addition, we plan to expand the sample size across ages to assess other neurodegenerative changes in elephant brains to better understand the evolution of age-related brain pathology in a broad comparative context.

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Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.06/W29

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association AARFD-16-440750
Janell and Joe Marek 57 Alzheimer's Disease Research Fund

Title: Chronic Staphylococcus aureus Exposure Exacerbates Sex-Dependent Mortality and Motor Deficits in APP/PS1 Mice

Authors: *J. S. REYES[1], M. JACKSON[2], J. IANNUCCI[3], H. SMITH[4], A. ESSOH[6], E. IGLESIAS[7], K. M. SOUZA[5], R. MORALES[8];
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Abstract: Chronic inflammation is increasingly recognized as a major contributor to Alzheimer's disease (AD) pathogenesis, and bacterial infections have been associated with amyloid deposition and neurodegeneration. To investigate the interaction between chronic infection, sex, and AD pathology, female and male APP/PS1 and non-transgenic (NTg) mice (6 months old) were inoculated intranasally with Staphylococcus aureus three times per week for four months to model persistent low-grade inflammation. Body weight and survival were monitored weekly throughout the treatment period. APP/PS1 mice exposed to S. aureus exhibited reduced survival compared to NTg controls, with female APP/PS1 mice showing the greatest mortality. Weight trajectories were also differentially affected by genotype and infection, with female APP/PS1 mice displaying greater susceptibility to weight loss. These findings suggest a sex-dependent interaction between amyloid pathology and chronic inflammatory challenge. To assess functional outcomes, mice underwent motor and cognitive testing, including rotarod, DigiGait analysis, Barnes maze, open field, and novel object recognition tasks. Male APP/PS1 mice exposed to S. aureus demonstrated significant motor impairments, including reduced rotarod performance and increased brake and stance times during gait analysis. In contrast, cognitive deficits were not substantially exacerbated by infection at the time points examined. Histological analyses further revealed increased amyloid plaque burden in infected animals. Together, these findings demonstrate that chronic bacterial exposure worsens disease-related outcomes in APP/PS1 mice and that females may be particularly vulnerable to infection-induced reductions in survival and body weight. These results support the hypothesis that chronic peripheral inflammation contributes to AD progression and highlight the importance of considering biological sex as a modifier of disease susceptibility and trajectory.

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Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.07/W30

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01-DC018561
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Title: Window into Auditory Vulnerability in Early Alzheimer's Disease (WAVE-AD): The Auditory Brainstem Response As a Very Early Biomarker in AD Risk in Rats and Humans

Authors: E. YOUSSEF[1], K. LEFFINGWELL[1], L. SANKARI[1], A. GUNGOR AYDIN[4], E. B. TORRES[5], A. WESTBROOK[2], *K. M. BIESZCZAD[3];
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Abstract: Hearing loss is the largest modifiable mid-life risk factor for Alzheimer's disease and related dementias (AD/ADRD), yet the neurophysiological mechanisms bridging auditory dysfunction and early AD pathophysiology remain poorly understood. Presented here, is the potential for a *very early* neurophysiological biomarker of AD risk through the non-invasive, rapidly acquired, pre-attentive and clinically translatable auditory brainstem response (ABR). Recently reported in normal hearing knock-in rats (Swedish familial AD risk variant to Amyloid precursor protein, AppS; male and female (Aydin et al. 2026, *Sci Rep,* PMID:42106438), a key metric is derived from multidimensional parametric feature extraction on the distribution statistics of continuous neurophysiological time series data from ABR data. Metrics first used in human neurodevelopmental studies (Torres et al. 2023, *PNAS Nexus,* PMID: 36798622) significantly separate neurodegenerative risk in APP Swedish from healthy APP humanized control rats in a sex- and age-dependent manner. The findings suggest that subtle fluctuations in sound-evoked neural activity in the auditory pathway provides a window into synaptic-level processes that are disrupted very early in AD progression, before hallmark AD-like pathophysiology. The goal is now to bridge these preclinical findings for application in human subjects. Identically derived metrics from tone-evoked ABRs in humans will be presented to determine if ABR features correlate with traits of mild cognitive impairment (MCI) vs. healthy age-matched controls (up to N=10 human subjects per group). Further, the data will be presented alongside resting state EEG to gain a mechanistic understanding of how ABR metrics may be a proxy for E/I imbalances in human neuropsychiatric disease (Mitsuto, ⋯Westbrook et al. 2025, *bioRxiv,* PMID: 41279470). ABRs may provide a cost-effective, accessible, and non-invasive physiological proxy for broad cortical circuit dysfunction relevant to AD/ADRD risk. The future of this work is to refine novel ABR metrics as a very early biomarker of disease risk and prognosis, including expanding its application to diverse cognitive and clinical populations. There is potential for its use to easily track therapeutic intervention efficacy, which could greatly revolutionize its utility in early screening for AD/ADRD and improve outcomes for individuals and their families by allowing earlier and more personalized intervention strategies. As a rapidly acquired, pre-attentive, and inexpensive brain signal to access, the sound-evoked ABR represents a highly promising candidate for future clinical use.

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Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.08/X1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: A cross-model biomarker matrix across mouse models of neurodegenerative and lysosomal storage disorders

Authors: I. PEREZ-RUIZ[1], I. SCHILCHER[1], S. KRASSNIG[1], M. DAURER[1], L. BREZNIK[1], ***T. LÖFFLER**[1], M. PROKESCH[2];
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Abstract: Neurodegenerative disorders are characterized by overlapping pathological processes, including protein aggregation, neuroinflammation, synaptic dysfunction, and cellular senescence. However, biomarker studies are often performed within individual disease models, limiting the identification of shared pathological mechanisms across indications. To establish a comparative framework for translational biomarker assessment, we generated a cross-model biomarker matrix using brain tissue from a diverse panel of mouse models representing Alzheimer's disease, synucleinopathies, and lysosomal storage disorders. Brain tissue samples from transgenic and non-transgenic cohorts of Alzheimer's disease (5xFAD), Parkinson's disease (Line 61), Gaucher disease (GBA D409V KI and 4L/PS-NA), Niemann-Pick disease type C ($NPC1^{-/-}$), and Pompe disease (6^{neo}) mouse models were analyzed at disease-relevant ages corresponding to established disease pathology in each model. Proteinopathy-, inflammation-, synaptic-, and senescence-associated biomarkers were quantified using multiplex immunoassays, capillary-based immunoassays, and enzymatic activity measurements. Assessed endpoints included amyloid-β (Aβ), α-synuclein, tau, TDP-43-related markers, lysosomal and neurodegeneration-associated proteins, NLRP3 pathway markers, synaptic markers, β-galactosidase activity, inflammatory mediators, and matrix metalloproteinase-9 (MMP9). Distinct biomarker profiles were observed across all models, with alterations detected in each functional biomarker category. Notably, lysosomal storage disease models, including 4L/PS-NA and $NPC1^{-/-}$ mice, exhibited changes in tau- and Aβ-associated markers, suggesting that impaired endolysosomal pathways may contribute to Alzheimer’s Disease-related tau and Aβ dysregulation. In parallel, senescence-associated β-galactosidase activity and inflammatory mediators, including MMP9, were altered across these indications, suggesting convergence on shared neuroinflammatory and cellular stress pathways. These findings support the existence of common biomarker networks across genetically and mechanistically distinct neurological disorders. The biomarker matrix provides a translational framework for comparative model characterization, identification of shared therapeutic targets across indications, and informed selection of preclinical models for mechanism-based drug discovery.

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Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.09/Web Only

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Reminiscence Therapy, Pupil Size, Facial Affect and Episodic Memory in Dementia

Authors: *C. KOCH[1], B. QUINTANA-BAKER[2];
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Abstract: Reminiscence therapy (RT) uses photos, music, objects, and life stories to trigger past memories. Meta-analyses and large RCT reviews show that RT produces small but significant improvements in global cognition in people with dementia and cognitive impairment (Saragih et al., 2022; Huang et al., 2015; Cammisuli et al., 2022; Pérez-Sáez et al., 2021). Reminiscence therapy has also been shown to improve autobiographical memory (e.g., Thomas & Sezgin, 2021; Soria-Urios et al., 2025). Therefore, RT is a low-risk and relatively simple activity that is frequently included in memory care for dementia patients. This study compares cue type and recognition memory of episodic events along with pupil size and facial affect analysis. Two separate four-week sessions were conducted. Each session focused on a different central prompt. Subjects replied to the prompt following different sensory cues (e.g., visual, tactile, auditory, and olfactory). An analysis of responses indicated that tactile cues produced more detailed memories than other cue types. Responses from each session were combined to create a personalized memory for each subject. The personalized story was compared to a generic memory. Even though subjects did not typically remember the personalized memory as their own, they rated it more positively than the generic memory. Further, there were differences between the personal and generic memory in regard to pupil size and affective responses. Overall, the results suggest that pupillary and affective responses can be used as physiological indicators of episodic memory recognition without conscious awareness of the memory.

Disclosures: C. Koch: None. **B. Quintana-Baker:** None.

Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.10/X2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG49749 (RZ)
NIH Grant R56AG074613 (AMS)
NIH Grant RF1AG084134 (AMS)
AHA Grant 19EIA34760279 (AMS)

Title: Plasma angiogenic growth factors as biomarkers of aerobic exercise response in hypertensive older adults at risk for Alzheimer's disease: rrAD trial

Authors: *P. YANEV[1], D. MERCURIO[2], J. TURCHAN-CHOLEWO[3], J. LUTSHUMBA[4], C. STUART[2], D. R. BRITSCH[5], K. COTTER[5], R. ZHANG[6], D. ZHU[7], A. M. STOWE[8];
[1]Col. of Med. - Neurol. & Neurosci., [3]Dept of Neurol., [4]Neurol., [5]Neurosci., [2]Univ. of Kentucky, Lexington, KY; [6]Departments of Neurol. and Neurotherapeutics and Intrnl. Med., Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [7]Gruss Magnetic Resonance Res. Ctr., Albert Einstein Col. of Med., New York, NY; [8]Neurol., Univ. of Kentucky Med. Ctr., Lexington, KY

Abstract: Background
Angiogenic growth factors (VEGF-A, VEGF-D, placental growth factor [PlGF], and basic fibroblast growth factor [bFGF]) influence vascular remodeling, neurogenesis, and cerebrovascular adaptations and have been proposed as biomarkers of exercise efficacy in adults at risk for Alzheimer's disease and related dementias (AD/ADRD).
Methods
In the multicenter 2×2 factorial Risk Reduction for Alzheimer's Disease (rrAD) trial, hypertensive adults aged 60-85 with a family history of dementia and/or subjective cognitive decline, but without dementia, were randomized to aerobic exercise, intensive vascular risk reduction (IRVR), exercise+IRVR, or standard care (SC) for 24 months. Plasma VEGF-A, VEGF-D, PlGF, and bFGF were measured at 0, 12, and 24 months. Longitudinal trajectories were modeled with mixed-effects models. At 24 months, cross-sectional Spearman correlations related biomarkers to MRI-derived brain volumes and cortical thickness (normalized to intracranial volume), VO_2max, and composite cognitive scores (PACC, NIH-Toolbox).
Results
All four angiogenic factors showed small overall increases over 24 months, with no significant main effects of exercise or IRVR and no evidence of a treatment×time interaction, indicating no differential biomarker trajectories between intervention and SC. Higher PlGF was associated with smaller normalized total brain volume ($\rho=-0.17$, $P=0.0019$, FDR-adj. $P=0.015$) and cerebral white matter volume ($\rho=-0.17$, $P=0.0016$, FDR-adj. $P=0.015$), and lower PACC scores ($\rho=-0.13$, $P=0.009$, FDR-adj. $P\approx0.06$). Higher VEGF-D related to thinner global cortical thickness ($\rho\approx -0.18$ bilaterally, $P\leq0.0008$, FDR-adj. $P\approx0.01$), whereas higher bFGF was associated with thicker cortex ($\rho\approx0.17$-0.18, $P\leq0.0015$, FDR-adj. $P\approx0.01$) and better NIH composite cognition ($\rho=0.17$, $P=0.0008$, FDR-adj. $P\approx0.03$). VO_2max showed a modest negative association with VEGF-A (global: $\rho=-0.16$, $P=0.005$, FDR-adj. $P\approx0.02$).

Conclusions
In hypertensive older adults at elevated AD/ADRD risk, plasma VEGF-A, VEGF-D, PlGF, and bFGF did not track randomized exercise or IRVR interventions. Cross-sectional patterns suggest these factors index brain atrophy/thinning and cognitive vulnerability more than modifiable exercise response, arguing against their use as standalone exercise biomarkers in this population.

Disclosures: P. Yanev: None. **D. Mercurio:** None. **J. Turchan-Cholewo:** None. **J. Lutshumba:** None. **C. Stuart:** None. **D.R. Britsch:** None. **K. Cotter:** None. **R. Zhang:** None. **D. Zhu:** None. **A.M. Stowe:** None.

Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.11/X3

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: BMP type I receptor signaling and selective neuronal vulnerability in Alzheimer's disease

Authors: *J. G. K. ALLEN[1], T. MCGUIRE[1], C.-Y. PENG[2], J. A. KESSLER[3];
[1]Northwestern Univ., Chicago, IL; [2]Northwestern Univ., Chicago, IL, ; [3]Neurol., Northwestern Univ., Chicago, IL

Abstract: Selective neuronal vulnerability is a hallmark of Alzheimer’s disease (AD), but much remains unknown about the factors that contribute to specific neuronal death or survival. Age is the primary non-genetic risk factor for AD, and our previous work has revealed an age-related increase in bone morphogenetic protein (BMP) signaling in mice and humans, which we have linked to tau hyperphosphorylation and cognitive decline. BMP signaling is effectuated through receptor complexes composed of type I and type II receptors. Previous work regarding functional differences between the type I receptors BMPR1a and BMPR1b has yielded mixed results across different contexts, and it is unclear whether these receptors are functionally redundant in the context of AD. This project aims to characterize the role of BMP signaling in cell death and survival in AD. Specifically, we investigate the relationship between BMPR1b receptor expression and selective neuronal vulnerability. Analysis of RNA-sequencing data from the Seattle Alzheimer’s Disease Brain Cell Atlas (SEA-AD) reveals that while BMPR1a is widely expressed across different cell types in the medial temporal gyrus (MTG), neuronal BMPR1b expression is limited to L2/3 and L5 intratelencephalic (IT) excitatory neurons, which show early vulnerability to pathology and death in AD. Moreover, certain populations of BMPR1b-expressing cells also express the vulnerability marker RORB. Immunohistochemistry (IHC) for BMPR1b in C57BL/6 mice confirms expression in L2/3 and L5 of the entorhinal cortex. We also use postmortem human hippocampal tissue to correlate BMP receptor expression with low/intermediate (n=8) and high (n=7) levels of tau and amyloid pathology. Immunoblotting indicates that BMPR1a levels increase with age, while levels of BMPR1b decrease and BMPR2 levels exhibit no significant change, which is consistent with a selective loss of BMPR1b-

expressing populations. Additional results from our in vitro neuronal models transduced with constitutively active or dominant negative forms of BMPR1b will also be presented. Taken together, our findings indicate a relationship between BMPR1b expression and selective neuronal vulnerability in AD, thus enhancing our understanding of both basic BMP biology and the role of BMP signaling in AD.

Disclosures: J.G.K. Allen: None. **T. McGuire:** None. **C. Peng:** None. **J.A. Kessler:** None.

Poster

PSTR013: Alzheimer's Disease: Other Biomarkers

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.12/X4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG078299
R01AG084624

Title: From Blood to Brain: Exploring microRNA Biomarker Candidates in Alzheimer’s Disease

Authors: *N. UMESH GANESH;
Boston Univ., Boston, MA

Abstract: From Blood to Brain: Exploring microRNA Biomarker Candidates in Alzheimer’s Disease MicroRNAs (miRNAs) circulating in plasma have emerged as promising biomarkers for Alzheimer's disease (AD). In our previous analyses of cross-sectional samples from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we identified several miRNAs associated with AD diagnosis and progression from mild cognitive impairment (MCI) to AD. Furthermore, multiple circulating miRNAs showed significant relationships with the amyloid/tau/neurodegeneration (AT/N) framework, supporting their potential utility as indicators of disease status and progression. To investigate whether plasma miRNA alterations reflect changes occurring within the brain, we examined miRNA expression profiles in matched human brain cell populations. Small RNA sequencing was performed on 3-5 longitudinal plasma samples collected before and after AD diagnosis, as well as on postmortem brain tissue from 21 participants in the Framingham Heart Study. The cohort included individuals without neurodegenerative disease and individuals with pathologically confirmed AD (Braak stages 3-6). Using laser-capture microdissection, ~4,000 neurons, astrocytes, and microglia were collected from the prefrontal cortex and hippocampus of each brain and subjected to small RNA extraction and sequencing. Cell-type and region-specific differential expression analyses identified multiple dysregulated miRNAs, several of which have established roles in memory-related processes, neuroinflammation, and AD pathogenesis. To explore their functional relevance, selected candidate miRNAs were manipulated in induced pluripotent stem cell (iPSC)-derived neuronal and glial cultures using mimic and inhibitor approaches. These studies revealed distinct cellular and phenotypic responses, providing insight into molecular pathways that may contribute to

disease development and progression.Collectively, our findings demonstrate that integrating longitudinal plasma miRNA measurements with brain cell-type-specific miRNA profiling can reveal biologically meaningful biomarker candidates and improve understanding of the mechanisms linking peripheral and central molecular changes in AD.

Disclosures: N. Umesh Ganesh: None.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.01/X5

Topic: C.06. Neuromuscular Diseases

Title: TDP-43 loss-of-function in astrocytes drives cell-type-specific cryptic exon dysregulation, and is amplified by NMD inhibition

Authors: *I. NYARKO-DANQUAH[1], I. PERVAIZ[8], A. BLAZIER[2], S. KINTON[1], S. ARYAL[1], T. ZHAO[3], J. PHILLIPS[4], D. OFENGEIM[5], D. MALHOTRA[6], F. RAPINO[9], S. RYAN[7];
[1]Sanofi, Cambridge, MA; [2]Sanofi, Wayland, MA; [3]Sanofi, Sanofi, MA; [4]Sanofi, Pace, FL; [5]Rare and Neurologic Dis. Res. TA, Sanofi, Framingham, MA; [6]Sanofi, Cambridge Crossing, MA; [7]Sanofi, Framingham, MA; [8]Texas Tech. Univ., AMARILLO, TX; [9]PRECISION NEURTOLOGU AND NEUROIMMUNOLOGY, sanofi-aventis, Framingham, MA

Abstract: TDP-43 loss-of-function in astrocytes drives cell-type-specific cryptic exon dysregulation, and is amplified by NMD inhibition Ivan Nyarko-Danquah[1], Iqra Pervaiz[†], Anna S. Blazier[1], Sofia Kinton[1], Sandeep Aryal[1], Zhonglin Zhao[1], Juniper Phillips[1], Dimitry Ofengeim[†], Dheeraj Malhotra[1], Francesca Rapino[†], and Sean K Ryan[1].[1] Sanofi, Cambridge, MA, 01701, USA.[†] Employee of Sanofi when this work was undertaken
Abstract:TDP-43 is an RNA-binding protein that plays a crucial role in the regulation of RNA splicing. Depletion of TDP-43 from the nucleus is an early pathological feature in ALS and FTLD, leading to the inclusion of aberrant ‘cryptic exons’ that frequently introduce premature termination codons and trigger degradation of affected transcripts through nonsense-mediated mRNA decay (NMD). While TDP-43 loss-of-function-associated cryptic exons have been extensively characterized in neurons, much less is known about the cryptic exon signature in astrocytes, particularly given that TDP-43 cryptic exons are highly variable across cell types. Using two complementary astrocyte models of TDP-43 loss of function, an inducible TDP-43 dNLS model and a TDP-43 knockdown astrocyte model, we performed deep bulk RNA-sequencing under basal conditions and following treatment with the NMD inhibitor, 11j. Computational analysis using cryptic exon discovery pipelines to identify differential exon inclusion events, cryptic splice junctions, and transcript-level changes associated with TDP-43 dysfunction revealed an astrocyte-specific TDP-43 loss-of-function cryptic exon signature that partially overlapped with previously described neuronal cryptic exons, while also uncovering

novel cryptic transcripts unique to astrocytes. Inhibition of NMD further unmasked additional cryptic exon events, underscoring the role of NMD pathway in concealing TDP-43-dependent splicing defects and expanding the repertoire of potential target for TDP-43-related neurodegenerative disorders. **Keywords:** TDP-43, astrocytes, cryptic exon, nonsense-mediated decay

Disclosures: I. Nyarko-Danquah: A. Employment/Salary (full or part-time):; Sanofi. **I. Pervaiz:** A. Employment/Salary (full or part-time):; Sanofi. **A. Blazier:** A. Employment/Salary (full or part-time):; Sanofi. **S. Kinton:** A. Employment/Salary (full or part-time):; Sanofi. **S. Aryal:** A. Employment/Salary (full or part-time):; Sanofi. **T. Zhao:** A. Employment/Salary (full or part-time):; Sanofi. **J. Phillips:** A. Employment/Salary (full or part-time):; Sanofi. **D. Ofengeim:** A. Employment/Salary (full or part-time):; Sanofi. **D. Malhotra:** A. Employment/Salary (full or part-time):; Sanofi. **F. Rapino:** A. Employment/Salary (full or part-time):; Sanofi. **S. Ryan:** A. Employment/Salary (full or part-time):; Sanofi.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.02/X6

Topic: C.06. Neuromuscular Diseases

Title: Modeling ALS with patient-derived iPSC motor neurons: TDP-43 mislocalization and drug responsiveness

Authors: *V. E. EVANSON, D. KURGANOVA, B. FRAHER, T. TANAKA;
Ricoh Biosci., Baltimore, MD

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder defined by progressive motor neuron loss, yet its mechanisms remain poorly understood. Research has relied heavily on animal models that inadequately recapitulate human disease, contributing to poor translation of candidate therapies. Because brain and spinal cord tissue cannot be safely sampled from patients, disease-specific pathways and patient stratification are difficult to define, underscoring the need for representative human models. To address this gap, we used patient-derived induced pluripotent stem cells (iPSCs) to generate human spinal motor neurons. A rapid, reproducible transcription factor-mediated differentiation protocol was applied to iPSCs from healthy and ALS donors. Within 10 days, neurons expressed the pan-neuronal marker TUBB3 (>95%), the cholinergic marker ChAT (>70%), and the motor neuron marker HB9 (>70%) by immunostaining. In this exploratory study, sporadic ALS patient-derived motor neurons recapitulated a hallmark feature: TDP-43 mislocalization. By immunofluorescence, TDP-43 localized preferentially to the nucleus in healthy neurons but showed significantly increased cytoplasmic localization in ALS neurons ($p<0.0001$, one-way ANOVA). One of two ALS lines also exhibited poor survival by day 7 in vitro. ALS-derived neurons responded to compounds modulating ALS-related pathways: Tubastatin A, a casein kinase 1 (CK1) inhibitor, Sephin1, and

Edaravone each significantly reduced cytoplasmic TDP-43. These findings indicate that a patient-specific, iPSC-based platform can model key ALS pathology and offers a scalable tool to accelerate therapeutic discovery.

Disclosures: V.E. Evanson: A. Employment/Salary (full or part-time):; Ricoh Biosciences. **D. Kurganova:** A. Employment/Salary (full or part-time):; Ricoh Biosciences. **B. Fraher:** A. Employment/Salary (full or part-time):; Ricoh Biosciences. **T. Tanaka:** A. Employment/Salary (full or part-time):; Ricoh Biosciences.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.03/X7

Topic: C.06. Neuromuscular Diseases

Support: AMED 26be1004103h0002

Title: Single-Cell Electrophysiological Phenotyping of Isogenic hiPSC-Derived TDP-43 M337V Motor Neurons Using Ultra-High-Density CMOS-MEA to Evaluate Drug Efficacy

Authors: H. KURASHIKI, R. YOKOI, N. MATSUDA, B. NODA, ***I. SUZUKI**;
Tohoku Inst. of Technol., miyagi, Japan

Abstract: Background: Amyotrophic lateral sclerosis (ALS) is characterized by progressive motor neuron loss, with TDP-43 aggregation as a key hallmark. Genetic variations in patient-derived iPSCs often obscure functional phenotypes, and conventional multi-electrode array (MEA) metrics mask individual neuronal heterogeneity by averaging population-wide activities. To resolve this, we developed a ultra-high-resolution single-cell evaluation platform using isogenic human iPSC-derived ALS models. Methods: Isogenic human iPSC-derived motor neurons with homozygous or heterozygous TDP-43 M337V mutations and wild-type (WT) controls were co-cultured with iPSC-derived astrocytes on an ultra-high-density CMOS-MEA system. Firing activities were captured at the single-cell level. We extracted unique firing features (e.g., firing rate, burst periodicity) and classified individual neurons into 14 functional clusters. Results: Cluster analysis identified a robust disease phenotype. A distinct population designated as Cluster 2 (C2), characterized by hyperexcitability with elevated firing rates and burst frequencies, was significantly expanded in both homozygous and heterozygous TDP-43 mutant models compared to WT controls. To test the platform for drug screening, we applied Riluzole, an anti-glutamatergic agent that inhibits voltage-gated sodium channels. Riluzole dose-dependently reduced the hyperexcitable C2 cluster proportion. However, even at 3 μM, the overall cluster distribution failed to fully revert to the healthy WT baseline, indicating that Riluzole suppresses hyperactive neurons rather than restoring network homeostasis. Conclusion: Combining isogenic human models with single-cell MEA phenotyping successfully isolated an ALS-specific hyperexcitable cell cluster. Our approach enables high-resolution drug evaluation

based on the capacity to shift cellular compositions back toward a healthy state, offering a powerful tool for screening next-generation ALS therapeutics.

Disclosures: H. Kurashiki: A. Employment/Salary (full or part-time):; VitroVo.inc,. **R. Yokoi:** A. Employment/Salary (full or part-time):; VitroVo.inc,. **N. Matsuda:** A. Employment/Salary (full or part-time):; VitroVo.inc,. **B. Noda:** None. **I. Suzuki:** A. Employment/Salary (full or part-time):; VitroVo.inc,.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.04/X8

Topic: C.06. Neuromuscular Diseases

Support: Maryland Stem Cell Research Fund 2025-MSCRFD-00013

Title: Role of P2X7 Signaling in ALS Motor Neuron Vulnerability

Authors: *E. G. LUCIANI[1], A. TAGA[2], N. J. MARAGAKIS[2];
[2]Neurol., [1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motor neuron loss and dysfunction of neuron-glia interactions. Extracellular ATP serves as an important signaling molecule in the nervous system and can drive both inflammatory and excitotoxic responses through purinergic receptors such as P2X7. To examine the role of P2X7 signaling in ALS, we differentiated human induced pluripotent stem cells (hiPSCs) into spinal motor neurons and astrocytes. We found that P2X7 receptors are expressed and functionally active in both control and familial ALS hiPSC-derived motor neurons. Further, activation of P2X7 with BzATP induced dose-dependent motor neuron death in control and familial hiPSC-derived motor neurons, which was effectively mitigated with a selective P2X7 antagonist, JNJ-47965567. In transwell coculture experiments, P2X7 inhibition also protected motor neurons from both familial and sporadic hiPSC-derived astrocyte mediated toxicity. These findings suggest that ATP-mediated P2X7 signaling may contribute to motor neuron vulnerability and be a therapeutic target in ALS.

Disclosures: E.G. Luciani: None. **A. Taga:** None. **N.J. Maragakis:** None.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.05/X9

Topic: C.06. Neuromuscular Diseases

Support: HT9425-23-1-0312

Title: Plasma and CSF Biomarkers to Predict ALS Disease Progression

Authors: *M. STENGELIN[1,2], C. DEMOS[2], B. NGO[2], J. ABRAHAM[2], N. PADMANABHAN[2], B. FILLINGHAM[3], J. D. ROTHSTEIN[4], J. BERRY[3], G. SIGAL[2], J. WOHLSTADTER[2];
[1]Meso Scale Diagnostics, LLC., Hillsboro Beach, FL; [2]Meso Scale Diagnostics, LLC., Rockville, MD; [3]Harvard - MGH, Boston, MA; [4]Brain Sci. Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative illness with heterogenous disease progression. Biomarkers that stratify individuals into a slow versus fast disease progression group are useful for enrollment into clinical trials and for assessing treatment effects. CSF and plasma biomarkers were measured in more than 2,500 serially drawn samples from more than 900 individuals provided by the Answer ALS cohort (Baxi 2022) and the LABB study (Huang 2020) for analysis using the research use only MSD S-PLEX Neurology Panel 1, Proinflammatory Panel 1, BD-Tau, pTau217, and TDP-43 kits. Approximately 90% of sample concentrations were within the assay ranges. Recovery of QC samples included on each plate were between 80% and 120% for a vast majority of assays. Clinical information for the entire cohort (e.g., > 3,500 ALSFRS scores from more than 900 individuals; provided by Harvard/MGH) was used to classify individuals into slow and fast progressors. Classifications using linear regression, a linear mixed model with and without covariates, and analysis with and without a score at presumed disease onset were compared and provided overall similar classification. NfL in plasma or in CSF was the best biomarker to separate samples in the fast-progressing tertile from those in the slow one, with an ROC area of 0.86. Using random forest or logistic regression, the ROC area was marginally improved if additional plasma biomarkers such as GFAP, brain-derived tau, IL-6 or IL-17A were included. NfL was also the best biomarker to separate individuals whose breathing capacity declined rapidly versus slowly. The database included serum NfL concentrations measured with the Siemens Atelica assay. A method comparison between the Siemens serum NfL and MSD S-PLEX plasma NfL using >1,800 samples showed excellent correlation (R = 0.92) but the absolute concentrations were approximately tenfold higher for the MSD assay. The index of individuality, the ratio of within-person and between-person variability, was lowest for NfL followed by GFAP and TNFa. Plasma and CSF concentrations correlated well for NfL and GFAP, but, as expected, poorly for cytokines. CSF and plasma tau forms did not correlate well, which may indicate that a substantial part of plasma tau is not from brain but from the periphery. A prototype S-PLEX assay for TDP-43 performed well analytically but could not discriminate between fast and slow progressors. Plasma concentrations of MSD S-PLEX Total Tau, brain-derived Tau and pTau217 correlated moderately (pairwise R of approximately 0.5), indicating that each of these three assays provides independent information for individuals with ALS.

Disclosures: M. Stengelin: A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC.. 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.; CDMRP grant HT9425-23-1-0312. **C. Demos:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **B. Ngo:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **J. Abraham:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **N. Padmanabhan:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC.. **B. Fillingham:** None. **J.D. Rothstein:** None. **J. Berry:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research support from Biogen, Coya Therapeutics, Mitsubishi Tanabe, Transposon Therapeutics, Alexion, Neurizon, Rapa Therapeutics, ALS association, Muscular Dystrophy Association, ALS Finding a Cure,. F. Consulting Fees (e.g., advisory boards); Regeneron, Biogen, Mitsubishi Tanabe, Takeda, Trace Nutraceuticals. **G. Sigal:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **J. Wohlstadter:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC.. Other; Ultimate beneficial owner, MSD LLC..

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.06/X10

Topic: C.06. Neuromuscular Diseases

Support: DHSI Grant P031S230210

Title: In vitro model for investigating the role of CCS in Sod1 maturation and folding in Amyotrophic Lateral Sclerosis

Authors: *M. E. LAFON, L. KANE BARNESE;
Natural Sci., Concordia Univ. Irvine, Irvine, CA

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by the loss of motor neuron function, primarily in the brain and spinal cord. This disease is fatal, with those affected having a life expectancy of 2-5 years after diagnosis, with very few treatment options available. Despite the fatality of this disease, 90% of cases remain idiopathic, and only 10% are linked to genetic causes. Several genes have been linked to genetic ALS cases, but one of particular interest is the SOD1 gene, which is responsible for approximately 2% of all ALS cases. The SOD1 gene encodes the Sod1 protein, which is responsible for protecting neurons and other cells from oxidative stress. However, when this gene is mutated, free radicals can no longer be broken down due to the protein being misfolded. Although it is widely accepted that the protein must be properly folded to function, the mechanism by which this occurs is not understood. Our research aims to better understand this process by using the CCS (Copper Chaperone for Sod1) protein. CCS's main function is to help Sod1 acquire copper, as well as oxidize Sod1 in order for it to fold into its homodimeric quaternary structure. An essential

copper-binding motif that enables this is the CXC motif in Domain III of CCS. This is made up of two cysteines at positions 229 and 231, which we mutate to serine (C229S, C231S, C229S/C231S), as well as test CCSΔ and Sod1Δ strains to determine CCS's relationship to Sod1's structure and function. Using *Saccharomyces cerevisiae* as a model organism, which is 50% homologous to human Sod1, cells are cultured, lysed, and analyzed by SDS-PAGE, western blotting, and densitometry. Our preliminary results show that the C229S, C231S, and C229S/C231 strains yielded 40.6%, 27.4%, and 32.7% oxidized protein, respectively, compared to the WT protein being fully oxidized, suggesting that the cysteine at position 231 is more essential to the oxidation of Sod1. Additionally, CCSΔ and Sod1Δ strains showed 19.2% and 0.00% oxidation, respectively, indicating that CCS isn't the only mechanism responsible for Sod1 oxidation. Both CCS-dependent and independent mechanisms are prevalent in human Sod1 function, and because of this, CCS is a potential target for drug and gene therapies for SOD1-ALS. By developing a deeper understanding of how CCS helps Sod1 become functional, this could lead to promising new treatments for these cases of ALS.

Disclosures: M.E. Lafon: None. **L. Kane Barnese:** None.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.07/X11

Topic: C.06. Neuromuscular Diseases

Support: MSCRF

Title: Precision CRISPR Rescue of the ALS-Associated SOD1 G94A Mutation Enables High-Efficiency Correction and Recovery of Validated Rescue Clones

Authors: *M. A. USMANI, M. JANOWSKI;
Diagnos. Radiology and Nuclear Med., Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Precision CRISPR Rescue of the ALS-Associated *SOD1* G94A Mutation Enables High-Efficiency Correction and Recovery of Validated Rescue ClonesMuhammad A. Usmani[1], Yajie Liang[1], Brian G. Pierce[2], Piotr Walczak[1], Miroslaw Janowski[11]Program in Image Guided Neurointerventions (PIGN), Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland Baltimore, USA[2]Department of Cell Biology and Molecular Genetics, University of Maryland College Park, USAAmyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the progressive loss of motor neurons controlling voluntary muscle movement. The disease progresses relentlessly, carries a lifetime risk of approximately 1 in 300, and currently has no cure. Mutations in the SOD1 gene account for approximately 9–23% of familial ALS cases. Genome editing, combined with engineered stem cell–based delivery systems, represents a promising strategy for correcting disease-causing mutations and reducing the substantial morbidity, mortality, and economic burden associated

with ALS. As a proof of concept, we used CRISPR-Cas9 and prime editing to introduce the ALS-associated SOD1 G94A mutation into HEK293T cells, achieving up to 43% editing efficiency. The engineered G94A cells exhibited more severe pathological phenotypes and reduced total SOD1 expression compared with wild-type controls. In addition, we observed nuclear-to-cytoplasmic mislocalization of TDP-43, recapitulating a key molecular hallmark of ALS pathology. In a second step, we successfully corrected the G94A mutation back to the wild-type sequence using CRISPR-mediated genome editing, achieving approximately 70% rescue efficiency. Moving forward, we aim to restore normal SOD1 function using high-efficiency CRISPR-Cas9 editing delivered on-demand through engineered stem cells, establishing a foundation for mutation-specific, cell-based therapeutic approaches for ALS and related neurodegenerative disorders.

Disclosures: M.A. Usmani: None. **M. Janowski:** None.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.08/X12

Topic: C.06. Neuromuscular Diseases

Title: Integrated Molecular and Functional Profiling of ALS in Human iPSC-Derived Motor Neurons for Target Validation and Therapeutic Assessment

Authors: *B. HALL[1], M. GURNEY[1], X.-F. LI[1], S. GIACHETTI[1], H. SCOTT[1], T. MODEBADZE[1], J. GORDON-BLAKE[2], N. COLE[2], **E. MALAVASI**[1];
[1]Concept Life Sci., Edinburgh, United Kingdom; [2]Cortexa Therapeut. Inc., Phoenix, AZ

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal adult-onset neurodegenerative disorder characterized by progressive loss of upper and lower motor neurons, leading to muscle weakness, paralysis, and death, with limited disease-modifying therapies available. While familial and sporadic ALS share core pathological features, including protein aggregation, RNA dysregulation, impaired axonal transport, and neuroinflammation, their pathogenesis remains poorly understood, and their complexity is hard to recapitulate in traditional models. Human induced pluripotent stem cell (iPSC)-derived *in vitro* models now enable patient- and genotype-specific interrogation of ALS-relevant neuronal and glial phenotypes in a controlled environment, providing a powerful platform to dissect disease mechanisms, capture human-specific pathology, and evaluate candidate therapeutics with improved translational relevance. Here we present a suite of validated assays enabling in-depth phenotypic and functional characterisation of human iPSC-derived motor neurons modelling ALS, including patient-derived lines and genetically edited lines carrying ALS-causing mutations in C9orf72 and TDP-43 genes, alongside healthy control or isogenic control lines.
Digital PCR and an optimised Jess Protein Simple Western assay were used to quantify expression levels of all three C9orf72 transcript variants, and protein, in either ALS iPSC-

derived motor neurons carrying a repeat expansion mutation, or control lines. The subcellular distribution of total and phosphorylated TDP-43 was quantified using high-content immunofluorescence, integrated with analyses of lysosomal morphology and function. Deep mRNA sequencing with variant calling was leveraged to profile glutamate receptor subunit expression and RNA editing, which was aligned with corresponding protein measurements. To provide a functional perspective, intracellular calcium concentration at baseline was directly compared between ALS and control lines, as well as after glutamate receptor activation. These data were then correlated with measurements of neuronal health and viability. Finally, proof-of-concept data was generated demonstrating that ALS-associated phenotypes in this platform are pharmacologically modifiable.
Together, this tool set supports target validation, mechanism-of-action studies, and preclinical assessment of novel ALS therapeutics in *in vitro* models of high translational value.

Disclosures: B. Hall: A. Employment/Salary (full or part-time):; Concept Life Sciences. **M. Gurney:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **X. Li:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **S. Giachetti:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **H. Scott:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **T. Modebadze:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **J. Gordon-Blake:** A. Employment/Salary (full or part-time):; Cortexa Therapeutics Inc. **N. Cole:** A. Employment/Salary (full or part-time):; Cortexa Therapeutics Inc. **E. Malavasi:** A. Employment/Salary (full or part-time):; Concept Life Sciences.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.09/X13

Topic: C.06. Neuromuscular Diseases

Support: GR026184

Title: The effects of ROCK2 and S6K1 co-inhibition on axonal integrity and neuronal viability in iPSC models of ALS

Authors: *I. MELO[1], J. LAVERDE-PAZ[3], H. ALI[2], Z. ZEIER[1];
[2]The Miami Project to Cure Paralysis, [1]Univ. of Miami, Miami, FL; [3]Univ. of Miami Neurosci. Grad. Program, Miami, FL

Abstract: The neuropathological hallmarks of Amyotrophic Lateral Sclerosis (ALS) are corticospinal tract degeneration and neuronal death, preceded by the accumulation of TAR DNA-binding protein 43 (TDP-43) in affected motor neurons. At the Miami Project to Cure Paralysis, Dr. Ali and colleagues employed a novel polypharmacological drug discovery approach to identify Rho kinase 2 (ROCK2) and S6 kinase 1 (S6K1) as negative modulators of

axonal regeneration in models of spinal cord injury (SCI). This exploratory study evaluated the effects of ROCK2/S6K1 co-inhibition on axonal growth, regeneration, and neuronal survival in induced pluripotent stem cell (iPSC)-derived models of ALS. ROCK2/S6K1 was inhibited through a small molecule co-inhibitor, RO48 in TDP-43-deficient iPSC-derived neurons. To ensure scientific rigor, all experiments utilized a minimum sample size of three independent biological replicates ($n \geq 3$) with internal technical replication, and a scrambled gRNA lentiviral transduction control was used to account for off-target effects during TDP-43 knockdown. Neurite outgrowth was assessed in 2D motor neuron cultures via high-content imaging, and axonal growth was evaluated using a 2.5D motor neuron spheroid assay to achieve advanced neuronal differentiation. DNA damage was measured via a γH2AX immunocytochemistry assay. Additionally, a SYTOX green viability assay was performed to quantify cell survival. Knockdown of TDP-43 significantly reduced axonal growth. Treatment with RO48 rescued this phenotype in a dose-dependent manner in the 2D neurite outgrowth assay and significantly reduced the accumulation of γH2AX-positive DNA damage. Furthermore, the SYTOX viability assay demonstrated significantly improved survival in TDP-43-deficient neurons exposed to RO48. Similarly, 2.5D spinal spheroids exposed to neurotoxins exhibited decreased axonal growth, which was significantly restored by treatment. These exploratory findings demonstrate that robust phenotypic rescue can be achieved via ROCK2/S6K1 co-inhibition, supporting its further validation as a therapeutic strategy for ALS neurodegeneration.

Disclosures: I. Melo: None. **J. Laverde-Paz:** None. **H. Ali:** 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.; Collaborator UM. **Z. Zeier:** 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.; DoD grant GR026184.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.10/X14

Topic: C.06. Neuromuscular Diseases

Support: NRF Grant RS-2023-00211443

Title: BMAA induces zinc-dependent neuronal death through MMP9 activation in cortical neurons

Authors: *H. KANG[1,3], J. CHOI[4], J. HWANG[5], Y.-H. KIM[6], J.-Y. KOH[2], H. KIM[2]; [1]ASAN MEDICAL CENTER, seoul, Korea, Republic of; [2]Neurol., ASAN MEDICAL CENTER, Seoul, Korea, Republic of; [3]Med. Sci., Univ. of Ulsan Col. of Med., Seoul, Korea,

Republic of; [4]Neural Injury Res. Ctr., [5]Asan Inst. for Life Sciences, Asan Med. Ctr., Seoul, Korea, Republic of; [6]Integrative Biosci. and Biotech., Sejong Univ., Seoul, Korea, Republic of

Abstract: β-Methylamino-L-alanine (BMAA) is an environmental neurotoxin produced by cyanobacteria and has been implicated in ALS/Parkinsonism-dementia complex. Although BMAA-induced neurotoxicity has been linked to excitotoxicity and oxidative stress, the downstream mechanisms leading to neuronal death remain incompletely understood. Because intracellular zinc accumulation is a critical mediator of neuronal injury, we investigated whether zinc dysregulation contributes to BMAA-induced neuronal death and whether MMP9 activation is involved in this process. Primary cortical neurons prepared from embryonic day 14 ICR mouse fetuses were exposed to BMAA for 15 hours. Neuronal death was quantified using lactate dehydrogenase release assays, intracellular zinc accumulation was assessed by Zinpyr-1 staining, and MMP9 activity was evaluated using in situ zymography. To determine the functional role of zinc and MMP9, neurons were co-treated with the membrane-permeable zinc chelator TPEN or the MMP9 inhibitor minocycline. BMAA exposure significantly increased neuronal death by 60% compared with untreated controls ($p = 0.0002$). BMAA also induced intracellular zinc accumulation, suggesting disruption of zinc homeostasis in cortical neurons. Importantly, chelation of intracellular zinc with TPEN significantly attenuated BMAA-induced neuronal death by 55% compared to BMAA-only controls, indicating that zinc accumulation is functionally involved in BMAA neurotoxicity ($p = 0.0019$). BMAA further enhanced MMP9 activity, and pharmacological inhibition of MMP9 with minocycline significantly reduced neuronal death following BMAA exposure by 63% ($p = 0.0079$). These findings suggest that MMP9 activation acts downstream of zinc dysregulation in BMAA-induced neuronal injury. Together, these results demonstrate that BMAA induces zinc-dependent neuronal death in cortical neurons, at least in part through MMP9 activation. Our findings identify zinc dysregulation and MMP9 activation as potential downstream mediators of BMAA neurotoxicity and provide mechanistic support for a link between environmental neurotoxin exposure and ALS-related neurodegeneration.

Disclosures: H. Kang: None. **J. Choi:** None. **J. Hwang:** None. **Y. Kim:** None. **J. Koh:** None. **H. Kim:** None.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

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Program #/Poster #: PSTR014.11/X15

Topic: C.06. Neuromuscular Diseases

Support: NIH (1R15NS125394-01)

Title: Effect of Heavy Metal Exposure on Histone Post-Translational Modifications

Authors: *D. RUSSEL;
Brooklyn College-CUNY, Brooklyn, NY

Abstract: Heavy metal exposure is a known risk factor associated with many neurodegenerative diseases. Metals such as lead, zinc, copper and manganese have been implicated in the pathology of these diseases. Zinc serves protective mechanisms in the eukaryotic cell, however in excess it contributes to oxidative stress. Zinc acts as cofactor for enzymes including histone deacetylases (HDACs), histone acetyl transferases (HATs) and superoxide dismutase (SOD1). Therefore, careful regulation of zinc levels in the cell is imperative to maintaining transcription rates and cell function. Here, we study the impact of zinc exposure on post-translational modifications (PTMs) of histone proteins which surround DNA and impact gene expression by regulating transcription. The addition of acetyl and phosphate groups to histone N-terminal tails are typically associated with increased transcription and chromatin accessibility. Previous work shows that changes in levels of histone PTMs are linked to neurodegeneration. We hypothesize that heavy metal exposure also leads to altered levels of histone PTMs. Due to the conservation of many biological mechanisms between mammals and budding yeast, we use Saccharomyces cerevisiae (S. cerevisiae) to explore how histone PTMs (H3S10ph and H3K14ac) are affected by zinc. Cell viability assays show reduced cell survival when wild-type W303 yeast are treated with zinc. Additionally, western blotting illustrates that exposure to zinc (II) chloride corresponds to lower levels of H3S10ph and H3K14ac compared to control yeast. These results indicate that exposure to zinc is linked to changes in the epigenome and decreased cell survival. Future work will explore the links between other heavy metals like lead and their impact on histone PTMs and neurodegeneration.

Disclosures: D. Russel: None.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.12/X16

Topic: C.06. Neuromuscular Diseases

Title: Decoding Neurodegeneration: From HibiT Screening to Gene Expression Signatures

Authors: A. MOLTENI[1], P. BONETTI[1], S. ZERBI[1], P. ARIOLI[1], I. COTELLESSA[1], S. CIARDELLI[1], A. SEGNALI[2], S. MEINI[1], R. DI GUIDA[1], I. MICCO[1], ***K. HEADLAND**[1], J. ROLLAND[1];
[1]Axxam SpA, Bresso, Italy; [2]Axxam SpA, Bresso (MI), Italy

Abstract: Neurodegenerative disorders impact the life of millions globally. Decades of research indicate that several genetic factors and biochemical pathways significantly contribute to the risk of developing these conditions. Developing effective treatments has been difficult, and recent therapies have not succeeded in controlling the disease, restoring motor function, or improving

quality of life. The target protein of this discovery program is present at elevated levels in neuronal tissues from patients with neurodegenerative diseases such as ALS and FTLD-TDP and plays a pivotal role in neuronal communication, maintaining synaptic active zones and restoring its function.To advance this research, the SH-SY5Y neuroblastoma cell line, stably expressing the target of interest tagged with HibiT at the C-terminus, has been used to identify small molecules able to modulate target's protein and mRNA level.A cell-based High Throughput Screening was conducted on over 350,000 compounds from the AxxDiversity and RNA targeting libraries using the HibiT technology to measure the target protein levels. The overall hit rate was 0.43%, with hit compounds showing activity % ranging between 10% and 50% depending on the collection assessed. To further investigate the pathway influenced by the active compounds, an RT-qPCR orthogonal assay was set up and validated under automated conditions. Up to 1% of screened compounds were evaluated in parallel on both assays: among these, 202 compounds, confirmed active on the primary HibiT assay, exhibited modulation of the target gene expression, resulting in fold change values from 2.5 to 10. Moreover, to select additional analogs of the active hit compounds, a rescue by Cluster Analysis was performed using Tanimoto similarity measure based on Morgan fingerprints. This analysis contributed substantially to the outcome, enriching the final pool of hits with 9 additional chemotypes. Out of 320 compounds selected for potency determination through dose-response assessment on both primary and orthogonal assays, 13 hits were confirmed as clear modulators of the targets' protein levels and gene expression. Notably, the 5 hits with the ideal profile, considering their potency and efficacy, belong to 5 different chemotypes. To prioritize the most promising compounds, further characterization of their biological profiles and chemical tractability is underway.This study confirms that RT-qPCR and HibiT technologies are robust and reliable methods for screening small molecules, facilitating the advancement of new therapies for neurodegenerative disease.

Disclosures: A. Molteni: None. **P. Bonetti:** None. **S. Zerbi:** None. **P. Arioli:** None. **I. Cotellessa:** None. **S. Ciardelli:** None. **A. Segnali:** None. **S. Meini:** None. **R. Di Guida:** None. **I. Micco:** None. **K. Headland:** None. **J. Rolland:** None.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR014.13/X17

Topic: C.06. Neuromuscular Diseases

Support: NRF Grant RS-2025-00560220

Title: Distinct Acute and Chronic Mechanisms of BMAA Neurotoxicity Reveal Therapeutic Targets for ALS

Authors: *S. KIM;
Dept. of Integrative Biosci. and Biotechnology, Sejong Univ., Seoul, Korea, Republic of

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by motor neuron degeneration. L-BMAA (BMAA), a cyanobacterial neurotoxin linked to the high incidence of Guam ALS-parkinsonism-dementia complex (ALS-PDC), has been suggested as an environmental contributor to ALS pathogenesis. Here, we investigated the mechanisms underlying BMAA-induced neurotoxicity and evaluated potential therapeutic strategies.Elevated intracellular Zn2+ levels observed in BMAA-treated neurons implicated Zn2+ dysregulation as a potential contributor to neurotoxicity. In primary cortical neurons, high-concentration BMAA induced acute neuronal injury through glutamate receptor-mediated excitotoxicity, as cell death was attenuated by the NMDA receptor antagonist MK-801 and the AMPA/kainate receptor antagonist CNQX. Toxicity was further reduced by the Zn2+ chelator TPEN and the antioxidant Trolox, indicating critical roles for Zn2+ dysregulation and oxidative stress. We also investigated matrix metalloproteinase-9 (MMP-9), a protein selectively enriched in vulnerable fast-fatigable motor neurons and implicated in their degeneration in ALS. Pharmacological inhibition of MMPs using ZCC1, a compound developed in our laboratory, significantly attenuated BMAA-induced neuronal death, supporting a pathogenic contribution of MMP-9 signaling to acute BMAA neurotoxicity. In contrast, prolonged exposure to subtoxic concentrations of BMAA produced features more relevant to chronic neurodegeneration. Low-dose BMAA promoted the formation of stress granules and reduced expression of the lysosomal Ca2+ channel TRPML1, consistent with impaired lysosomal homeostasis. These findings suggest that chronic BMAA exposure may facilitate protein aggregation and disrupt lysosomal function through suppression of the TRPML1-calcineurin-TFEB signaling axis, thereby contributing to ALS-related neurodegenerative processes.Given the emerging role of lysosomal dysfunction in BMAA-mediated neurodegeneration, we examined the therapeutic potential of ZCS1, a lysosomal activator. In vivo, ZCS1 alleviated hallmarks of BMAA-induced neurodegeneration, including TDP-43 proteinopathy and elevated plasma neurofilament light chain levels. Collectively, these findings identify two distinct pathogenic mechanisms of BMAA toxicity—acute Zn2+-dependent excitotoxic injury and chronic lysosomal dysfunction—and highlight ZCC1 and ZCS1 as promising therapeutic candidates for ALS.

Disclosures: S. Kim: None.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.14/X18

Topic: C.06. Neuromuscular Diseases

Title: A Human iPSC-Based ALS Platform for Disease Modelling and Therapeutic Evaluation Across Molecular and Functional Endpoints

Authors: C. VAN BERKEL[1], K.-C. PITSA[2], **J. LAMB**[3], *S. SCHWENGBERG[3], S. JAIN[2]; [1]Discovery Technol., [2]Ncardia, Leiden, Netherlands; [3]Ncardia Services B.V., Leiden, Netherlands

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive motor neuron degeneration and neuroinflammation. A hallmark of ALS pathology is aggregation and mislocalization of the RNA-binding protein TDP-43, observed in approximately 97% of patients. Loss of nuclear TDP-43 function causes widespread splicing abnormalities, including reduced expression of STMN2, a critical regulator of axonal maintenance and repair. Development of effective therapies has been hindered by the lack of predictive human-relevant models that recapitulate key molecular and functional disease phenotypes. To address this need, Ncardia developed a scalable human induced pluripotent stem cell (iPSC)-based ALS platform comprising motor neuron-enriched cultures that reproduce clinically relevant disease hallmarks. Upon induction of TDP-43 pathology, iPSC-derived motor neurons exhibit cytoplasmic TDP-43 aggregation and nuclear depletion, accompanied by reduced full-length STMN2 mRNA and protein levels and increased expression of truncated STMN2 transcripts. These molecular changes are associated with functional deficits, including impaired neuronal network activity, reduced firing rates, decreased burst frequency, and disrupted synaptic connectivity. The platform enables assessment of therapeutic efficacy through integrated molecular, cellular, and functional endpoints and is compatible with small molecules, RNA therapeutics, and gene therapies. As a representative example, the platform was used to evaluate NUZ-001, a lead small-molecule therapeutic developed by Neurizon that promotes proteostasis through autophagy activation. Treatment of ALS iPSC-derived motor neurons for 5-7 days significantly reduced TDP-43 aggregation, resulting in a 50-65% decrease in total TDP-43 levels measured by HTRF ($p < 0.001$). Electrophysiological analysis using multi-electrode arrays demonstrated significant improvements in burst and network burst parameters ($p < 0.001$), while calcium imaging confirmed restoration of neuronal network activity to levels comparable to healthy controls. Collectively, these findings demonstrate the utility of Ncardia's human iPSC-based ALS platform as a translational system for disease modelling and therapeutic evaluation. By combining disease-relevant molecular pathology with quantitative functional readouts, the platform provides a robust framework for screening and characterizing therapeutics targeting TDP-43-driven ALS pathology and supports more predictive preclinical drug development

Disclosures: C. van Berkel: A. Employment/Salary (full or part-time):; Ncardia Services B.V. **K. Pitsa:** A. Employment/Salary (full or part-time):; Ncardia Services B.V. **J. Lamb:** A. Employment/Salary (full or part-time):; Ncardia Services B.V. **S. Schwengberg:** A. Employment/Salary (full or part-time):; Ncardia Services B.V. **S. Jain:** A. Employment/Salary (full or part-time):; Ncardia Services B.V..

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

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Topic: C.06. Neuromuscular Diseases

Support: ICMR –Centre for advance research and excellence (5/4-5/Neuro/184/CAR-Phase-II/2018-NCD-1), INDIA

Title: Elucidating the role of kv1.3 potassium channel and its blocker in modulating microglial responses to cerebrospinal fluid from sporadic amyotrophic lateral sclerosis patients

Authors: *N. SARKAR[1], A. MURUGAN[4], D. KRISHNA[2], M. VENKATASWAMY[4], S. VENGALIL[4], A. NALINI[3], T. R. RAJU[5], T. N. SATHYAPRABHA[6], K. VIJAYALAKSHMI[7]; [2]Neurophysiol., [1]Natl. Inst. of Mental Hlth. and Neuro Sci. (NIMHANS), Bengaluru, India; [3]Neurol., Natl. Inst. of Mental Hlth. and Neuro Sci. (NIMHANS), Bangalore, India; [4]Natl. Inst. of Mental Hlth. and Neurosciences (NIMHANS), Bangalore, India; [5]Natl. Inst. of Mental Hlth. Neurosciences (NIMHANS), Bangalore, India; [6]Neurophysiol., NIMHANS, Bangalore,, India; [7]Neurophysiol., Natl. Inst. of Mental Hlth. and Neuro Sci., Bangalore, India

Abstract: Neuroinflammation is a hallmark of many neurodegenerative disorders, including Amyotrophic Lateral Sclerosis (ALS), arising largely from dysregulated immune signaling within the brain. Microglia, the resident immune cells of the brain, contribute to these neuroinflammatory processes through their morphological and functional transformations. These cells are regulated by other cell types through the interplay of ion channels, receptors, and transporters present in them. Among these regulators the voltage gated potassium channel, Kv1.3 has emerged as a pivotal determinant of microglial activation. Upregulation of Kv1.3 promotes a pro-inflammatory, neurotoxic phenotype characterized by the release of cytotoxic molecules. Pharmacological inhibition of Kv1.3, therefore, represents a promising strategy to regulate microglial activation. PAP-1 [5-(4-phenoxybutoxy)psoralen], a selective Kv1.3 blocker, has been shown to attenuate pro-inflammatory microglial responses. While Kv1.3 has been implicated in animal models of various neurodegenerative diseases, its relevance to ALS remains to be investigated. To elucidate the role of Kv1.3 in sporadic ALS, we used a human microglial cell line, HMC-3, which was exposed to cerebrospinal fluid (CSF) from sporadic ALS patients (ALS-CSF; 10% v/v). Cells were examined for Kv1.3 channel expression by immunocytochemistry and flow cytometry. ROS, glutamate and NO levels were assessed and the inflammatory profile was estimated by qPCR. We then co-treated the cells with the channel blocker, PAP-1 (1 μM), for 24 hours. To assess the impact of the secretome released from HMC3 cells exposed to ALS-CSF, we further exposed it to motor neurons, specifically NSC-34, and evaluated its viability.The findings demonstrated toxic effects of ALS-CSF on HMC3 cells, characterized by morphological alterations with an increased number of activated amoeboid cells that release elevated levels of ROS, glutamate, and NO. Furthermore, upregulated Kv1.3 expression, alongside increased pro-inflammatory cytokines, confirms the role of Kv1.3 in driving microglial cells toward toxic insults in ALS-CSF. Interestingly, PAP-1 could ameliorate the ALS-CSF-induced changes in HMC3 cells. Furthermore, the HMC3 secretome could enhance the survival of NSC-34 cells, suggesting a neuroprotective effect. These findings identify PAP-1 as a candidate molecule for modulating Kv1.3-induced microglial activation and suggest its therapeutic potential. Further exploring its downstream pathways will unravel the molecular targets for mitigating the Kv1.3 mediated microglial activation and related neuroinflammatory mechanisms.

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Poster

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Program #/Poster #: PSTR014.16/X20

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant 1R21NS135044-01A1

Title: Assessing ligand-free mutant AR-induced cytotoxicity in SBMA using an isogenic hiPSC-derived NSC model

Authors: *X. FENG, S. ENG, C. BLACKSTONE;
Neurol., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Spinal bulbar muscular atrophy (SBMA) is an X-linked neuromuscular disorder displaying progressive dysfunction and degeneration of lower motor neurons and skeletal muscle cells. Mitochondrial abnormalities are a hallmark of SBMA across cell lines, animal models, and human patients. Emerging evidence indicates that mitochondrial dysfunction occurs early in SBMA, implying its deleterious role during initial stages of neurodevelopment. Previous studies, including our own, demonstrate that the mutant androgen receptor (AR),encoded by the *AR* gene with pathological expanded CAG repeats, has a mitochondrial localization—likely driven by a non-canonical mitochondrial targeting sequence at its N-terminus—where it preferentially interacts with mitochondrial proteins. In line with these observations, we showed that ligand-free, mitochondria-localized mutant AR leads to mitochondrial abnormalities in neurites of differentiated motor neurons via a gain-of-function mechanism. Moreover, ligand-free mutant AR aberrantly interacts with F-ATP synthase, compromising mitochondrial respiration and driving ligand-independent pathogenesis. To determine whether ligand-free mutant AR-induced cytotoxicity is an early driver of motor neuron degeneration in SBMA, we have established an isogenic human induced pluripotent stem cell (hiPSC)-derived neural stem cell (NSC) model. Using this model, we are characterizing the mitochondrial dysfunction and other cellular defects at the NSC stage, which may evolve into persistent motor neuron dysfunction and drive pathogenic SBMA progression.

Disclosures: X. Feng: None. **S. Eng:** None. **C. Blackstone:** None.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

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Program #/Poster #: PSTR014.17/X21

Topic: C.06. Neuromuscular Diseases

Title: Modeling Neuroinflammation Using Control and Alzheimer's Disease Model iPSC-Derived Neurons, Astrocytes, and Microglia in 2D Tri-Culture and 3D Spheroid NAM Platforms

Authors: *G. S. SAHIN[1], G. STADLER[3], K. JANKE[3], L. KONG[2], R. ALVAREZ[3], K.-D. CHOI[1], M. L. HENDRICKSON[3], K. XU[4];
[2]R&D, [1]BrainXell, Madison, WI; [3]BrainXell, Inc., Madison, WI; [4]BrainXell Inc., Madison, WI

Abstract: New approach methodologies (NAMs) are gaining increasing attention as the pharmaceutical industry moves away from reliance on animal testing. Human induced pluripotent stem cell (iPSC)-derived neurons and glial cells have emerged as highly relevant platforms for studying central nervous system (CNS) physiology and disease, as they retain human genetic background, expression profile and signaling pathways. In this study, we integrated iPSC-derived neurons, cortical astrocytes, and microglia to establish functional in vitro platforms for modeling neuroinflammation using a NAM-based approach. We first characterized complex 2D and 3D spheroid culture systems consisting of neuron-astrocyte co-cultures, neuron-microglia co-cultures, and neuron-astrocyte-microglia tri-cultures. Cytokine secretion profiles from astrocytes and microglia were evaluated individually and in combination to better capture the complexity of CNS inflammatory signaling. These assays were optimized in a 384-well plate format to support high-throughput screening applications. In addition, we modeled an Alzheimer's disease-associated genetic background using ApoE4/E4-expressing cells and assessed inflammatory responses within this system. Collectively, this study demonstrates the utility of NAMs for modeling neuroinflammation using physiologically relevant human iPSC-derived CNS cell types and highlights how genetically defined models can be selectively incorporated into a model to study neurodegenerative diseases such as Alzheimer's disease.

Disclosures: G.S. Sahin: A. Employment/Salary (full or part-time):; BrainXell. **G. Stadler:** A. Employment/Salary (full or part-time):; BrainXell. **K. Janke:** A. Employment/Salary (full or part-time):; BrainXell. **L. Kong:** A. Employment/Salary (full or part-time):; BrainXell. **R. Alvarez:** A. Employment/Salary (full or part-time):; BrainXell. **K. Choi:** A. Employment/Salary (full or part-time):; BrainXell. **M.L. Hendrickson:** A. Employment/Salary (full or part-time):; BrainXell. **K. Xu:** A. Employment/Salary (full or part-time):; BrainXell.

Poster

PSTR014: ALS and Motor Neuron Diseases: *In Vitro* Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.18/X22

Topic: C.06. Neuromuscular Diseases

Title: Human spheroid assay platform: analysis of lysosome activity in wild type and ALS mutant spheroids containing iPSC-derived motor neurons, spinal astrocytes, and microglia.

Authors: C. HIELSBERG[1], C. PERRY[2], K. XU[5], A. MASSMAN[3], K. REMONDINI[6], H. RUETH[7], A. JOHNSON[7], **M. L. HENDRICKSON**[7], K.-D. CHOI[1], *J. LAWSON[4]; [2]Quality Control, [1]BrainXell, Madison, WI; [3]BrainXell, madison, WI; [4]BrainXell, MADISON, WI; [5]BrainXell Inc., Madison, WI; [6]Brainxell, inc, madison, WI; [7]Brainxell, inc, Madison, WI

Abstract: The role of Motor Neurons (MN), Spinal Astrocytes (SA), Microglia (MG), play in their lysosomal interactions in neurodegenerative diseases has not yet been fully elucidated. These cell types are highly implicated in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), epilepsy, schizophrenia, anxiety, and chronic pain. Currently, there is an urgent need for physiologically relevant cell models for drug screening. Preclinical animal models fail to translate to human biology because they exhibit distinct genomic and proteomic differences. Immortalized cell lines become senescent and inadequate in expressing complex pathological pathways. Furthermore, the availability and viability of human biopsy tissue is limited. The ability to differentiate human induced pluripotent stem cells (hiPSCs) into various neuronal lineages improves the field of drug discovery and personalized medicine by providing scalable and human-relevant models. In addition, hiPSC-derived neuronal progenitors can be used to generate spheroids that contain multiple neural cell types for High-Throughput Screening (HTS) assays. Here, we have developed a tri-culture spheroid screening platform for viability and lysosome functional assays with hiPSC-derived wild type and ALS mutated MN, SA, and MG in u-bottom Elplasia plates. To determine lysosome function, a Lysotracker assay was used with and without IFN-γ and Chloroquine control compounds. Immunocytochemistry confirmed morphology of MN, SA, and MG of the tri-culture spheroid models. A CellTiter-Glo assay was used to assess viability in response to Staurosporine. This tri-culture model is a powerful tool that could be used to investigate neural responses to novel therapeutic compounds, molecular mechanisms involved in cell-cell signaling, and neurological disorders.

Disclosures: C. Hielsberg: A. Employment/Salary (full or part-time):; full time, BrainXell. **C. Perry:** A. Employment/Salary (full or part-time):; BrainXell. **K. Xu:** A. Employment/Salary (full or part-time):; BrainXell. **A. Massman:** A. Employment/Salary (full or part-time):; BrainXell. **K. Remondini:** A. Employment/Salary (full or part-time):; BrainXell. **H. Rueth:** A. Employment/Salary (full or part-time):; BrainXell. **A. Johnson:** A. Employment/Salary (full or part-time):; BrainXell. **M.L. Hendrickson:** A. Employment/Salary (full or part-time):; BrainXell. **K. Choi:** A. Employment/Salary (full or part-time):; BrainXell. **J. lawson:** A. Employment/Salary (full or part-time):; full time, BrainXell.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.01/X23

Topic: E.01. Somatosensation – Pain and Itch

Title: Electrophysiological Properties of Cultured Human Trigeminal Ganglion Neurons

Authors: *M. K. SCHAUB[1], K. GABRIEL[2], T. J. PRICE[4], G. O. DUSSOR[3];
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Abstract: Migraine is the most disabling neurological disorder worldwide with its main debilitating symptom being severe pain. Despite the vast prevalence of the disease, the mechanisms underlying migraine and the pain associated with it are not fully understood. Historically, pre-clinical migraine research has been conducted primarily in rodent models which have led to great improvements in the understanding of the disease. However, findings exclusively from rodent models do not always provide sufficient rationale for translation of therapeutic targets into humans. We have developed methods to recover and culture human trigeminal ganglia (hTG) from which we can conduct functional experiments to help address these challenges. Through a partnership with the Southwest Transplant Alliance in Dallas, TX, we recovered hTG from tissue donors that is then cultured and investigated with numerous techniques. We have found that hTG neurons can be cultured and kept alive *in vitro* for up to 90 days and are viable for various electrophysiology experiments. We used patch-clamp electrophysiology to collect baseline excitability and action potential property data from > 60 neurons across 8 donors. The resting membrane potential of hTG cells was -51.62 mV +/- 1.8 mV, mean rheobase was 697 +/- 91.44 pA, and 17% of cells were spontaneously active. In addition, hTG neurons express functional acid-sensing ion channel current with 94% of cells responding to a pH stimulus of 6.0, and 62% responding to pH 6.8. These data provide the foundation for mechanistic studies using functional assessments of hTG neurons. Establishment of baseline characteristics of hTG neurons will allow for future migraine target validation and enhanced rationale for development of these targets as novel therapeutics.

Disclosures: M.K. Schaub: None. **K. Gabriel:** None. **T.J. Price:** None. **G.O. Dussor:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.02/X24

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R41NS127637
NIH R01NS098826

Title: Activation of Protease-Activated Receptor 2 Causes Hyperexcitability in Human Sensory Neurons

Authors: M. SCHAUB[1], J. B. LESNAK[2], S. I. SHIERS[3], M. KUME[4], T. J. PRICE[5], ***G. O. DUSSOR**[6];
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Abstract: Activation of protease-activated receptor 2 (PAR2) has been identified as a robust contributor to pain- and migraine-like behavior in rodent models and it has been proposed as a novel therapeutic target for both pain and migraine. PAR2 is expressed in 3-4% of murine sensory neurons. However, PAR2 is expressed in >30% of human sensory neurons, and this discrepancy likely results in an underestimation of the role of PAR2 in human migraine and other pain disorders. We used patch-clamp electrophysiology to examine effects of PAR2 activation on excitability of dissociated human dorsal root ganglion neurons. Cells were treated with PAR2 activators including the selective agonist 2at-LIGRL-NH2 as well as elastase, an endogenous protease that activates the receptor. Spontaneous activity, rheobase, action potential frequency, and action potential properties were measured. Additionally, cells were pre-treated with a PAR2 antagonist prior to PAR2 activators, and the same excitability measures were determined. We found that cells treated with PAR2 activators were hyperexcitable; there were more spontaneously active neurons in the treatment groups; cells had lower rheobase and fired more action potentials than controls. These effects could be completely blocked by pre-treatment with a selective PAR2 antagonist. These data indicate that both selective and physiological PAR2 activators induce hyperexcitability of human sensory neurons, and these effects can be fully blocked with PAR2 antagonism. This work establishes that PAR2 signals to mechanisms that cause hyperexcitability in human sensory neurons and further supports the rationale for investigating PAR2 as a target for treating pain and migraine in humans.

Disclosures: M. Schaub: None. **J.B. Lesnak:** None. **S.I. Shiers:** None. **M. Kume:** None. **T.J. Price:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PARMedics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PARMedics. **G.O. Dussor:** 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.; PARMedics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PARMedics.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.03/X25

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant EY034680

Title: Trigeminal Sensory Neurons that Project to the Dura versus the Cornea

Authors: *D. B. SEMIDEY[1], D. M. HEGARTY[1], C. JIANG[1], C. GUNTER[1], C. W. MORGANS[1], T. M. LARGENT-MILNES[2], S. A. AICHER[1];
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Abstract: Both migraine and ocular surface injuries can evoke pain and photoallodynia, which are thought to be mediated by activation of dural or corneal sensory neurons, respectively. The mechanisms of photoallodynia are poorly understood, and this common symptom could be mediated by crosstalk between neurons in the trigeminal ganglion (TG). To test this hypothesis, we examined neurons in TG that project to the dura and cornea in the same animal using the retrograde tracer cholera toxin B (CTb), conjugated to different fluorophores. Specifically, CTb-555 was applied to the dura and CTb-488 was applied to the cornea in 12 Sprague-Dawley rats. One week later, rats were perfused with 4% paraformaldehyde, and TGs were removed and briefly postfixed. Whole TGs were mounted in CFM-1 in a chamber slide and tile-scanned at 10x magnification with a Zeiss LSM 900 confocal microscope. Cases in which both types of retrogradely labeled cells were detected were examined in detail (n = 6 females, n = 6 males). Retrogradely-labeled neurons were located in the TG for each animal and one optical slice in the z-stack was chosen for each neuron that represented the center of that neuron through its nucleus. The perimeter of each neuron was traced in Zen software, and the cross-sectional area was calculated in μm^2. Dural- and corneal-projecting neurons could be classified as small, medium, or large. On average, corneal neurons (598 $\pm$ 16 μm^2; mean area $\pm$ SEM) were significantly smaller than dural neurons (854 $\pm$ 62 μm^2; Mann-Whitney Rank Sum Test, $P < 0.001$). Corneal neurons (n =515) were more abundant than dural neurons (n = 57), partially due to the circumscribed region of dural injections, which were confined to cortical regions that evoked spreading depression associated with migraine. Although no cells contained both retrograde tracers, dural neurons were generally in proximity to corneal neurons, suggesting that crosstalk between these groups of neurons may be possible, perhaps due to their associated satellite glia. While there were no sex differences in the density of corneal epithelial nerves (% corneal epithelium volume that contained β-tubulin-labeled nerve volume; males: 2.6 ± 0.3%; females: 2.7 ± 0.3%; t-test, P = 0.8) or the number of labeled corneal TG neurons (males: 52 ± 14; females: 34 ± 4; Welch's t-test, P = 0.3), we did find that the average size of corneal-projecting neurons was greater in females (632 ± 25 μm^2) than in males (576 ± 22 μm^2; Mann-Whitney Rank Sum Test, P = 0.005). Taken together, this study shows that corneal- and dural-projecting neurons in TG are morphologically distinct but also positioned for potential interactions within TG that may mediate common responses to nerve injury.

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Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.04/X26

Topic: E.01. Somatosensation – Pain and Itch

Support: NEI U01 EY034681-01

Title: Population and sparse labeling of corneal nerves reveal unique distributions of sensory afferent functional groups

Authors: *T. CANNONIER[1], K. LAISE[2], V. LEE[3], W. LUO[1];
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Abstract: The cornea is the most densely innervated tissue in the body sensitive to temperature, touch, and noxious stimuli mediated by TRPM8, Piezo2, and TRPV1 expressing sensory afferents respectively. These sensory afferents facilitate reflexively protective behaviors, such as blinking, lacrimation, and wiping, to protect the eye and preserve vision. Pathological conditions, such as dry eye disease (DED), are known to damage corneal sensory afferents, which can potentially lead to decreased vision and patient quality of life. Little is known about the morphologies and distributions of these sensory afferent subgroups at baseline or their plastic dynamics in pathology. To address this knowledge gap, we induced a surgical model of DED in transgenic mice (*TRPM8-GFP*, *TRPV1-Cre; Ai9, SST-Cre; Ai9*) and used immunohistochemistry to characterize the morphologies, distributions, and plastic dynamics of functional groups of corneal sensory afferents at baseline, 4-weeks, and 8-weeks after surgery. We used *Advillin-CreERT2; Ai9* mice to sparsely label and perform 3D reconstruction of sensory afferents. Population quantification was performed using 6-12-week-old *TRPM8-GFP*, *TRPV1-Cre; Ai9,* and *SST-Cre; Ai9* mice. Mice were anaesthetized with isoflurane, and lacrimal glands were surgically excised to induce DED in the right eye. Corneas were flat mounted for comparison of baseline, 4-week, and 8-week post-DED timepoints. Corneas were immunostained with neurofilament heavy chain (NFH) and calcitonin gene-related peptide (CGRP). Whole cornea z-stack confocal images were acquired. Sparse labeling was performed using 6-12-week-old *Advillin-CreERT2; Ai9* mice. Without induction, stochastic and unbiased labeling of individual nerves was observed. Sample images were masked and thresholded to create 3-dimension representations. Morphology was categorized into functional groups using immunostaining staining.
TRPM8+, CGRP+, and NFH+ sensory afferents show normal distribution around the cornea. NFH+ afferents show greater density in the periphery of the cornea compared to other functional groups. TRPM8+ afferents showed striping innervation with branches starting in the periphery and projecting to the central cornea. At 4-weeks, TRPM8+, CGRP+, and NFH+ sensory afferents lose their organization from baseline while SST+ afferents retract projections. At 8-weeks, NFH+ and TRPV1+ afferents show hyperinnervation in central and peripheral cornea. SST+ afferents were largely ablated by 8-weeks post-DED. These results, correlated with molecular and behavioral responses, may elucidate mechanism underlying aberrant corneal sensitivity.

Disclosures: T. Cannonier: None. **K. Laise:** None. **V. Lee:** None. **W. Luo:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.05/X27

Topic: E.04. Interoception

Support: NYU Whitehead Fellowship for Junior Faculty
NYU Deans Undergraduate Research Fund

Title: Neuronal and molecular mechanisms of laryngeal proprioception

Authors: *J. LI[1], C. WEST[2,1], J. GENDY[1], W. PENNINGTON-FITZGERALD[3], N. BOWES[1], I. HERNANDEZ-MORATO[3,5], M. PITMAN[3], J. C. DE NOOIJ[4], A. JOHNSON[6], Y. MOAYEDI[1];
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Abstract: Laryngeal proprioception enables us to modulate speech production and achieve rapid, adaptable airway defense. Loss of laryngeal mechanosensation results in devastating effects, including dysphagia, dysphonia, and aspiration, which depreciate quality of life and increase morbidity and mortality. Despite their importance, laryngeal sensory innervation and mechanisms of proprioception remain poorly understood. In skeletal muscle proprioceptive sensory neurons consist of muscle spindle and Golgi tendon organ afferents. However, our previous studies failed to identify these canonical proprioceptors in rodent intrinsic laryngeal muscles (ILM). This poses the question: What is the cellular mechanism of laryngeal proprioception? We hypothesize that Piezo2-dependent mechanosensory neurons mediate laryngeal proprioception and modulate phonation. Consistent with this, our anatomical analyses identified neuronal and mucosal Piezo2 expression in ILM and adjacent mucosa. Neuronal morphologies include free nerve endings and, interestingly, neurons innervating motor endplates. We tested whether *Piezo2* is necessary for normal vocal output by recording maternal separation-evoked ultrasonic vocalizations (USVs) in mice in which *Piezo2* was conditionally ablated in PV+ sensory neurons ($Parv^{Cre}$; proprioceptors and mechanoreceptors), Chat+ cholinergic neurons neurons ($Chat^{Cre}$, motor, sympathetic, and some sensory neurons), or Phox2b+ neurons ($Phox2b^{Cre}$; nodose, petrosal, and geniculate sensory neurons; brachial and visceral motor neurons). All methods of *Piezo2* ablation resulted in differences in USV features, with differential effects on the number, length, frequency components, pitch modulation, and tone of USVs. These results suggest that neural populations contribute in differing ways but they all seem to use *Piezo2* to do so. Our current work aims to further tease apart the roles of sensory neuron subpopulations in modulating phonation, define the physiological features of putative laryngeal proprioceptors, and conduct a 3D-analysis of neuronal end organs within ILM. These findings will improve our understanding of phonation and the roles of proprioceptors in non-skeletal structures.

Disclosures: J. Li: None. **C. West:** None. **J. Gendy:** None. **W. Pennington-FitzGerald:** None. **N. Bowes:** None. **I. Hernandez-Morato:** None. **M. Pitman:** None. **J.C. De Nooij:** None. **A. Johnson:** None. **Y. Moayedi:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.06/X28

Topic: E.01. Somatosensation – Pain and Itch

Support: DoD HT9425-24-1-0788
NIH R56EY037692
DoD HT9425-23-1-1045

Title: Electrical Stimulation Promotes Corneal Nerve Regeneration and Functional Recovery in Diabetic Neuropathy through KCNN-Dependent Mechanisms

Authors: *M. YANG[1,2], L. HUANG[2], D. CHEN[2];
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Abstract: Purpose: Diabetic neuropathy (DN) is the most common complication of diabetes mellitus (DM) and often involves the cornea, which significantly impacts quality of life, ranging from delayed corneal wound healing, dry eye, and ocular pain, to corneal ulceration. Very limited treatment has been proven effective. Transcutaneous electrical stimulation (TES) non-invasively delivers microcurrent electricity to evoke a clinical skin response. This study investigates the neural regenerative potential of TES in a type I DM-induced DK model and the mechanism of electrical-induced neuroregeneration. **Method:** Male C57BL/6J mice, 8-week-old, were induced with type I DM through intraperitoneal streptozotocin (STZ) injection. Starting at week 15 post-STZ, daily 4-minute TES sessions were administered for 14 days. Sham controls received electrode placement without current. hiPSC-derived sensory neurons were cultured from commercially available healthy human iPSC line SCTi004-A. **Result:** TES significantly restored the nerve density and sensory function in STZ-induced DM cornea. Isolated trigeminal ganglia (TG) neurons from the TES group displayed significantly longer neurites and higher neural response (n=8). In iPSC-derived sensory neurons, ES significantly blocked the neural response to nociceptive stimulus capsaicin, but not mechanosensory agonist ATP nor the thermoreceptor agonist TRPM8. To investigate the underlying mechanism, transcriptomics analysis of TGs from in vivo ES pointed to neural regeneration and Ca^{2+} signaling alteration, as well as Ca^{2+}-activated transcription factors (n=4). Consistently, membrane potential recording in TGs showed a rapid hyperpolarization upon ES accompanied by increased $[Ca^{2+}]_i$ level. Inhibition with the chemical blocker of Ca^{2+}-activated K^+ Channel (KCNN), Apamin, abolished the hyperpolarization and neural regeneration process induced by electrical stimulation, while KCNN overexpression significantly increased the neural regeneration process. **Conclusion:** TES

restores corneal nerve density and function in diabetic neuropathy via KCNN activation, offering a novel, non-invasive, and clinically translatable therapeutic strategy.

Disclosures: M. Yang: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor of a pending patent US20250256100A1. **L. Huang:** None. **D. Chen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor of a pending patent US20250256100A1.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.07/X29

Topic: E.01. Somatosensation – Pain and Itch

Support: JSPS KAKENHI Grant Number 25K09805

Title: Reduced barometric pressure at the cornea activates trigeminal nociceptive neurons and evokes reflex tear secretion in rats

Authors: Y. KANI, ***A. TASHIRO**;
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Abstract: Barometric pressure changes can trigger headaches and modulate autonomic function, yet the peripheral neural mechanisms underlying these effects remain unclear. Previous studies have shown that trigeminal nociceptive neurons receiving inputs from the dura mater and cornea respond to changes in barometric pressure. Because the cornea is densely innervated by trigeminal afferents and directly exposed to the external environment, corneal sensory endings may act as peripheral detectors of pressure changes. These findings suggest that barometric pressure reduction may directly activate corneal trigeminal afferents, leading to trigeminal nociceptive activation and reflex tear secretion.To address this issue, extracellular single-unit activity was recorded under isoflurane anesthesia in male rats from corneal-responsive neurons in the trigeminal subnucleus interpolaris/caudalis (Vi/Vc) transition and laminae I-II of the Vc/cervical cord (Vc/C1) junction. Localized barometric pressure reduction (LBP; -50, -100, and -200 hPa, 30 s each) was applied to the cornea at 20-min intervals. LBP increased neuronal firing in both regions in a pressure intensity-dependent manner, with more prominent responses in the Vi/Vc transition. Topical corneal lidocaine (2%) markedly attenuated LBP-evoked responses, whereas the selective TRPV4 antagonist HC-067047 (0.01-0.1 mM) inhibited these responses in a dose-dependent manner.Reflex tear secretion was measured in urethane-anesthetized rats (1.2 g/kg, i.p.). LBP stimulation at -50, -100, and -200 hPa increased tear secretion in a pressure intensity-dependent manner, and topical corneal lidocaine markedly attenuated LBP-evoked tear secretion.These results indicate that localized barometric pressure reduction applied to the cornea directly activates trigeminal nociceptive pathways through corneal afferent input. The inhibitory

effects of lidocaine and HC-067047 suggest that barometric pressure reduction is detected at the ocular surface and that TRPV4-mediated signaling contributes to LBP-evoked trigeminal activation. The prominent activation of Vi/Vc neurons further suggests that corneal pressure-sensitive signals may activate trigeminal reflex circuits, leading to autonomic responses such as tear secretion and potentially contributing to headaches triggered by barometric pressure changes.

Disclosures: Y. Kani: None. **A. Tashiro:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.08/X30

Topic: E.01. Somatosensation – Pain and Itch

Support: Research Assistant 2197801 by SNII 410 (M.C.L.).

Title: Anatomical characterization of the trigeminal sensory pathway and its relationship to nociceptive processing in the trigeminovascular system in Wistar rats

Authors: *P. MARTÍNEZ AGUILAR, A. GONZÁLEZ-HERNÁNDEZ, M. CONDES-LARA, G. MARTINEZ-LORENZANA;
Neurobiología del desarrollo y neurofisiología, Inst. de Neurobiología, UNAM, Querétaro, Mexico

Abstract: Migraine is the most disabling neurological disorder, characterized by recurrent episodes of pulsatile headache frequently accompanied by non-infectious inflammation, a process involving mast cells and fibroblast in the meninges. Although previous studies provide evidence of projections conducting nociceptive signals directly from the trigeminal ganglion (TG) to the dural vasculature, there is still limited evidence regarding the anatomical organization and cellular changes associated with the trigeminal projection of the TG to the dura mater. This project aims to characterize the trigeminal pathway in trigeminovascular nociceptive pain processing in Wistar rats, as well as the role of ganglion cells, mast cells and fibroblasts in inflammation and vasoconstriction associated with migraine. To characterize the trigeminal projection to the dura mater and its associated cellular changes, three groups of female Wistar rats were used (control, sham, ligated; n = 8 per group). In the last group, the supraorbital nerve (SON) was ligated to induce nociception resembling migrainous trigeminal headache. Nocifensive behavior was assessed during the seven days following surgery using the Von Frey up-down method. Subsequently, a retrograde neuronal tracer (DY) was injected into the dural transverse sinus (TS). After a seven-day uptake tracer, animals were euthanized by intracardiac perfusion, and the meninges and TGs were collected. Ganglion cells were quantified in the TG, whereas mast cells and fibroblasts were quantified in the meninges. Results: surgical intervention significantly reduced the mechanical withdrawal threshold, with a more pronounced effect in

SON-ligated animals (Tukey's post hoc test, p = 0.0003). Retrograde tracer injection into the TS identified increase ipsilaterally labelled ganglion cells, primarily from trigeminal division TG-V1, providing evidence of hyperactivity neuronal and ganglionic neuroinflammation a preferential projection between TG-V1 and the dural vasculature. In parallel, SON ligation was associated with increased numbers of degranulated mast cells, while reducing the numbers of the fibroblasts in meningeal regions proximal to the supraorbital nerve ipsilateral side. These findings suggest activation of the trigeminovascular system and the development of an inflammatory process, as well as tissue remodeling in the meninges, mediated by peripheral nerve injury.

Disclosures: P. Martínez Aguilar: None. **A. González-Hernández:** None. **M. Condes-lara:** None. **G. Martinez-Lorenzana:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.09/X31

Topic: E.01. Somatosensation – Pain and Itch

Support: Supported by the National Institutes of Health Grant R01DE032061 (F.T.).

Title: Role of miR-223-3p in Orofacial Pain Comorbidity

Authors: *A. KHAN, S. LIU, F. TAO;
Dept. of Biomed. Sci., Texas A&M Univ. Col. of Dent., DALLAS, TX

Abstract: Migraine commonly coexists with temporomandibular joint disorders (TMDs), yet the mechanisms underlying this comorbidity remain poorly understood. MicroRNAs (miRNAs) are key regulators of pain pathways. In this study, we investigated the role of miR-223-3p in a validated mouse model of TMD-migraine comorbidity. Our previous study has developed the mouse model that combines unilateral masseter muscle tendon ligation (MMTL) with a subthreshold dose of nitroglycerin injection. Orofacial mechanical hypersensitivity in the V1 (periorbital) and V3 (masseter) regions was assessed using von Frey testing. Expression levels of candidate microRNAs in the spinal trigeminal nucleus caudalis (Sp5C) were determined by qPCR. To examine the functional role of miR-223-3p, agomir, antagomir, and their respective negative controls were microinjected into the ipsilateral Sp5C, followed by behavioral assessment of orofacial pain. Furthermore, trigeminal neuronal sensitization was evaluated by calcitonin gene-related peptide (CGRP) immunofluorescence. Our results showed that MMTL combined with NTG induced marked hypersensitivity in both V3 and V1 regions. Among the candidate miRNAs, miR-223-3p expression was significantly downregulated in the ipsilateral Sp5C. Microinjection of miR-223-3p agomir into the Sp5C attenuated orofacial mechanical hypersensitivity in both V1 and V3 regions, whereas miR-223-3p antagomir further enhanced pain responses. Additionally, CGRP immunostaining revealed elevated CGRP immunoreactivity

in the Sp5C of the TMD-migraine model, whereas miRNA-223-3p agomir treatment attenuated the CGRP immunoreactivity. These findings suggest that miR-223-3p is a key regulator of orofacial pain comorbidity. Restoration of miR-223-3p activity in the Sp5C can alleviate orofacial pain hypersensitivity, highlighting that miR-223-3p could be a potential therapeutic target for TMD-migraine comorbidity.

Disclosures: A. Khan: None. **S. Liu:** None. **F. Tao:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

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Topic: E.01. Somatosensation – Pain and Itch

Support: Basic and Frontier Science Support CBF2023-20243878 from the Secretariat of Science, Humanities, Technology and Innovation (SECIHTI)

Title: Salvinorin A produces antiallodynic behavior in mice submitted to chronic constriction injury of the infraorbital nerve

Authors: *G. N. QUIÑONEZ-BASTIDAS[1], M. OLIVAS VILLA[2], M. F. HERNANDEZ ZAZUETA[2], G. G. ESCOBAR-LÓPEZ[2], A. NAVARRETE-CASTRO[3];
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Abstract: Introduction: Trigeminal neuralgia (TN) is a rare pain condition characterized by paroxysmal pain that affects women in a major proportion (3:1). Often, the clinical efficacy of pharmacological treatments is limited by side effects, and there aren't many pharmacological options to continue the pharmacological management of the patient. **Objective:** This study was performed to evaluate the antiallodynic effect of salvinorin A (SA) in mice submitted to chronic constriction injury of the infraorbital nerve. **Methodology:** Female and male CD1/ICR mice (20-25 g) were submitted to chronic constriction injury of the infraorbital nerve. Allodynic behavior was evaluated using von Frey filaments. Female ovariectomized (female-Ovx) surgery was included to evaluate the sex dependent effect. Increased doses of SA were administered to animals. Moreover, specific antagonists for the metabotropic CB1 and 5-HT1A receptors, and the ionotropic $GABA_A$, TRPV1, and K_{ATP} receptors, were administered to evaluate the mechanism underlying the antiallodynic effect of SA. All experiments were approved by the Institutional Animal Care and Use Committee (FQ/CICUAL/580/24). **Results:** The administration of 1.78 and 3.2 mg/kg of SA produces a strong decrease in tactile allodynia in female mice, while the male and female-Ovx required increased doses of 10 mg/kg to produce effects like the 1.78 mg/kg dose in female mice. Moreover, the administration of AM251 (1

mg/kg) and WAY100635 (1 mg/kg) (specific antagonists of CB1 and 5-HT_{1A} receptors, respectively) prevented the antiallodynic effect of SA. Furthermore, the systemic administration of bicuculline (a $GABA_A$-specific antagonist, 1 mg/kg), capzazepine (a TRPV1 antagonist, 3 mg/kg), or glibenclamide (an ATP-sensitive K^+ channel blocker, 10 mg/kg) prevented allodynia in mice. **Conclusions:** SA produces an antiallodynic effect in a sex-dependent manner, involving the CB1, 5-HT_{1A}, $GABA_A$, TRPV1, and K_{ATP} receptors.

Disclosures: G.N. Quiñonez-Bastidas: None. **M. Olivas Villa:** None. **M.F. Hernandez Zazueta:** None. **G.G. Escobar-López:** None. **A. Navarrete-Castro:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.11/Y1

Topic: E.01. Somatosensation – Pain and Itch

Support: TTUHSC startup funds (JLW)

Title: Comparative evaluation of cannabidiol and sumatriptan in the nitroglycerin mouse model of chronic migraine

Authors: *K. FRIMPONG-MANSON[1], L. KHODAVIRDILOU[1], B. OJO[1], J. WILKERSON[2]; [1]Dept. of Anesthesiol., Rutgers, The State Univ. of New Jersey, Newark, NJ; [2]Dept. of Anesthesiol., Rutgers New Jersey Med. Sch., Newark, NJ

Abstract: Chronic migraine headache is a highly disabling neurological disorder for which existing treatments are not universally effective for all patients. Cannabidiol (CBD) is a major phytocannabinoid in *Cannabis sativa*, which may act on multiple receptor targets relevant to pain signaling with associated immunomodulatory activity. Yet, there is conflicting preclinical and clinical evidence of the efficacy of cannabidiol in treating migraine headaches. In our study, we aimed to systematically compare the efficacy of cannabidiol with that of sumatriptan, an approved migraine treatment, in attenuating migraine-like behavioral and biochemical effects in the nitroglycerin model of chronic migraine. A total of 62 young adult (8 to 10 weeks) male and female C57BL/6J mice were tested on alternating days over a 9-day period. Baseline periorbital and hind paw von Frey tests were performed to measure mechanical allodynia. Mice were pretreated with intraperitoneal injections of 10 mg/kg nitroglycerin (NTG) or vehicle prior to receiving 0.56 mg/kg sumatriptan, 100 mg/kg cannabidiol, or vehicle. This was followed by post-treatment von Frey tests. An open field test was performed on the last day, and the mice were euthanized. The plasma, cortex, thalamus, and trigeminal ganglia, which are important sites for migraine pathophysiology, were harvested. ELISA was used to measure concentrations of calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38). A Luminex multiplex assay was conducted to measure plasma concentrations of pro-inflammatory interleukin-6 (IL-6), growth-regulated-oncogene-alpha (GRO-α),

interleukin-18 (IL-18), and interleukin-2-receptor (IL-2R), a biomarker for T-cell activation. In our results, sumatriptan attenuated periorbital and hind paw allodynia. CBD reduced hind paw allodynia with a modest effect on periorbital allodynia. NTG elevated thalamic CGRP concentration, but this was reversed by sumatriptan. CBD restored decreased thalamic PACAP-38 to baseline levels, but it had no effect on the decreased cortical CGRP concentration. CBD also exhibited a pleiotropic effect by elevating plasma IL-6 while decreasing IL-2R concentration. Sumatriptan exhibited anti-inflammatory activity by reducing elevated GRO-α and IL-18. Moreover, none of the treatments affected locomotion. In summary, CBD had immunomodulatory activity but was inferior to sumatriptan in attenuating allodynia. While CBD has the potential as a treatment for chronic migraine, it may have some limitations.

Disclosures: K. Frimpong-Manson: None. **L. Khodavirdilou:** None. **B. Ojo:** None. **J. Wilkerson:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.12/Y2

Topic: E.01. Somatosensation – Pain and Itch

Support: NS106264
NS136108

Title: Characterization of Satellite Glial Cells in a Mouse Model of Chronic Migraine

Authors: *J. WANG[1], R. TONELLO[2], A. PRUDENTE[3], T. BERTA[3];
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Abstract: Characterization of Satellite Glial Cells in a Mouse Model of Chronic Migraine Jiaxiang Wang[1,2], Raquel Tonello[3], Arthur Silveira Prudente[1], Temugin Berta[11]Pain Research Center, Department of Anesthesiology, University of Cincinnati Medical Center, Cincinnati, OH 45267, USA.[2]Neuroscience Graduate Program, College of Medicine, University of Cincinnati, Cincinnati, OH 45267, USA.[3]Pain Research Center, Department of Molecular Pathobiology, College of Dentistry, New York, NY 10010, USA.Satellite glial cells (SGCs) are a major glial cell type in the peripheral nervous system that surround neuronal cell bodies and provide essential supportive and regulatory functions. Despite sharing many functional similarities with astrocytes, SGCs have historically received far less attention and remain understudied. Interest in SGCs has grown in recent years, accompanied by emerging evidence linking them to chronic pain conditions, including migraine. To better characterize SGCs and their role in migraine, improved tools are needed for their isolation, molecular profiling, and functional analysis. Here, we identified hepatocyte cell adhesion molecule (HepaCAM) as a highly expressed marker of SGCs. By combining a HepaCAM antibody with magnetic bead-

based isolation, we established a cost-efficient protocol that purifies SGCs within 2 hours. Using this approach, we performed RNA sequencing on isolated SGCs and identified candidate genes involved in migraine pathology. Among these, glutathione *S*-transferase mu 1 (*Gstm1*) was significantly upregulated in SGCs from mice subjected to repeated nitroglycerin injections, a well-established model of chronic migraine. Importantly, knockdown of *Gstm1* attenuated migraine-associated pain behaviors, implicating Gstm1 as pain signaling in SGCs during migraine. This role may parallel that of *Gstm1* in astrocytes, where it promotes proinflammatory signaling and amplifies neuroinflammation. Ongoing studies aim to determine whether a similar mechanism operates in SGCs and whether it contributes to peripheral sensitization and migraine chronification. Together, these findings provide a transcriptomic resource for SGC biology and identify Gstm1 as a novel candidate of SGC-mediated pain signaling, with implications for understanding and treating chronic migraine.

Disclosures: J. Wang: None. **R. Tonello:** None. **A. Prudente:** None. **T. Berta:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.13/Y3

Topic: E.01. Somatosensation – Pain and Itch

Support: NS140790-01A1

Title: Progesterone receptors regulate migraine susceptibility through delta opioid receptor signaling

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Abstract: Migraines disproportionately affect women during reproductive years, implicating female hormones in their pathophysiology. We have found that progesterone receptors (PRs) regulate migraine susceptibility in mice: the PR agonist segesterone increases susceptibility and promotes migraine transformation, whereas PR deletion (PR knockout, PRKO) is protective. To probe mechanisms underlying PR's regulation of migraine susceptibility, we examined opioid receptors (OPRs). Three types of OPRs, μ, δ, and κ (MOR, DOR, and KOR respectively), and their endogenous ligands endorphins, enkephalins, and dynorphins constitute the endogenous analgesic system. We evaluated the expression of OPRs and their endogenous ligand mRNA using qRT-PCR from cortical tissue isolated from ovariectomized and estrogen-primed mice treated with segesterone or vehicle, or from gonadally-intact female PRKO and wild-type (WT) mice. The cortical DOR expression was lower (55 ± 11%, n=9) in the segesterone-treated mice

compared to vehicle-treated mice. On the other hand, DOR (143 ±13%), prodynorphin (210 ± 39%), and proenkephalin (154 ± 8%) mRNA expression was higher in the cortex of PRKO mice (n=7) compared to WT mice (n=8). The western blotting confirmed that the expression of DOR in PRKO mice was 54 ± 16% higher that in the WT mice (n=5 each). Immunohistochemical localization of DOR protein expression revealed that PRKO mice have higher DOR expression (2.7 ± 0.3) than WT mice (1.9 ± 0.2, n=5 each, p=0.03), particularly in the superficial layers of the primary and secondary somatosensory cortices, which are critical for the cortico-cortical spread of the sensory and nociceptive stimuli. The DOR expression was also higher in the insular cortex of PRKO than WT mice (1.8 ± 0.2 and 1.2 ± 0.3, respectively, n=5); but, that in the anterior cingulate cortex was unchanged (PRKO: 1.5 ± 0.1 and WT: 1.7 ± 0.4, n=5). Finally, DOR blockade with the specific antagonist naltrindole also made PRKO mice (n=8) as susceptible to periorbital mechanical pain as WT mice (n=8) during experimental migraine evoked by nitroglycerin. These studies indicate that PR signaling regulates migraine susceptibility through DOR modulation. Ongoing studies are evaluating the effect of somatosensory cortex-specific deletion of PRs on the DOR expression and migraine susceptibility. Current studies are also focused on evaluating how DOR activation and blockade alters somatosensory cortical neuronal activity.

Disclosures: D. Etcheberrigaray: None. **F. Naqshbandi:** None. **P. van den Oord:** None. **Y. Patel:** None. **J. Williamson:** None. **J. Kapur:** None. **S. Joshi:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.14/Y4

Topic: E.01. Somatosensation – Pain and Itch

Title: CGRP-stimulated vascular smooth muscle cells release pro-nociceptive factors that induce migraine-like responses in mice

Authors: *S. NEMATGORGANI[1], G. O. DUSSOR[2];
[2]Neurosci., [1]Univ. of Texas at Dallas, Richardson, TX

Abstract: BackgroundThe contribution of cranial blood vessels to migraine pathophysiology remains controversial. Genetic studies have identified an enrichment of migraine-associated genes in vascular and smooth muscle tissues. While early vascular theories proposed that vasodilation is the driver of migraine attacks, recent studies suggest that vessel dilation is neither necessary nor sufficient to trigger these attacks. In this study, we aim to examine the contribution of vascular smooth muscle cells (VSMCs) to migraine through mechanisms independent of vasodilation. We hypothesize that VSMCs release factors that sensitize dural afferents and induce migraine-like behavior in mice in response to calcitonin gene-related peptide (CGRP), and that these effects can be inhibited by migraine therapeutics.MethodsTo investigate the study aim, primary VSMCs were isolated and cultured from mouse aortas. Cells were treated with

CGRP (1 μM), after which conditioned media was collected to assess the effects of factors released by VSMCs following CGRP stimulation. Then, 5 μL of conditioned media was applied to the mouse dura using a non-invasive dural injection model. To assess whether migraine therapeutics prevent pro-nociceptive signaling, VSMCs were pretreated with sumatriptan (3 μM) or olcegepant (1 μM) for 30 minutes before CGRP stimulation, and the resulting conditioned media was applied to the dura. Migraine-like behaviors were evaluated in female mice by assessing periorbital mechanical sensitivity using von Frey filaments and facial grimace scores. ResultsDural application of conditioned media from CGRP-treated VSMCs induced significant reductions in periorbital withdrawal thresholds from 1–5 hours after injection compared with vehicle-treated control. Moreover, facial grimace scores were elevated, particularly at early post-injection time points. Conditioned media from VSMCs pretreated with 3 μM sumatriptan showed a trend toward reduced facial hypersensitivity compared with the CGRP group; however, this effect did not reach statistical significance. In contrast, pretreatment with olcegepant, significantly attenuated the reduction in periorbital withdrawal thresholds at 1-hour post-injection and reduced facial grimace scores compared with conditioned media from VSMCs treated with CGRP alone.ConclusionThese findings demonstrate that CGRP stimulation of VSMCs generates factors that promote migraine-like behaviors. The results support the hypothesis that vascular cells can contribute to migraine pathophysiology by releasing pro-nociceptive mediators, independent of vasodilation.

Disclosures: S. Nematgorgani: None. **G.O. Dussor:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.15/Y5

Topic: E.01. Somatosensation – Pain and Itch

Title: Characterization of chemically-induced migraine models in mice using behavioral and functional imaging readouts

Authors: A. SUHONEN, R. IMMONEN, T. MIETTINEN, *A.-M. PENTTINEN, **J. RYTKÖNEN**, T. HUHTALA;
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Abstract: Global migraine prevalence is 14-15% and it causes significant burden to economy as sick leaves and reduced productivity, not to mention the reduced quality of life for the individuals affected. It is a complex neurological disorder in which multiple neuropeptides modulate nociceptive and sensory pathways. Some of the most studied neuropeptides, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) promote vasodilation and neurogenic inflammation but act through different pathways. Preclinical animal models can shed light on migraine pathophysiology and can be used to test novel treatments for migraine. In this study we characterized chemically

induced migraine rodent model with behavioral readouts and vascular imaging of the brain using functional ultrasound (fUS).
Male CD1 mice were dosed either with vehicle or a mixt of PACAP+CGRP (0,6 mg/kg + 0,6 mg/kg, 5 ml/kg, i.p.) and light aversion test using open field chamber with dark box insert (Med Associates Inc, St Albans, VT). Habituation to the chambers and dosing was done one day before the actual test. A separate cohort of mice was scanned with fUS. The imaging consisted of structural scan and vasodilation challenge. During the scanning the heart rate was monitored. The vasodilation was reported as a change to the baseline as relative cerebral blood volume (rCBV%).
The light aversive behavior was prominent in PACAP and CGRP dosed animals. The total time spent in light was lower compared to vehicle group as well as other explorative behavior (number of entries, total distance travelled in light). In fUS, rCVB% increases were seen in several brain surface vessels (Dorsal surface vessel, Lateral surface vessel, Sagittal sinus and Extracerebral vessel) compared to baseline. As a conclusion, functional and behavioral readouts are complementary in testing novel therapies for migraine.

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

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.16/Y6

Topic: E.01. Somatosensation – Pain and Itch

Title: Levcromakalim Induced Migraine Like Behavior is Associated with Dynamic HMGB1 Responses in Wistar but Not GAERS Rats

Authors: *A. GEZEN YILMAZ[1], E. TOPA[2], H. BOLAY[3], Y. SARA[1];
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Abstract: Background:
Migraine is associated with altered neuronal excitability, metabolic stress, and neuroinflammatory signaling. High mobility group box 1 (HMGB1) is a stress responsive nuclear protein that may link neuronal stress to inflammatory responses during migraine pathophysiology. We investigated temporal HMGB1 alterations in migraine related central and

peripheral tissues following levcromakalim (K_{ATP} channel opener) induced migraine like phenotype in Wistar and Genetic Absence Epilepsy Rats from Strasbourg (GAERS), a strain previously shown to be resistant to levcromakalim induced migraine like symptoms.**Methods:** Male Wistar and GAERS rats (250-300g) received levcromakalim (1mg/kg). Mechanical thresholds were assessed to evaluate migraine like allodynia. HMGB1 protein levels were measured in parietal cortex (PCTX) and trigeminal ganglia (TG) at 1h and 6h following treatment. Immunofluorescence studies were also performed to identify the cellular localization of HMGB1 in both strains.**Results:**
In Wistar rats, levcromakalim induced a migraine like phenotype characterized by a significant reduction in both periorbital and hind paw mechanical thresholds, reaching maximal effect at 1h. At this time point, HMGB1 levels were significantly increased in the nuclear fraction of both the PCTX and TG compared with controls. At 6h, total HMGB1 levels in the PCTX remained elevated relative to controls. In the TG, HMGB1 levels showed substantial variability and no significant difference was detected at 6h. In contrast, GAERS rats did not develop mechanical hypersensitivity following levcromakalim administration. Consistent with the absence of behavioral responses, HMGB1 levels remained unchanged compared with strain-matched controls in both the PCTX and TG at either time points.**Conclusions:**
These preliminary findings demonstrate that levcromakalim induced migraine like behavior is associated with dynamic and region specific HMGB1 responses in Wistar rats, whereas the migraine resistant GAERS strain exhibits neither behavioral sensitization nor HMGB1 alterations. The presence of a migraine-like phenotype and HMGB1 activation in Wistar but not in GAERS rats, indicates that HMGB1 signaling is involved in migraine headache development, suggesting HMGB1 as a viable therapeutic target.

Disclosures: A. Gezen Yilmaz: None. **E. Topa:** None. **H. Bolay:** None. **Y. Sara:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.17/Y7

Topic: E.01. Somatosensation – Pain and Itch

Support: 000000Department of Defense – W81XWH2110485

Title: Functional antagonism of the S1P - S1PR1 signaling axis decreases trigeminocervical sensitization and migraine like neuronal activation in stress-induced rats.

Authors: *A. SALINAS ABARCA[1], M. ROMERO[1], D. SALVEMINI[2], S. AKERMAN[3]; [1]Dept. of Neural and Pain Sci. UM Ctr. to Advance Chronic Pain Res., Univ. of Maryland, Baltimore, Baltimore, MD; [2]Pharmacol. and Physiological Sci., St. Louis Univ. Dept. of Pharmacol. and Physiological Sci., Saint Louis, MO; [3]Dept. of Neural and Pain Sci. UM Ctr. to Advance Chronic Pain Res., Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Emerging evidence suggests that dysregulated sphingolipid metabolism within neurons is correlated with various pain conditions due to the overproduction of sphingosine-1-phosphate (S1P) in spinal dorsal horn neurons. Functional S1PR1 antagonists, such as ozanimod, have shown efficacy in preclinical models of chronic pain. However, it remains unclear whether S1P-S1PR1 activation contributes to trigeminovascular sensitization in migraine models. Here, we examine how S1P-S1PR1 signaling affects migraine-like neuronal activation and sensitization in the trigeminocervical complex (TCC). We used in vivo extracellular electrophysiology to record TCC neurons in naïve and sensitized male and female rats. Latent trigeminovascular sensitization was induced by restraint stress (2 h/day for 4 days) and unmasked with a non-noxious dose of the nitric oxide donor sodium nitroprusside (SNP; 30 µg/kg, IV). Acute effects of ozanimod (1 mg/kg, IV) were assessed in naïve and stressed rats; preventive treatment (1 mg/kg, i.p., daily for 5 days) was administered to stressed animals. Ongoing neuronal activity, cranial-evoked responses, and periorbital mechanical-evoked responses were assessed for 3 h after SNP administration. Periorbital mechanical sensitivity was assessed before electrophysiological recording. Female rats (n = 12) exhibited a lower baseline periorbital withdrawal threshold. Restraint stress caused a prolonged and reversible periorbital hypersensitivity in both sexes, lasting significantly longer in females (28-32 days) than in males (18-22 days). In naïve rats, the electrical activation threshold of intracranial meningeal afferents was also notably lower in females. Additionally, in stressed/SNP rats (n=7 per group), a non-noxious dose of SNP enhanced activation and sensitization of dural-responsive Aδ and C-fiber TCC neurons in both sexes. However, responses were significantly more pronounced in stressed females than in males. Acute treatment with ozanimod (1 mg/kg, IV, n=7) significantly inhibited ongoing spontaneous neuronal firing and intracranial dural-evoked Aδ- and C-fiber responses in naïve and stressed rats. Preventive ozanimod (n=7) inhibits activation and hypersensitivity to cranial stimulation in the stress/SNP model, with stronger effects in males than females. These data demonstrate that a functional S1PR1 antagonist attenuates dural-TCC pathway activity in a migraine model, highlighting the role of the S1P-S1PR1 pathway in activating and sensitizing dural trigeminovascular neurons associated with migraine. Further, S1PR1 emerges as a promising new target for migraine therapy.

Disclosures: A. Salinas abarca: None. **M. Romero:** None. **D. Salvemini:** None. **S. Akerman:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.18/Y8

Topic: E.01. Somatosensation – Pain and Itch

Support: UA department of Pharmacology

Title: Region-specific changes in 5-HT1/2 receptor subtypes mRNA expression in acute and chronic migraine-like symptoms in female Sprague-Dawley rats

Authors: *S.-F. CHEN[1,2], E. LIKTOR-BUSA[3], T. M. LARGENT-MILNES[4];
[1]Neurosci., [2]Dept. of Neurosci., [3]Dept. of Pharmacol., [4]Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: Migraine, a lifelong neurological disorder, affects over one billion people worldwide, with a prevalence three times higher in women than in men. Despite this, the precise physiological triggers remain incompletely understood, and effective clinical therapies are lacking. Migraine pathophysiology, including cortical spreading depression (CSD) and medication-overuse headache (MOH) components, is deeply linked to serotonergic dysregulation. While serotonin (5-HT) receptor 5-$HT_{1B/1D/1F}$ agonists are used for acute relief and 5-$HT_{2A/2C}$ antagonists for prophylaxis, their repetitive use often leads to secondary complications, where MOH exacerbates severe migraine-like symptoms. Nevertheless, 5-HT receptor expression networks have not been systematically evaluated within nociceptive circuits, from the medial prefrontal cortex (mPFC), visual cortex, periaqueductal gray (PAG), to the brainstem rostral ventromedial medulla (RVM) and spinal trigeminal nucleus caudalis (Vc), down to the peripheral trigeminal ganglion (TG). To address this, female Sprague-Dawley rats were divided into acute and chronic models (n=12/group). Acute migraine was induced via dural cannulation and CSD triggered by KCl microinjection into the visual cortex. Chronic MOH was modeled via osmotic pump implantation for continuous sumatriptan infusion. Periorbital mechanical allodynia was evaluated using von Frey filaments at 30/90 minutes post-CSD (acute) or on day 7 post-implantation (chronic), with saline serving as the vehicle control. Both models successfully induced facial allodynia compared to baseline and to control. Biochemical assays revealed distinct receptor alterations. Compared to controls, the MOH model exhibited increases in 5-HT_{1B} (cortex and RVM), 5-HT_{1D} (cortex and TG), and 5-HT_{2C} (cortex), with decreases in 5-HT_{1D} (PAG) and 5-HT_{1F} (mPFC). Conversely, the CSD model showed increased 5-$HT_{1B/1D}$ in the PAG but decreased 5-$HT_{1D/2C}$ in the mPFC. Notably, 5-HT_{2A} expression remained unaffected in both models. In sum, these findings demonstrate that 5-HT receptor expression undergoes highly regional- and model-specific changes within nociceptive pathways. These insights highlight the complex, heterogeneous role of the serotonergic system in modulating acute and chronic migraine states.

Disclosures: S. Chen: None. **E. Liktor-Busa:** None. **T.M. Largent-Milnes:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.19/Y9

Topic: E.01. Somatosensation – Pain and Itch

Support: the National Natural Science Foundation of China (32571184)
the National Natural Science Foundation of China Young Student Basic Research Program (for Ph.D. students) (324B2030)

Title: Distinct parafascicular neuronal ensembles mediate the sensory and affective dimensions of trigeminal neuralgia

Authors: *Y. Y. L. LU, C. CEN;
Peking Univ., Beijing, China

Abstract: Trigeminal neuralgia (TN) is a severe orofacial pain disorder accompanied by anxiety, yet its central mechanisms remain elusive. Analysis of human fMRI data identified the parafascicular nucleus (PF) as a candidate region. Using a TN mouse model, we uncovered two spatially and functionally distinct PF neuronal ensembles that separately encode sensory and affective dimensions of pain. One population receives inhibitory input from GABAergic neurons in the oral spinal trigeminal nucleus (Sp5O) and mediates nociception. The second population, driven by a glutamatergic Sp5O-lateral parabrachial nucleus (lPBN)-PF pathway, encodes pain-related anxiety. The engagement of the anxiety-encoding ensemble lags behind that of the pain-encoding ensemble, with a shorter delay in females. Single-nucleus RNA sequencing identified *Col25a1* and *Syn2* as markers of the anxiety-encoding ensemble. Notably, this population, localized in the medial PF, forms a reciprocal lPBN-mPF-lPBN excitatory-feedback loop that sustains affective pain. These findings position PF as a key node linking pain and emotion in TN.

Disclosures: Y.Y.L. Lu: None. **C. Cen:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.20/Y10

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH contract 75N95024D00038

Title: Effect of acute isosorbide dinitrate (ISDN) administration on plasma and brain concentrations of therapeutic compounds in rats

Authors: *Y. ZHANG[1], M. CIKLIC[1], R. PELTZ[1], J. KINCAID[1], D. P. BUDAC[1], M. URBAN[1], C. CONRAD[2], S. A. WOLLER[2], S. IYENGAR[2], T. HANANIA[1], A. GHAVAMI[1];
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Abstract: In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), we characterized the behavioral pain phenotype and pharmacology associated with a rat model of headache involving a single administration of the nitric oxide donor isosorbide dinitrate (ISDN). By releasing nitric oxide, ISDN can alter blood flow via vasodilation, and may also affect drug metabolism, absorption, or other interactions. As a result, plasma and brain concentrations of investigational compounds may be altered in the presence of ISDN. In the present study, we measured plasma and brain concentrations of several clinically used drugs (gabapentin, sumatriptan, duloxetine, and diazepam) to assess potential effects of ISDN on drug

exposure. Adult male and female Sprague Dawley rats were used in these studies. For each drug evaluated, all animals received a single pharmacologically effective dose. Five minutes later, half of the animals were given ISDN (10 mg/kg, IP). Animals were then returned to their home cages and continuously monitored for any drug-related behaviors. Brain and plasma samples were collected 2 hours after drug treatment for exposure analysis. In animals treated with gabapentin (100 mg/kg, PO), ISDN did not alter plasma or brain concentration when compared to animals that were not treated with ISDN. However, in animals treated with diazepam (10 mg/kg, PO), ISDN significantly increased plasma diazepam levels in female rats. These data indicate that ISDN affects the plasma or brain concentration for some compounds but not others. Additional experiments are ongoing to evaluate ISDN's effect on plasma and brain concentrations of various reference analgesics, including sumatriptan and duloxetine. The study's outcome will guide future study designs, especially for novel compounds, and thus support the use of this model in the NIH HEAL initiative PSPP program to identify novel, non-opioid, non-addictive treatments for headache and pain.

Disclosures: Y. Zhang: A. Employment/Salary (full or part-time):; PsychoGenics Inc. **M. Ciklic:** A. Employment/Salary (full or part-time):; PsychoGenics Inc. **R. Peltz:** A. Employment/Salary (full or part-time):; PsychoGenics Inc. **J. Kincaid:** A. Employment/Salary (full or part-time):; PsychoGenics Inc. **D.P. Budac:** A. Employment/Salary (full or part-time):; PsychoGenics Inc. **M. Urban:** A. Employment/Salary (full or part-time):; PsychoGenics Inc. **C. Conrad:** A. Employment/Salary (full or part-time):; NIH/NINDS. **S.A. Woller:** A. Employment/Salary (full or part-time):; NIH/NINDS. **S. Iyengar:** A. Employment/Salary (full or part-time):; NIH/NINDS. **T. Hanania:** A. Employment/Salary (full or part-time):; PsychoGenics Inc. **A. Ghavami:** A. Employment/Salary (full or part-time):; PsychoGenics Inc..

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.21/Y11

Topic: E.01. Somatosensation – Pain and Itch

Title: Development and pharmacological validation of capsaicin and nitroglycerin induced migraine models in mice

Authors: M. DING[1], Y. BAI[1], F. ZHANG[1], X. LI[1], G. YANG[1], D. XU[2], ***D. ZHU**[1];
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Abstract: Migraine is a prevalent neurological disorder characterized by recurrent headache attacks and sensory hypersensitivity. Reliable preclinical models are essential for evaluating therapeutic candidates and investigating migraine-associated pathophysiology. In this study, we established and optimized two commonly used mouse migraine models induced by capsaicin and nitroglycerin (NTG), respectively, and characterized their behavioral, pharmacological, and molecular features.In the capsaicin model, topical administration of capsaicin to the ear induced

robust neurogenic inflammation, as evidenced by increased Evans Blue extravasation and elevated local blood perfusion measured by laser blood flow imaging. Pharmacological validation was performed using prophylactic administration of aprepitant, atogepant, and fremanezumab, all of which significantly attenuated capsaicin-induced vascular leakage and hyperemia, supporting the translational relevance of this model for evaluating migraine-related CGRP-targeted therapies. In the NTG model, both acute and repeated NTG administration paradigms were evaluated to mimic episodic and chronic migraine-like states. We optimized an orofacial mechanical sensitivity training protocol to improve behavioral consistency and successfully detected NTG-induced facial hypersensitivity. In addition, hindpaw and periorbital mechanical sensitivity testing revealed significant increases in nociceptive responses following NTG administration, suggesting widespread sensory sensitization.To further characterize migraine-associated molecular responses, peripheral and central tissues were collected for CGRP-related signaling and inflammatory marker analyses using quantitative PCR and ELISA. Brain-wide c-fos mapping is performed with fMOST-based 3D imaging to establish functional activation atlases associated with distinct migraine-like states.Together, these findings establish robust and pharmacologically responsive migraine models and provide integrated behavioral, vascular, and molecular endpoints for migraine research and preclinical therapeutic evaluation.

Disclosures: M. Ding: A. Employment/Salary (full or part-time):; PharmaLegacy Laboratory. **Y. Bai:** A. Employment/Salary (full or part-time):; PharmaLegacy Laboratory. **F. Zhang:** A. Employment/Salary (full or part-time):; PharmaLegacy Laboratory. **X. Li:** A. Employment/Salary (full or part-time):; PharmaLegacy Laboratory. **G. Yang:** A. Employment/Salary (full or part-time):; PharmaLegacy Laboratory. **D. Xu:** A. Employment/Salary (full or part-time):; PharmaLegacy Laboratory. **D. Zhu:** A. Employment/Salary (full or part-time):; PharmaLegacy Laboratory.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.22/Y12

Topic: E.01. Somatosensation – Pain and Itch

Support: Congressionally Directed Medical Research Programs (CDMRP) award (W81XWH2120457)

Title: Central and Peripheral Sensitization in Pain Related Regions and Modulation of Endocannabinoid-Metabolizing Enzymes in Mild Traumatic Brain Injury

Authors: *G. NAGARAJAN[1,2], F. W. LISCHKA[2], J. WEN[2], Y. ZHANG[3];
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Abstract: Post-traumatic headache (PTH), a common mild traumatic brain injury (mTBI) comorbidity affecting at least a third of patients, is partly facilitated by the trigeminal pain pathway. Endocannabinoids (eCBs) offer neuroprotection but are rapidly degraded by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), which have region-specific expression. We recently characterized the spatial distribution of these enzymes in the trigeminal ganglion (TG), and the trigeminal nucleus caudalis (TNC). However, central and peripheral sensitization of neurons in these regions and modulation of eCBs following mTBI warrant further investigation. We hypothesize that neurons are differentially modulated in central and peripheral regions and that eCBs degrading enzymes have specific roles in pain modulation. Repetitive mTBI in 2 month old C57BL/6 mice (n=5-6/group; once daily for 4 days) significantly increased periorbital mechanical allodynia at 1 week ($p < 0.05$) and grimace scores ($p < 0.01$) until 1 month post-injury compared to shams. To assess neuronal sensitization, we measured Ca2+ fluorescence in tissue slices (TG, TNC, PAG, and cingulate cortex) using GCaMP6 Thy1 transgenic mice or the application of Ca2+ indicators. At 2 weeks post-injury, mTBI mice exhibited a significant increase in neuronal excitability across the central regions ($p < 0.05$) and a moderate increase in the TG ($p = 0.1$) following the application of a depolarizing agent (25 mM KCl). Specifically, network analysis showed that cingulate neurons were hyperactive in mTBI mice compared to controls. Following the administration of eCB hydrolyzing enzyme inhibitors, we found that periorbital allodynia and grimace scores were significantly reduced in mTBI mice ($p<0.05$). Furthermore, using RNA-seq, we found that retrograde endocannabinoid signaling gene set was enriched in the TG, but not in the TNC, of mTBI mice. Together, these results suggest that mTBI induces central and, to some extent, peripheral sensitization of neurons, and that eCB-hydrolyzing enzymes in the trigeminal region are critically involved in the maintenance of post-traumatic cephalic pain.

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Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.23/Y13

Topic: E.01. Somatosensation – Pain and Itch

Title: Human iPSC-Derived Trigeminal Ganglion Neurons Exhibit Robust NaV1.8 Function on Automated Patch Clamp and TRPV1 Activity for Pain Drug Discovery

Authors: *V. TRUONG[1], T. STRASSMAIER[2], Y.-L. LU[2], M. L. GRAY[2], R. HAEDO[2], P. WALSH[1];
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Abstract: Human trigeminal ganglion neurons (TGNs) mediate craniofacial pain, migraine, thermosensation, and other sensory modalities unique to the trigeminal system. However, studies of human trigeminal biology remain limited by the scarcity of primary tissue. Given the central

role of ion channels in nociceptor excitability and therapeutic response, defining the molecular and functional properties of human TGNs is critical for advancing migraine and craniofacial pain research. To address this need, we generated TGNs from human induced pluripotent stem cells (hiPSCs) through an anterior cranial neural crest lineage using a rapid, small molecule and growth factor-based differentiation protocol. TGNs were produced within 7 days without genetic manipulation or mitotic inhibitors and evaluated across three independent manufacturing batches following maturation in a fully defined maturation media. Immunocytochemical analysis demonstrated a highly enriched sensory neuron population expressing ISL1, BRN3A, TUJ1, and the trigeminal lineage marker SIX1, with consistent marker expression observed across differentiations. Transcriptomic characterization by bulk RNA sequencing and qPCR confirmed reproducible sensory neuron identity and revealed elevated expression of trigeminal-relevant ion channels including SCN10A (NaV1.8) and TRPM8 compared with primary human DRG controls. Functional maturation assessed using multielectrode array (MEA) recordings demonstrated spontaneous neuronal activity within two weeks post-thaw. By week four, cultures displayed widespread electrode activity and reproducible responses to the TRPV1 agonist capsaicin (100 nM) and PACAP (1 uM) across independent batches, confirming functional nociceptor phenotypes. To further evaluate ion channel function in a high throughput screening format, TGNs were analyzed using the SyncroPatch 384 automated patch clamp platform. Recordings identified robust TTX-resistant sodium currents consistent with NaV1.8 activity that were inhibited by 30 nM Suzetrigine. These findings establish compatibility with high-throughput automated electrophysiology workflows and demonstrate the utility of TGNs for scalable NaV1.8 pharmacology studies. Together, these results establish a reproducible human trigeminal neuron platform with consistent molecular identity, robust TRPV1 responsiveness, and functional NaV1.8 activity across independent manufacturing batches. This system provides a scalable tool for investigating trigeminal biology, migraine mechanisms, ion channel pharmacology, and pain therapeutic discovery.

Disclosures: V. Truong: A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated. **T. Strassmaier:** A. Employment/Salary (full or part-time):; Nanion Technologies. **Y. Lu:** A. Employment/Salary (full or part-time):; Nanion Technologies. **M.L. Gray:** A. Employment/Salary (full or part-time):; Nanion Technologies. **R. Haedo:** A. Employment/Salary (full or part-time):; Nanion Technologies. **P. Walsh:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.24/Y14

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 1DP2OD028965-01
McKnight Foundation
BBRF Young Investigator Award
U.S. Department of Veterans Affairs
NIH Grant 3DP2MH126377-01S1

Title: CGRP induces frequency-, time-, and light-dependent brain-wide neurophysiological alterations

Authors: *Y. FILALI[1,2], L. P. SOWERS[1], R. HULTMAN[2];
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Abstract: Introduction: Migraine is a primary headache disorder characterized by head pain, sensory sensitivity, and gastrointestinal distress. Migraine also presents with symptoms of autonomic, affective, and cognitive dysfunction. Our understanding of how the brain regions that underly these symptoms coordinate their neural activities in migraine is not well understood. Thus, we used resting-state functional magnetic resonance imaging (rsfMRI) and multi-site in-vivo electrophysiology to characterize brain-wide neural activity changes following administration of calcitonin gene-related peptide (CGRP), a preclinical model of migraine, in adult CD1 mice. **Methods:** We firstly performed rsfMRI recordings (CD1; >P56, N = 29) across two treatment days, 30 minutes after intraperitoneal administration of CGRP and vehicle control. These recordings consistent of collecting blood oxygen level-dependent (BOLD) activity using T2* weighted echo-planar gradient-echo imaging. After rsfMRI experimentation, the mice underwent a craniotomy where tungsten wires were placed across 16 migraine relevant regions to collect local field potential (LFP) activity. Recordings were performed throughout a Forced Light Assay (FLA), designed to capture LFP activity after CGRP administration and during a simultaneous period of bright light exposure. **Results:** We found that intraperitoneal administration of CGRP induces wide-spread change in posterior thalamic (Po) resting-state functional connectivity across cortical, sub-cortical, and brainstem structures. Similarly, we found that CGRP induces a decrease in mean LFP power within the Po, in a window 35-40 minutes after injection. This time-dependent response was observed in the 9-12 Hz frequency band. Furthermore, we found that bright light increased the strength of a neural network that encodes for stress vulnerability, which was observed during control but not after CGRP treatment. Interestingly, we found a negative linear relationship between the strength of the stress vulnerability network response to bright light, for the vehicle control condition, and time spent in light after CGRP administration in a light-aversion assay. **Conclusion:** Our results contribute to mounting evidence that migraine is a brain-wide systems disorder, where multiple interconnected systems are working in concert. We specifically identified activity changes within the Po, at the level of BOLD and LFP dynamics. Most intriguingly, we have preliminarily observed that mice that have increased stress vulnerability, have a higher susceptibility to the migraine-like inducing effects of CGRP.

Disclosures: Y. Filali: None. **L.P. Sowers:** None. **R. Hultman:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.25/Y15

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH NS120930

Title: Selective adenosine A3 receptor (A_3AR) agonism as a new approach for migraine treatment

Authors: *M. GAMAL-ELTRABILY[1], M. ROMERO REYES[2], D. SALVEMINI[3], S. AKERMAN[1];
[1]Univ. of Maryland Baltimore, Baltimore, MD; [2]Univ. of Maryland, Sch. of Dent., Maryland, MD, ; [3]St. Louis Univ. Dept. of Pharmacol. and Physiological Sci., Saint Louis, MO.

Abstract: Migraine is a complex neurological condition and a leading cause of disability. Despite newly developed treatments, there is still an evident lack of satisfactory results provided by current therapeutic options. This drives the apparent need to identify new targets to improve the efficiency of migraine treatment. The adenosine A3 receptor (A_3AR) is a G_i protein-coupled receptor that is expressed in the central nervous system and could represent a safe, novel option for targeted therapy. A_3AR agonism helps in alleviating neuropathic pain via modulation of spinal dorsal horn neurons, however, its role in migraine is unknown. In this study, we evaluated the effect of selective A_3AR agonists on periorbital allodynia and migraine-like trigeminal neuronal activity in preclinical migraine models. In male/female C57bl/6 mice, repeated administration of nitroglycerin (NTG, 10mg/kg, IP) induced persistent periorbital hypersensitivity. The effects of two selective A_3AR agonists (Cl-IB-MECA, selective; MRS5980, highly selective, both 1mg/kg, IP) were evaluated under acute, preventive and reversal conditions. Also, in male/female Sprague Dawley rats, *in vivo* electrophysiological extracellular recordings of trigeminocervical complex (TCC) neurons were performed. We tested the effects of the A_3AR agonists (IV) in naïve and rats that had undergone a stress-restraint protocol, with latent sensitization unmasked with a non-noxious dose of sodium nitroprusside (SNP, 30µg/kg, IV) 14-28 days later. We evaluated the effects on ongoing firing and response to intra and extracranial stimulation over 180 min, compared to naratriptan (3mg/kg, IV) or vehicle. Cl-IB-MECA and MRS5980 prevented the development and reversed established NTG-induced periorbital hypersensitivity. Also, in naïve rats, they attenuated TCC neuronal responses to dural electrical stimulation and ongoing spontaneous firing, with no significant changes on cutaneous responses comparable to naratriptan. In stress-restrained animals, SNP caused activation and sensitization of TCC neurons, with increased neuronal responses to intracranial and cutaneous stimulation. However, prior administration of MRS5980 prevented this neuronal response. Immunoassays confirmed A_3AR expression within TCC and trigeminal ganglia. Together, these data provide preclinical support that A_3AR agonism could have a potential role in migraine-related mechanisms, including inhibition of dural-responsive TCC neurons, supporting the rationale for considering A_3AR as a novel target for therapeutic development in migraine. Further studies will focus on the role of A_3AR signaling in migraine pathogenesis.

Disclosures: M. Gamal-Eltrabily: None. **M. Romero Reyes:** None. **D. Salvemini:** None. **S. Akerman:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.26/Y16

Topic: E.01. Somatosensation – Pain and Itch

Support: Multidisciplinary Research Training in Dental, Oral, and Craniofacial Sciences (MARTDOCS) T32DE032994
National Institute of Dental and Craniofacial Research/National Institutes of Health R03 DE033966
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OSU Startup funds awarded to Dr. Sarah Peters

Title: SEMA7A Deletion Impairs Reparative Dentin Bridge Formation After Direct Pulp Capping

Authors: *G. M. WANDLING[1], S. CHHIBBER[1], A. SHARMA[1], F. FENESHA[1], S. PETERS[2]; [1]Biosciences- Col. of Dent., The Ohio State Univ., Columbus, OH; [2]Div. of Biosci., The Ohio State Univ. Col. of Dent., Columbus, OH

Abstract: Background: Primary sensory afferents from the trigeminal ganglion are crucial for tooth maintenance and repair. After direct insult, dental pulp sensory nerves sprout to modulate inflammation and promote migration of dental pulp stem cells that differentiate into odontoblast-like cells, surround the damaged area, and secrete a new, reparative tertiary dentin layer. Vital pulp therapy, or direct pulp capping, aims to preserve tooth vitality during endodontic procedures by reactivating developmental signaling pathways that promote pulpal healing. Axon guidance protein SEMA7A is known to promote neuronal outgrowth and is expressed in odontoblasts during development and adulthood. Further, our lab has observed that SEMA7A global knockout mice have an altered nerve cytoskeletal phenotype in molar crowns. Here, we investigated whether these mice would exhibit impaired dentin bridge formation in a direct pulp capping mouse model. Methods: 8-week-old WT and *Sema7a*$^{-/-}$ mice were anesthetized, and first maxillary molars were treated with a deep dentin pulpal injury. Exposed pulps were capped with EndoSequence RRM Putty and sealed with a glass ionomer cement. Injured first molars were harvested at 21 days post injury for analysis of tertiary dentin density and volume with Micro-Computed Tomography (MicroCT). Fixed tissues were then decalcified, sectioned, and stained for histological evaluation with hematoxylin and eosin (H&E). Results: We observed that *Sema7a*$^{-/-}$ mice had significantly lower tertiary dentin density and volume three weeks post injury compared to WT mice. Furthermore, in lieu of reparative dentin, H&E examination of the

Sema7a$^{-/-}$ injured molars revealed an abundance of inflammatory cells surrounding the injury site. Conclusion: SEMA7A protein expression could play an important role in directing pulpal healing response after injury. Due to the importance of sensory innervation in pulpal repair and the potential for SEMA7A expression to promote axon outgrowth, we are now conducting experiments to elucidate whether the impaired healing response observed in *Sema7a*$^{-/-}$ mice is caused by altered odontoblast-sensory nerve signaling after injury.

Disclosures: G.M. Wandling: None. **S. Chhibber:** None. **A. Sharma:** None. **F. Fenesha:** None. **S. Peters:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.27/Y17

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH 5U19NS130608 (P.M.D)
UTMDACC Cancer Neuroscience Program (M.L.U., J.P.C)

Title: Pro-oncogenic tyrosine kinase signaling at the intersection of oral squamous cell carcinoma and neurotoxic chemotherapy-induced pain

Authors: *M. L. UHELSKI[1], D. SAH[3], M. HELEŠ[4], H. ELAHI[5], Y. LI[1], C. TATSUI[6], J. P. CATA[1], P. M. DOUGHERTY[2];
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Abstract: Pain is one of the most common and debilitating symptoms in head and neck cancer, affecting 54% - 98% of this population. Pain can result from cancers grossly invading neural structures, but early communication between cancer cells and neurons can also induce mutual sensitization. Frontline treatments like cisplatin can cause pain by damaging peripheral nerves, leading to chemotherapy-induced peripheral neuropathy. Cancer therapies can also regulate cancer-nerve interactions. However, the intersection between cancer-related pain and chemotherapy-induced pain has not been fully explored. While a diversity of pro-nociceptive molecules released by cancer cells and immune cells in the tumor microenvironment has been identified, their translation into effective analgesic therapies has largely failed, which may be the result of investigations and experimental models only focused on tumor-induced pain (cancer-nerve interaction) or chemotherapy-induced pain. Using murine MOC1 oral squamous cell carcinoma (OSCC) cells, we examined how the introduction of cisplatin affected orofacial nociception and membrane electrical properties of trigeminal ganglion (TG) sensory neurons. We found robust hyperexcitability in TG neurons from OSCC tumor-bearing mice and in

neurons cultured with OSCC conditioned media (OSCC-CM). The addition of cisplatin enhanced neuronal sensitization compared to either condition alone, suggesting OSCC primes TG neurons to enhance the effect of cisplatin. Further, mice bearing OSCC tongue tumors and treated with cisplatin also had enhanced pain-like behavior. In examining systems that regulate pro-nociceptive substances in the tumor microenvironment, we have identified pro-oncogenic tyrosine kinase (TK) activity as a potential candidate. OSCCs release TK ligands, and TK ligands and receptors are upregulated in pain-associated dorsal root ganglia (DRGs) from cancer patients. Among these, epidermal growth factor receptor (EGFR) and insulin-like growth factor 1 receptor (IGF-1R) are markers for poorer prognosis in OSCC, and their ligands increased sensory neuron excitability when applied acutely. TKs also regulate cellular senescence, a process induced by stress or injury that triggers a proinflammatory senescence-associated secretory phenotype (SASP). Senescence markers were higher in pain-associated cancer patient DRGs, suggesting that senescence contributes to ongoing pain in this population. Our investigations suggest that the addition of neurotoxic chemotherapy significantly impacts cancer-driven nociception and that targeting enhanced TK activity may present a novel approach to cancer-related pain.

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Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.28/Y18

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant NS109059
NIH Grant DE018661
NIH Grant DE023090

Title: Infraorbital Nerve Chronic Constriction Injury Enhances Excitability of Trigeminal Aβ- and Aδ-Afferent Neurons and Induces Orofacial Mechanical Allodynia in Mice

Authors: *T. UEDA[1], S. GUPTA[2], J. GU[3];
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Abstract: Orofacial pain affects approximately 20% of the population and substantially impairs quality of life. The pain condition is often caused by trigeminal injury, but its underlying mechanisms remain poorly understood. Here, we used a mouse model of chronic constriction injury of the infraorbital nerve (IoN-CCI) to investigate how trigeminal A-afferents may contribute to orofacial pain. Male C57BL/6J mice aged 8 weeks were surgically prepared to generate either the IoN-CCI group or the sham surgery group. All procedures were approved by

the Institutional Animal Care and Use Committee (IACUC) at the University of Alabama at Birmingham. Four weeks post-surgery, orofacial mechanical sensitivity was assessed using the von Frey test and machine-learning-based orbital tightening analysis. IoN-CCI mice showed a significant increase in response frequency to a 0.02-g von Frey stimulation compared with sham controls. Eyelid distance was significantly reduced (orbital tightening) in IoN-CCI mice, indicating spontaneous pain. *Ex vivo* trigeminal ganglion (TG) preparations were then made from these animals, and patch-clamp recordings were conducted at 33°C to investigate the membrane excitability and voltage-activated ionic currents in nociceptive and non-nociceptive A-afferents. The afferent types were classified based on conduction velocity, with Aβ-afferents being conduction velocity (CV) > 10 m/s and Aδ-afferents being 1.0 m/s < CV < 10 m/s, and on action potential (AP) waveforms, with non-nociceptor being AP width < 1 ms and nociceptor being AP width ≥ 1 ms with repolarization inflection. In current-clamp recordings, AP threshold was found to be significantly reduced in both nociceptive and non-nociceptive Aβ- and Aδ-afferents of IoN-CCI mice. AP rheobase was significantly reduced in non-nociceptive Aδ-afferents. In voltage-clamp recordings, voltage-gated inward currents were significantly increased in both nociceptive and non-nociceptive Aβ afferents of IoN-CCI mice. These results suggest that trigeminal Aβ- and Aδ-afferent neurons display hyperexcitability and increased voltage-gated inward currents, which may contribute to the development of mechanical allodynia in orofacial regions following trigeminal nerve injury.

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Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.29/Y19

Topic: E.01. Somatosensation – Pain and Itch

Title: Murine oral cancer models reflect the greater pain experienced by patients with nodal disease

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Abstract: Seventy percent of patients with oral cavity cancer experience pain at the site of the cancer. Patients with metastatic (N+) cancer report greater pain. Oral cancer pain is attributed to mediators released from the cancers that sensitize or activate trigeminal ganglion nociceptors. Thus, the N+ tumor microenvironment is thought to be enriched for pain mediators. Oral cancer pain is treated with opioids, but treatment is associated with side effects and the need for escalating doses of drugs. Mouse xenograft and allograft tongue cancer models are used to study the etiology of oral cancer pain with the goal of developing more effective treatments that

obviate the use of opiates. To determine whether these models recapitulate differences in oral cancer pain experienced by patients, we evaluated nociceptive behavior elicited by human and mouse orthotopic tongue cancer models. Since oral cancer patients give the highest ratings to queries regarding function-related pain (pain when talking, eating, drinking), sensitivity to touch, and interference with daily life, we measured oral cancer cell line-associated pain with a reflexive and an operant assay. Human and mouse oral cancer cell lines were inoculated into the hind paw or tongue of immunocompromised NU/J or C57BL/6 mice, respectively. Cancer nociception was measured weekly for 4 weeks after inoculation using the paw von Frey filament and the dolognawmeter assay. Nociception elicited by human cell lines varied; the nociception elicited by HSC-3 and HSC-4 was greater than that observed with OSC-20. The HSC-3 cell line is reported to display a more invasive growth phenotype and to have higher metastatic potential in a direct comparison with OSC-20. Greater nociceptive behavior was elicited by murine allografts generated with the more aggressive and metastatic 4MOSC2 and MOC2 cells compared to the more indolent 4MOSC1. These observations demonstrate differences in nociceptive behavior elicited by oral cancer cell lines in orthotopic models that reflect patient-reported oral cancer pain, and they inform the selection of models for the study of oral cancer pain in patients depending on nodal status.

Disclosures: N. Huu-Tu: None. **P. Ramirez Garcia:** None. **D.G. Albertson:** None. **B.L. Schmidt:** None.

Poster

PSTR015: Trigeminal Circuits: Migraine, Headache, Orofacial, and Ocular

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.30/Y20

Topic: E.01. Somatosensation – Pain and Itch

Support: R01DE032501

Title: EGFR Activation Enhances α2δ1-NMDAR Signaling and Desensitizes μ-Opioid Receptors in Oral Cancer Pain and Morphine Tolerance

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Abstract: Oral cancer patients suffer severe, refractory pain and develop opioid tolerance faster than those with other chronic pain conditions, yet the mechanism remains poorly understood. Morphine tolerance arises from μ-opioid receptor (MOR) desensitization and internalization, combined with compensatory upregulation of N-methyl-D-aspartate receptor (NMDAR) signaling. We previously found that epidermal growth factor receptor (EGFR) is overexpressed

in sensory neurons innervating oral tumors in both patients and mouse models. EGFR activation induces pre- and postsynaptic NMDAR sensitization, promoting pain amplification and morphine tolerance. The α2δ1 subunit of voltage-gated calcium channels interacts with NMDARs, driving synaptic plasticity and nociceptor excitability. We hypothesized that EGFR activation increases α2δ1-NMDAR interactions and desensitizes MORs in trigeminal ganglia (TG) neurons, promoting oral cancer pain and morphine tolerance. In syngeneic mouse models of oral cancer pain and morphine tolerance, as well as in the MOC2 supernatant-induced pain model, mechanical (von Frey) and thermal (Hargreaves) nociceptive behaviors were assessed. Experiments were conducted in wild-type (WT), EGFR conditional knockout (cKO), and α2δ1 global knockout (KO) mice, as well as in mice treated with pharmacological inhibitors targeting α2δ1, NMDAR, or endocytosis. α2δ1, phosphorylated MOR (pMOR), and markers of MOR endocytosis (*e.g.*, GRK2) levels, were measured by Western blot in the mouse TG. EGFR-mediated formation of the α2δ1-NMDAR complex was evaluated by proximity ligation assay. MOR internalization and cAMP signaling were assessed in transfected HEK293T cells using BRET imaging. Our results show that EGFR activation suppressed MOR signaling by disinhibiting cAMP and promoting MOR internalization in HEK293T cells. MOC2-bearing mice showed elevated α2δ1, GRK2, and pMOR in TG neurons. EGFR signaling enhanced α2δ1-NMDAR interactions in cultured TG neurons. Pharmacological blockade of endocytosis, α2δ1, or NMDARs, together with genetic deletion of EGFR or α2δ1, significantly reduced cancer pain and improved the analgesic efficacy of morphine in vivo. Together, our findings reveal EGFR signaling as a critical regulator of oral cancer pain and morphine tolerance, via attenuation of MOR-dependent cAMP suppression and enhancement of MOR internalization and α2δ1-NMDAR interaction in TG neurons. Given that EGFR inhibitors are FDA-approved with established safety profiles, EGFR may offer a rapidly translatable strategy to alleviate oral cancer pain and mitigate opioid tolerance.

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Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.01/Y21

Topic: E.05. Auditory and Vestibular Systems

Support: Albstein Fund

Title: Towards a scalable platform to study the neural basis of compositional inference in mice

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Abstract: Continual learning allows animals to interpret new experiences in light of prior knowledge, enabling compositional inference. Although compositionality has been studied within sensory systems, such as how visual features combine into object representations, adaptive behavior requires a higher-order form of compositionality that links sensory cues, actions, outcomes, and contexts across experience. Because learning in natural environments is embedded in context, sensory cues acquire meaning through repeated experience within a structured world of actions, outcomes, and prior knowledge. We therefore developed a home-cage training system ("Mouse Playground") that naturalizes laboratory learning while preserving experimental control, allowing us to build defined histories of prior task experience and test whether mice can use these primitives to scaffold future compositional learning. We sequentially trained mice on an 8-task paradigm in which each task was defined by a unique combination of task structure (GoNo-Go, 2AFC) and auditory perceptual dimension (frequency, duration, rate, AM, sweep direction, intensity). The first six tasks exposed mice to every structure and dimension, but not every combination. Tasks 7 and 8 then presented novel combinations that could be solved (1) de novo or (2) by recombining previously learned components. We found that mice acquired all tasks efficiently with high retention, and that a subset exhibited compositional inference, immediately solving these novel combinations within the first 20 trials. Chemogenetic inactivation of the medial prefrontal cortex (mPFC) had no impact on expert task performance or de novo learning but revealed a trend for impaired compositional inference. These findings establish the Mouse Playground as a robust system to study continual and compositional learning and also establishes compositional inference as a measurable cognitive capacity in rodents that may depend on mPFC-mediated integration of previously-learned task components.

Disclosures: A. Bal: None. **A. Santi:** None. **P.H. Janak:** None. **K. Kuchibhotla:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.02/Y22

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01 DC018650
NIH R00 DC015014
NSF CAREER 2145247
BBRF NARSAD
Kavli Distinguished Graduate Fellowship

Title: An auditory multi-task curriculum reveals the emergence of shared task structure in cortical dynamics

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Abstract: Humans and other animals learn many tasks over a lifetime, often by acquiring new behaviors that share sensory, motor, or outcome structure with prior experience. This poses a fundamental representational problem: when learning related tasks, neural circuits could form independent task-specific representations, globally reorganize existing representations, or selectively preserve some variables while abstracting others across tasks. Here, we tested how cortical population dynamics are reorganized during multi-task learning. We trained mice on two related auditory two-choice tasks using a movable wheel and a sequential curriculum in which animals ultimately performed both tasks expertly in a block-based manner. We longitudinally tracked L2/3 pyramidal cell activity in auditory cortex (AC) and posterior parietal cortex (PPC) using multi-area mesoscopic two-photon calcium imaging, allowing us to follow single-cell neural dynamics across stages of learning. To disentangle task specificity, across-trial changes, and within-trial dynamics, we applied unsupervised low-rank tensor decomposition to tracked population activity. We found that action- and reward-aligned neural dynamics were not static features of task performance but evolved systematically over learning. Although motor actions and reward delivery might be expected to evoke inherently task-invariant activity, we observed a surprising trade-off: task-specific action- and reward-aligned dynamics were gradually suppressed, whereas robust task-invariant dynamics emerged primarily during late-stage and interleaved learning. The late acquisition of these invariant dynamics suggests that they reflect learned common structure across tasks, rather than basic motor execution or reward identity. In contrast, stimulus-aligned responses maintained stable dynamics throughout learning. Together, these results suggest that cortical circuits support multi-task learning by preserving a stable sensory scaffold while selectively reorganizing action- and outcome-related dynamics to extract shared structure across tasks.

Disclosures: Z. Zhu: None. **A. Charles:** None. **K. Kuchibhotla:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.03/Y23

Topic: E.05. Auditory and Vestibular Systems

Title: Construction of Context-Dependent Auditory Rules in Mice

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Abstract: The ability to flexibly switch between thoughts and actions based on context is a hallmark of adaptive behavior. For example, hearing a phone ring in a crowded room may prompt us either to localize the sound or attend to its melody, depending on the current goal. Studies of context-dependent decision-making in primates have revealed how neural circuits represent rules, context, and choices after extensive training. But a central question remains unresolved: how does an animal build the task space that makes flexible rule use possible? Here we exploit the Continual Learning Mouse Playground—an automated home-cage training platform—to train mice on a context-dependent auditory decision-making task designed to translate classic primate paradigms into a rodent framework amenable to longitudinal neural recordings. Mice perform tasks in two spatially distinct arenas, each associated with a different decision rule. In each arena, mice heard tones varying across 6 levels along two distinct feature dimensions (intensity and frequency), composing a 6 × 6 grid of 36 stimuli. Spatial context dictated which auditory dimension was relevant for the correct left/right choice, requiring animals to maintain two auditory decision rules over the same stimulus space. We show that mice can simultaneously express two different decision rules. In a pilot cohort (n=6), mouse peak performance significantly exceeded chance in both arenas (amplitude: $p<0.001$; frequency: $p<0.001$) with animals acquiring the task within several months, comparable to or faster than prior rat and primate studies. Mice performed near-perfectly on stimuli requiring the same action across contexts, and above 70% accuracy on stimuli requiring opposite actions, suggesting that decisions were guided by the context-relevant feature dimension rather than by a single stimulus-action mapping. Mice voluntarily alternated between arenas after 51 ± 7 trials and applied the appropriate rule immediately upon arena entry rather than gradually relearning it, indicating block-based rule-switching. Training curriculum also shaped rule acquisition: mice exposed to the full stimulus dimensions before context switching generalized to novel stimuli faster than those trained on context alternation first. Proof-of-principle mini two-photon imaging in the medial prefrontal cortex and auditory cortex demonstrates the feasibility of longitudinal neural recordings during this process. Together, these results establish mice as a tractable model for studying not only how context-dependent rules are represented after learning, but how the task space that supports those rules is constructed through experience.

Disclosures: M. Rabiei Ghahfarokhi: None. **C. Shuai:** None. **A. Bal:** None. **K. Kuchibhotla:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.04/Y24

Topic: E.05. Auditory and Vestibular Systems

Title: Role of the cholinergic system in early sensorimotor acquisition

Authors: *J. LAWLOR BLONDEL[1], S. ELNOZAHY[5], F. ZHU[2], Z. ZHU[3], A. WANG[6], F. DU[7], T. RAAM[8], K. KUCHIBHOTLA[4];
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Abstract: During sensorimotor learning, animals link a sensory cue with actions that are separated in time using distributed brain circuits. Learning thus requires neural mechanisms that can operate across a wide spatiotemporal scale and promote learning-related plasticity. Neuromodulatory systems, their broad projections and diverse timescales of activity, meet these criteria and have the potential to link various sensory and motor components. Yet, it remains unknown the extent to which this proposed model of plasticity occurs in real-time during behavioral learning. The acquisition of sensorimotor learning in a go/no-go task has been found to be faster and more stereotyped than previously thought (*Kuchibhotla et al., 2019*). We trained mice to respond to one tone for a water reward (S+) and withhold from responding to another (S-). We interleaved reinforced trials with those where reinforcement was absent ("probe"). Early in learning, animals discriminated between S+ and S- in probe but not reinforced trials. This unmasked a rapid *acquisition* phase of learning followed by a slower phase, termed '*expression*'. What role does cholinergic neuromodulation play in task acquisition? Here, we test if cholinergic neuromodulation provides a 'teaching signal' that drives primary auditory cortex (A1), and links stimuli with reinforcement. We exploit our behavioral approach and combine this with longitudinal two-photon calcium imaging of cholinergic axons in A1 during discrimination learning. At the population level, we report both robust stimulus-evoked cholinergic activity and stable licking-related activity throughout learning. Using dimensionality reduction on the tracked axonal population, we identify heterogeneous within-trial activity patterns that are sound-evoked, emerge late in the trial, or integrate both features, and that evolve rapidly prior to task acquisition. Additionally, we test the hypothesis that cholinergic neuromodulation impacts the rate of task acquisition. We expressed ChR2 bilaterally in cholinergic neurons within the basal forebrain of ChAT-Cre mice and activated these neurons on both S+ and S- trials throughout learning. Test animals acquired the task faster than control groups. These results suggest that phasic bursts of acetylcholine, directly impact the rate of discrimination learning. In two additional cohorts, we paired the activation with either the S+ or the S- stimulus. We observed a refinement of the action associated with the paired stimulus: increased licking for S+ and suppression of licking for S-. Together, these results suggest that CBF activation differentially modulates contingency-related actions.

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Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.05/Y25

Topic: E.05. Auditory and Vestibular Systems

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Title: Learning and performance depend on distinct temporal units of experience

Authors: *R. MONGA[1], C. DRIEU[2], K. KUCHIBHOTLA[3];
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Abstract: Learning studies often treat reinforced trials as the fundamental unit of experience: more pairings should produce more learning, and performance should improve as those pairings accumulate. Literature on spaced training has shown that this view is incomplete, because the temporal organization of experience strongly shapes learning and retention. Yet training is organized across multiple temporal scales—trials within bouts, bouts within sessions, and sessions across days—and it remains unclear which temporal units govern learning ('acquisition') of a task rule versus its expression in stable performance. We addressed this by training head-fixed mice in an auditory go/no-go task while holding both the inter-trial interval and 24-h inter-session interval constant and varying only the number of reinforced trials per day: 35, 70, 140, or 280. Latent acquisition was measured with mid-session, non-reinforced probe trials. Mice trained with 35 trials/day acquired the contingencies in less than half as many trials as mice trained with 280 trials/day. Acquisition therefore scaled more strongly with repeated sessions than with cumulative reinforced trials. In contrast, stable performance required long continuous bouts: all 280-trial mice reached criterion within ~1,680 trials, whereas only half of the 35-trial cohort ever reached criterion, even after matching or exceeding the amount of trial experienced by 280-trial mice. Quadrupling reward size or using pre-session reward devaluation shifted acquisition in opposite directions in 35-trial cohorts, but did not impact expression, indicating that expression was not limited by value or motivation. In contrast, giving 35-trial mice who have already acquired the task a long 280-trial session rapidly rescued expression, demonstrating that stable performance requires sufficiently long continuous experience rather than accumulated practice across days. To identify the behavioral process constrained by bout length, we fit a GLM-HMM to the 280-trial cohort and applied it across all cohorts, revealing four conserved behavioral states. Stable performance required transitioning from a stimulus-guided exploratory to high-performance state, but short sessions ended before mice were able to make such a transition. Together, these findings show that temporal structure does not act

through a single mechanism or scale. Acquisition is organized primarily across repeated sessions, whereas stable performance requires sufficiently long within-session bouts to complete an exploratory transition into a reliable behavioral policy. Thus, learning and performance depend on distinct temporal units of experience.

Disclosures: R. Monga: None. **C. Drieu:** None. **K. Kuchibhotla:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.06/Y26

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R00-DC015543
NIH Grant R01-DC021067

Title: Flexible rule switching dynamics in frontal and sensory cortical neurons during perceptual learning

Authors: *G. YU[1], T. HOU[3], A. ELDO[1], B. SIDLECK[2], D. SAEED[4], M. INSANALLY[5]; [2]Otolaryngology, [1]Univ. of Pittsburgh, Pittsburgh, PA; [3]Scripps Res., San Diego, CA; [4]Geisinger Col. of Hlth. Sci., Collegeville, PA; [5]Otolaryngology, Univ. of Pittsburgh SOM, Pittsburgh, PA

Abstract: The mammalian auditory system is remarkably adaptable, allowing animals to flexibly respond to sensory information. Flexible behaviors, such as perceptual learning, involve various neural circuits including top-down regions such as frontal areas. However, how multiple brain areas communicate to support learning is unclear. To investigate how frontal and sensory cortical areas interact to enable flexible behavior, we used high-density silicon probes to record single-unit responses simultaneously from auditory cortex (AC, n = 1,327 cells), and a downstream region in frontal cortex called secondary motor cortex (M2, n = 1,314 cells), while mice performed an auditory reversal learning task (N = 15 mice). Mice were trained to respond to a target tone for water reward, and to withhold from responding to a non-target tone. Once animals reached expert criteria, a rule switch was introduced, and the rewarded tone was reversed. Optogenetic silencing experiments indicated both regions are required for reversal learning. Single-unit responses in both regions were diverse, ranging from cells highly modulated to sensory stimuli (classically responsive) to those that appear to fire randomly (non-classically responsive). Surprisingly, M2 neurons were highly sensory-responsive and contained a larger fraction of sensory-responsive neurons compared to AC. Learning of the new task rules occurred in stages, first with sensory responses being enhanced on correct trials in M2 for ‘hits’ followed by ‘correct rejects’, reflecting a full remapping of sensory-motor variables. In contrast, AC sensory responses were enhanced on Misses, suggesting M2 reflects adaptive choices while AC reflects errors. During expert performance, M2 responses were enhanced on Go trials, consistent

with a shift from rule acquisition to task execution. Population-level decoding revealed that while non-classically responsive cells were preferentially recruited in AC during rapid learning periods, classically responsive neurons in M2 were recruited during expert performance. Using a dimensionality reduction approach (CCA), we found that interactions were feedforward dominated during early learning, and feedback dominated during periods of rapid learning. To further resolve this interaction, we used a transformer-based Directed Latent Decomposition model to distinguish population activity patterns that are local to AC or M2 from patterns reflecting coordinated activity across the two regions. This provides a learning-dependent view of local and inter-areal signals, offering a framework to identify directed latent signals that support flexible rule updating.

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Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR016.07/Y27

Topic: E.05. Auditory and Vestibular Systems

Support: T32-DC011499

Title: Distinct pre-stimulus behavioral motifs influence auditory perceptual decision-making

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Abstract: Perception is not determined by sensory input alone. Internal states such as arousal, attention, and engagement profoundly shape how we perceive and respond to sensory information. Previous work has shown the auditory cortex plays a central role in this process, serving as a hub for perception where sensory, motor, and neuromodulatory signals converge. Among these signals are sensorimotor inputs generated by spontaneous movements that are tightly coupled with neural population dynamics that reflect the animal's internal state conditions. However, the repertoire of movements expressed by animals is highly diverse and it remains unclear which behaviors facilitate or disrupt perception, as well as the neural mechanisms by which these opposing effects emerge. To investigate this, we combined a 2-alternative forced choice auditory categorization task with high-density in vivo electrophysiology and cholinergic fiber photometry from auditory cortex alongside computer-vision algorithms to track movement and pupil-based arousal (N= 12 mice). We trained an unsupervised machine learning framework on body tracking data to discover statistically recurring behaviors (B-SOiD),

providing a dictionary of behavioral motifs that could be compared within and across animals. We then trained a generalized linear model (GLM) to predict trial outcomes using the motifs expressed in the moments preceding stimulus onset. We found that some reliably predicted correct choices, while others predicted incorrect choices. GLM-derived motif weights were then used to classify each trial as an 'adaptive' or 'maladaptive' pre-stimulus state, based on whether correct or incorrect choice-predicting motifs dominated the 500 ms preceding the stimulus. We compared auditory cortical population activity between these behaviorally defined trial groups. Single-unit recordings from auditory cortex (n=711 neurons) revealed that 'maladaptive' pre-stimulus states were associated with significantly higher firing rates before stimulus onset as well as during sound-presentation compared to 'adaptive' states where firing rates were lower. These results suggest that animals exhibit specific anticipatory movements that reflect opposing cortical states: either a 'primed' adaptive state that may facilitate decision-making by constraining cortical processing to task-relevant inputs, or a maladaptive state in which elevated firing rates may disrupt sensory processing and impair performance.

Disclosures: T. Inbar: None. **N.H. Elste:** None. **M. Insanally:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R00-DC015543
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NARSAD Young Investigator Grant to Michele Insanally

Title: Dynamic gating of perceptual flexibility by non-classically responsive cortical neurons

Authors: *A. ELDO[1,2], J. TOTH[3,4], B. SIDLECK[4], O. LOMBARDI[4], T. HOU[5,4], M. KERLIN[4], X. ZENG[6,4], D. SAEED[4], P. AGARWAL[4], D. LEONARD[4], L. ANDRINO[7,4], T. INBAR[4], M. MALINA[7,4], M. N. INSANALLY[4];
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Abstract: The ability to flexibly respond to sensory cues in dynamic environments is essential to adaptive auditory-guided behaviors. Auditory neural responses during behavior are diverse, ranging from highly-reliable 'classical' responses (i.e. robust, frequency-tuned cells) to irregular or seemingly random 'non-classically responsive' firing patterns (i.e., nominally non-responsive cells) that fail to demonstrate any significant trial-averaged responses to sensory inputs or other

behavioral factors. While classically responsive cells have been extensively studied for decades, the contribution of non-classically responsive cells to behavior has remained underexplored despite their prevalence. We have previously shown that non-classically responsive cells in auditory cortex (AC) and secondary motor cortex (M2) contain significant stimulus and choice information, encode flexible task rules, and are essential for asymptotic task performance. However their role during learning is unknown. Here, we explore how diverse cortical responses emerge and evolve during flexible learning. We recorded single-unit responses from AC (n=1,327 neurons) while mice performed an auditory go/no-go reversal learning task (N=15 mice, d'=1.8±0.3). Cortical response profiles during learning were diverse, spanning the continuum from classically to non-classically responsive. We found that non-classically responsive neurons were preferentially recruited during rapid learning phases when the greatest gains in behavioral performance occur. Population-level decoding revealed that during rapid learning, mixed ensembles comprised of both classically and non-classically responsive cells encode significantly more task information than homogenous ensembles of either type and emerge as a functional unit critical for learning. While optogenetically silencing inputs from secondary motor cortex during post-reversal learning selectively modulated non-classically responsive cells in the auditory cortex and impaired flexible behavior by preventing the remapping of a previously learned stimulus-reward association, photoinhibition during pre-reversal learning preferentially modulated classically responsive cells and impaired initial task acquisition. Using advanced analyses of neural geometry, we found that top-down inputs orchestrated highly correlated non-classically responsive ensembles in sensory cortex providing a unique task-relevant manifold for flexible behavior. Thus, non-classically responsive cells in sensory cortex are preferentially recruited by top-down inputs to enable neural and behavioral flexibility.

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Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.09/Y29

Topic: E.05. Auditory and Vestibular Systems

Title: Home cage pretraining improves behavioral acquisition in head-fixed mice

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Abstract: Head-fixation is frequently used in many neuroscience studies because it allows animals to engage in behaviors in a configuration that is conducive to neurophysiological measurement. Despite the advantages, head-fixation places the animal in an environment that is inherently stressful and may disrupt motivation to engage in the desired behavior. Further, head restriction disrupts both large- and small-scale movements while limiting access to sensory information. These factors collectively slow behavioral acquisition, increase experimenter effort, and limit the complexity of behaviors that can be studied. Here, we address this limitation by pre-training animals in a home cage environment in order to build task understanding and motor skills prior to head-fixation. The home cage is a modified standard housing enclosure with an attached chamber containing the behavioral apparatus. We pre-trained mice across 3 behavioral tasks: an alternating motor pattern, a sensory guided lever press, and a sensory prediction task with licking as feedback. In the home cage environment, mice rapidly acquired the appropriate task rules and motor skills required for their task. Once the mice demonstrated a high level of task performance, they began training on the head-fixed apparatus. After receiving pre-training, mice were able to consistently transition their knowledge from the home cage to the head-fixed configuration. Mice were able to reach performance thresholds faster compared to control animals who did not receive pre-training and learned behaviors that control animals were unable to reliably acquire. Together, these findings show that home cage pre-training allows animals to perform more complex behaviors in a head-fixed paradigm while minimizing experimenter time.

Disclosures: Z. Fazzino: None. **N.J. Audette:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.10/Y30

Topic: E.05. Auditory and Vestibular Systems

Support: NIDCD R00DC020770

Title: Multiple simultaneous motor-sensory predictions in mice

Authors: *C. MIZEREK[1], A. I. MORE[2], N. J. AUDETTE[2];
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Abstract: Comparing expectation with experience is an important neural computation performed throughout the brain that is vital for behaviors ranging from predator avoidance to vocal communication. This computation is described by the framework of predictive processing in which the brain updates an internal model of the world based on incoming sensory input. Motor-sensory predictions, where the sensory outcome of a movement is anticipated based on motor commands, is one of the best-established examples of prediction in the brain. Experiments using a sound-generating lever-pressing task have shown that the auditory cortex learns a stable

association between motor and sensory events that results in suppressed responses to expected stimuli and facilitates the detection of errors. While informative, existing motor-sensory experiments typically use a single movement-outcome pair. Studying multiple predictions in parallel would provide new dimensions of insight into the circuit mechanisms that convert motor plans into sensory predictions, but is difficult to achieve using traditional head-fixed behavioral approaches. To address this, we developed a new behavioral training paradigm that enables mice to learn multiple, simultaneous motor-sensory predictions in a freely moving home cage environment and transfer their knowledge to a head-fixed configuration. The paradigm incorporates two levers that each trigger a specific sound linked to distinct forelimb movements. Preliminary data suggests that pre-training animals in their home cage improves behavior in the head-fixed configuration, allowing animals to execute more complex motor-sensory behaviors with less training time. Ongoing experiments use high-density extracellular probes to record in vivo neural activity from the primary auditory cortex and the thalamus of trained mice. These experiments will evaluate the extent to which cell-type specific circuits flexibly route motor and sensory information, providing novel insight into neurophysiological mechanisms underlying cortical prediction.

Disclosures: C. Mizerek: None. **A.I. More:** None. **N.J. Audette:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.11/Y31

Topic: E.05. Auditory and Vestibular Systems

Title: A behavioral paradigm for studying-sequence predictions in mouse auditory cortex

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Abstract: The mammalian cerebral cortex is believed to use predictive processing to direct neural activity towards informative stimuli and conserve metabolic energy. There is abundant evidence for motor-sensory predictions, which typically suppress neural responses to expected stimuli while increasing the representation of unexpected outcomes. These findings support the theory that the cerebral cortex learns and uses predictions, but it is unclear if a similar phenomenon occurs for other sources of predictive information. To test this, we create a behavioral paradigm that will enable neural recording in mice who have learned to predict an externally produced auditory sequence and detect deviations. Mice experience a single song, consisting of nine notes between 8 and16 khz, arranged in an arbitrary but consistent pattern, repeated intermittently across 12 hours in a home cage environment. After an introductory period, a small fraction of songs include one randomly selected, altered frequency, presenting

mice with an error in the expected pattern. Mice learn to lick at a lickspout for water to report deviations from the known sequence. Using lick sensing and SLEAP tracking of locomotion, mouse behavior was analyzed to quantify the extent of auditory learning and supports the ability of mice to accurately detect and report deviants. Following task acquisition, mice move to a head-fixed configuration and transfer their task knowledge to a static version of the same behavior. Once proficient in the head-fixed configuration, we recorded neural activity in the auditory cortex using high-density extracellular recording probes, while mice experience the same tone heard expectedly in the song, unexpectedly in the song, and during passive listening outside of the song context. We will compare the strength of neural responses across these conditions to determine whether the auditory cortex displays hallmarks of predictive processing for sensory sequences including prediction neurons, predictive suppression, and error neurons. These findings will provide insight into whether predictive processing is applied as a general computation process in the cerebral cortex.

Disclosures: A. Motter: None. **N.J. Audette:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.12/Y32

Topic: E.05. Auditory and Vestibular Systems

Title: The impact of probability on predictive processing in mouse auditory cortex

Authors: *S. ROSSBERG[1], N. J. AUDETTE[2];
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Abstract: Neural responses to expected sounds, especially those that are self-generated through movement, are suppressed in the auditory cortex compared to passive listening conditions. This phenomenon occurs broadly across sensory modalities and supports the predictive processing framework, which is thought to optimize processing by comparing incoming stimuli with an internal model. However, the relationship between stimulus probability and the neural suppression observed in the sensory cortex isn't clear. While we know that strong neural suppression occurs when an expected sound is guaranteed, the stimuli we encounter everyday exist along a range of probabilities. Here, we implement a head-fixed lever-pressing task where a movement results in either a high-probability tone or a low-probability tone. We perform dense neural recordings in the auditory cortex, identified through intrinsic signal imaging, of trained mice to determine how the degree of behavioral expectation impacts neural suppression. Analysis of preliminary results suggests that neural responses are suppressed between the passive listening condition and lever-pressing condition for expected tones with both high and low probabilities. However, neural suppression appears to be restricted to the two expected tones, as analysis of unexpected, novel tones does not show the same modulation. Ongoing data collection

will enable a direct comparison of the strength of neural suppression between the high- and low-probability tones and will include additional probability combinations. Knowing how the auditory cortex represents expected but non-guaranteed outcomes will provide important insight into the implementation and computational benefits of cortical predictive processing.

Disclosures: S. Rossberg: None. **N.J. Audette:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.13/Z1

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC018802
T90DA059110

Title: Cortical circuits for transforming acoustic feedback into adaptive action

Authors: *S. CHANG, D. M. SCHNEIDER;
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Abstract: Sound-guided behaviors rely on our ability to detect errors, interpret how we erred, and correct our movements based on sensory feedback. For instance, playing a wrong note on a piano generates an acoustic error that tells us something went wrong. In addition to detecting that a mistake has been made, it is equally important to correctly interpret what went wrong (e.g., was the note too sharp or too flat?) and how to fix it (e.g., move hands to the left or the right). The same wrong note can also be too sharp or too flat depending on what you wanted to play, requiring flexible interpretation of sensory outcomes. Although neural circuits in the auditory cortex are important for detecting errors, it remains unclear whether the auditory cortex flexibly encodes information about how to fix an error across changing behavioral goals. We propose that in addition to detecting errors, auditory cortical cells encode information about how to fix them, which is in turn routed to motor regions of the frontal cortex to influence changes in behavior. To test this hypothesis, we have developed a novel task where, like playing a musical instrument, mice make movements that can elicit context-dependent acoustic errors and require distinct corrections. While mice performed this behavior, we simultaneously recorded from neuronal populations in auditory (A1) and motor cortical regions (M2) to elucidate how error information is communicated across the sensorimotor axis to enact appropriate motor changes. In preliminary recordings in A1, we find cells with sound responses that scale with the extent to which the animal will correct distinct types of errors during future renditions, suggesting that these cells may interpret and predict corrective behavior. On a population level, we find that errors are linked to diminished shared dynamics between A1 and M2, indicating that behavioral errors may

arise predominantly when auditory-motor coupling is weak. These findings begin to reveal mechanistic insights into bidirectional sensorimotor interactions during goal-directed behavior.

Disclosures: S. Chang: None. **D.M. Schneider:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.14/Z2

Topic: E.05. Auditory and Vestibular Systems

Support: NIDCD F32DC022169
NIDCD R01DC018802

Title: Mouse motor cortex reflects movement, error and expectation of self-generated sounds

Authors: *A. M. KLINE[1], B. HOLEY[2], D. M. SCHNEIDER[3];
[2]Ctr. For Neural Sci., [3]Ctr. for Neural Sci., [1]New York Univ., New York, NY

Abstract: Many sensations we perceive are caused by our own actions, which we distinguish from externally generated stimuli. In the auditory system, the ability to differentiate between external and self-generated sounds is crucial for vocal communication, musical training, and general auditory perception. The auditory system leverages the tight correlation between movements and the timing of incoming sensory information to discern whether a sound is self-generated, and through experience, animals form expectations for the sensory consequences of their movements. The secondary motor cortex (M2) sends movement-related signals to auditory cortex and is a potential source for establishing specific associations between sounds and their corresponding movements, yet it remains unknown how M2 activity changes with experience as mice learn and update auditory-motor expectations. Using two-photon calcium imaging in awake behaving mice, we find a subset of M2 cells sensitive to deviations from the expected sensory outcomes of movements. Further analyses aim to uncover the extent to which M2 neuronal ensembles represent changing sensory-motor associations as animals form new expectations over time.

Disclosures: A.M. Kline: None. **B. Holey:** None. **D.M. Schneider:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.15/Z3

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC018802

Title: Auditory cortical representations of self-generated sounds during natural behavior

Authors: *A. CORREDERA ASENSIO[1], D. GARCIA[1], A. LA CHIOMA[2], D. M. SCHNEIDER[3];
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Abstract: In a world ruled by physics, movement cannot occur silently. Every step, every contact, every action animals make produces a sound. This creates a fundamental challenge: the brain must distinguish between sounds generated by the environment and those generated by the animal itself. In natural contexts, this distinction is essential for survival because the acoustic consequences of self-motion can be behaviorally irrelevant in isolation, beneficial in social contexts or critically important when they reveal an animal's location to predators. Thus, animals must continuously monitor the acoustic consequences of their actions and adjust behavior as environmental demands change. Non-vocal sounds, such as footsteps or rustling leaves, account for more than 90% of the acoustic environment rodents experience, yet how the auditory system processes these self-generated sounds remains largely unknown. Here, we show that mice learn to reduce the sounds they produce while navigating natural substrates. Leveraging wireless electrophysiology, we show that the auditory cortex encodes more than sound alone. Auditory cortical activity integrates acoustic, movement-related, and contextual information to represent the structure of the environment and predict future behavior. We further reveal that social and threat contexts dynamically modulate cortical responses to self-generated sounds. Together, these findings reveal how the auditory cortex processes the sensory consequences of action in natural environments and provide a framework for understanding how sensory, motor, and contextual signals are integrated to guide adaptive behavior.

Disclosures: A. Corredera Asensio: None. **D. Garcia:** None. **A. La Chioma:** None. **D.M. Schneider:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.16/Z4

Topic: E.05. Auditory and Vestibular Systems

Support: Simons Foundation
R01DC018802

Title: Neural circuits for learned auditory expectations

Authors: *E. DIMWAMWA[1], P.-N. BARTH[2], D. M. SCHNEIDER[2];
[2]Ctr. for Neural Sci., [1]New York Univ., New York, NY

Abstract: Whether it is the intended chime of a doorbell that we press, the unintended thud of our foot on the floor as we walk, or the trial-and-error process of learning to play an instrument, we constantly hear and learn to expect sounds caused by our actions. Such learned expectations for the sensory consequences of our actions require an internal model that integrates motor and sensory information. It has previously been shown that deep layer neurons of the primary auditory cortex (A1) integrate auditory information with motor information from areas such as secondary motor cortex (M2). Further, with learning of a motor-sensory association, movement-related activity in A1 remaps to represent the identity and timing of an expected, self-generated sound. However, the cellular and synaptic basis for the formation and expression of such an internal model remains unknown. Here, we hypothesize that the internal model for self-generated sounds lies within the plastic synapses of deep layer A1 neurons, specifically the synapse between M2 neurons and layer 6 corticothalamic (L6CT) neurons in A1. To test this hypothesis, we trained mice to produce a simple forelimb lever press coupled to a predictable sound and made translaminar recordings from A1, including optogenetically identified L6CT neurons. In ongoing experiments, we are testing the extent to which L6CT neuron activity represents the expected acoustic outcome of the movement. Additionally, we are manipulating synaptic plasticity within A1 and are measuring the functional synaptic strength of M2 inputs onto L6CT neurons to determine the role of M2-to-A1 synapses in the formation and expression of an internal model. Overall, these experiments will provide valuable insights into the identity of the motor and sensory neurons that learn internal models as well as the mechanism underlying motor-sensory transformations.

Disclosures: E. Dimwamwa: None. **P. Barth:** None. **D.M. Schneider:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR016.17/Z5

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC018802
Simons Foundation
F32DC022169

Title: Distinct and reciprocal pathways for the long-range processing of auditory and visual inputs from the frontal cortex

Authors: *P.-N. BARTH[1], E. DIMWAMWA[1], A. M. KLINE[2], D. M. SCHNEIDER[2];
[2]Ctr. for Neural Sci., [1]New York Univ., New York, NY

Abstract: Activity in primary sensory cortices is strongly influenced by action, internal state, and prior expectations. These non-sensory signals arise in part from top-down inputs from frontal cortex neurons, which send monosynaptic projections to the primary auditory and visual cortices. However, the circuit logic by which the frontal cortex communicates with distinct sensory modalities remains poorly understood. Here we employ viral tracing, electrophysiology, and 2-photon imaging in awake mice to test if frontal-sensory interactions with primary sensory areas are generalized or modality-specific. Tracing inputs from the primary auditory cortex (A1) and the primary visual cortex (V1) shows that while there is a moderate bias of inputs from the primary auditory cortex (A1) towards the medial extent of frontal cortex and visual inputs towards the lateral extent of the frontal cortex, the inputs from both modalities largely overlap. Yet, we observe that frontal cortex cells largely responded to either auditory or visual stimuli, with few responding to both. Additionally, retrograde tracing of frontal inputs to A1 and V1 reveal that few frontal neurons project to both A1 and V1. The anatomical and functional spatial organization of frontal projectors to A1 and V1 mirror that of the sensory inputs from A1 and V1, collectively supporting a model of modality-specific and closed-loop circuit organization of frontal-sensory interactions. In future experiments, we will directly test the reciprocity of frontal-sensory connections by implementing the Tracing the Relationship between Input and Output (TRIO) method to image the sensory targets of labeled frontal cortical neurons projecting to A1 or V1.

Disclosures: P. Barth: None. **E. Dimwamwa:** None. **A.M. Kline:** None. **D.M. Schneider:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR016.18/Z6

Topic: E.05. Auditory and Vestibular Systems

Support: T32-DC-00046

Title: Layer-Specific Correlates of Auditory Perceptual Learning in Primary Auditory Cortex

Authors: *M. J. RENEE[1], D. STOLZBERG[2], M. L. CARAS[3];
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Abstract: Auditory perceptual learning is the process by which training improves the detection, discrimination, or identification of sound stimuli. This ability supports real life perceptual skills such as learning a second language, playing an instrument, or detecting prey. Cortical plasticity

is a neural substrate of perceptual learning: suppression of auditory cortical activity prevents perceptual learning, whereas in the intact cortex, learning-related changes in neuronal sensitivity emerge in tandem with perceptual improvements.Information flow within the auditory cortex is shaped by a complex local microcircuit, including local recurrent excitatory and inhibitory connections that give rise to laminar-specific dynamics. A comprehensive understanding of how sensory representations are transformed during perceptual learning therefore requires a detailed examination of activity across cortical layers to disentangle their distinct contributions. However, our current understanding of how perceptual learning alters neural sensitivity is largely derived from extracellular recordings in supragranular layers, leaving the effects of learning across cortical layers poorly understood. To address this issue, we developed an approach for chronic recording of extracellular activity across cortical layers in freely moving, behaving animals, and used it to monitor translaminar neural activity in the auditory cortex throughout perceptual learning. Mongolian gerbils were water-restricted and trained on a Go/No-Go aversive paradigm for amplitude modulation (AM) detection. Animals learned to lick during unmodulated broadband noise (NoGo) and withdraw during AM noise (Go) to avoid a mild shock. Once procedural criteria were met, a chronic free-floating 16 or 32-channel laminar probe (A1x16-3mm-100-703 or A1x32-3mm-50-703, Neuronexus) was implanted in primary auditory cortex and animals began perceptual training. During perceptual training, the AM depth was progressively reduced making detection of the Go stimulus increasingly difficult. Neural activity was recorded under three conditions: passive exposure prior to training, active training, and passive exposure immediately post training. Neural activity was stably recorded across cortical layers in awake, freely-moving animals over the course of perceptual training. During perceptual training, detection thresholds improved progressively across 10 days, consistent with perceptual learning. Data collection and analysis of neural activity are ongoing. Results from this study will provide new insights into how cortical circuits transform sound representations during learning.

Disclosures: M.J. Renee: None. **D. Stolzberg:** None. **M.L. Caras:** None.

Poster

PSTR016: Auditory Perceptual Learning, Decision-Making, and Prediction: Animal Studies

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Program #/Poster #: PSTR016.19/Z7

Topic: E.05. Auditory and Vestibular Systems

Support: NIH 1R21DC023263
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NIH R01DC020742

Title: Midbrain dopaminergic neuron activity during auditory perceptual learning

Authors: *M. MACEDO-LIMA, N. SRINIVAS, M. L. CARAS;
Biol., Univ. of Maryland, College Park, MD

Abstract: During auditory perceptual learning (PL), subjects practice with progressively more challenging stimuli, ultimately culminating in enhanced detection thresholds or discrimination limens. This process supports core aspects of human social communication, including speech recognition and musical ability, and can improve outcomes in individuals with hearing loss. However, these gains often take weeks or years of intensive practice to materialize and often require high motivation and reinforcement—raising the possibility that manipulating the brain's reinforcement circuitry could accelerate learning. Auditory PL depends on auditory cortical activity and coincides with altered neuronal responses to sound stimuli. Pairing sounds with electrical stimulation of the ventral tegmental area (VTA)—a major source of brain dopamine—drives auditory cortical plasticity, suggesting that training-related VTA activation may support auditory PL. VTA dopaminergic neurons have an established role in encoding reinforcement prediction errors during associative learning (learning that a stimulus predicts a consequence). We propose that the brain recruits these same reinforcement prediction error mechanisms during PL to enhance the detection of weak acoustic signals. To test this hypothesis, we used fiber photometry to record VTA dopaminergic neuron activity in freely moving Mongolian gerbils as they learned to detect progressively weaker amplitude modulated (AM) cues embedded in noise. Our preliminary findings suggest that as thresholds improve with training, weak AM depth stimuli elicit progressively greater VTA activation, whereas reinforcement-driven responses move in the opposite direction—a signature consistent with the reinforcement prediction error framework. The contribution of VTA reinforcement prediction computations to associative learning is well established; here, we provide evidence that its role may extend to a distinct form of sensory learning: auditory perceptual learning.

Disclosures: M. Macedo-Lima: None. **N. Srinivas:** None. **M.L. Caras:** None.

Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.01/Z8

Topic: F.03. Basal Ganglia

Support: NIH MH113257

Title: Lifespan spatial organization of NPY-immunoreactive interneurons in the rhesus macaque striatum

Authors: *V. MENDOZA-SILVA[1], H. KONDO[1], M. ELLIOTT[2], P. RAKIC[1], A. DUQUE[1]; [2]Dept. of Neurosci., [1]Yale Univ., New Haven, CT

Abstract: The striatum (ST) contributes to motor control and higher order functions including cognition, motivation, and behavior, through cortical and thalamic circuits. Although ST interneurons are relatively sparse, they exert strong modulatory effects on local microcircuit activity and ST output. Neuropeptide Y (NPY) immunoreactive cells belong to the

NPY/SOM/NOS class of ST GABAergic interneurons. Even though there is substantial knowledge about ST interneurons in rodents, corresponding maps for the primate ST remain limited. Thus, defining the interneuron populations of the rhesus macaque ST is an essential step toward understanding how basal ganglia (BG) circuits are compromised in human neurodevelopmental, neuropsychiatric, and neurodegenerative diseases. Using macaque tissue from Collection 6 of the MacBrain Resource Center, this study addresses this translational gap. By mapping spatial organization and numbers of NPY+ interneurons, we can provide an anatomical baseline for future testing of how these cell population participates in local circuits and associated BG pathologies. Prior work from our group established an Artificial Intelligence Image Analysis (Aiforia) model for counting ST cholinergic (ChAT+) interneurons. We mapped NPY+ interneurons from the same specimens and nearby sections stained for ChAT, allowing comparison within matched anatomical material. The preliminary sample consists of 3M & 3F 1-year old brains with 92 sections analyzed covering the whole rostro-caudal extent of the ST. We quantified NPY+ somata as raw AI assisted counts within manually delineated ST regions using an Aiforia object detection model. Evaluation of the classification model via a confusion matrix normalized to actual training counts yielded an F1 score of 96.69% (94.06% precision, 99.48% sensitivity). Across specimens, total raw NPY+ soma counts ranged from 9,232 to 21,748, with mean section counts ranging from 659 to 1161. Initial data indicate that raw NPY+ soma counts vary across rostro-caudal position consistent with ST size. Counts are lowest at the anterior pole, increase through the middle, and decrease at posterior levels. Ongoing analysis will include additional ages and regional area measurements for density. So far, there is no evidence of sex differences.

Disclosures: V. Mendoza-Silva: None. **H. Kondo:** None. **M. Elliott:** None. **P. Rakic:** None. **A. Duque:** None.

Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

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Topic: F.03. Basal Ganglia

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Instituto de Salud Carlos III to J.B.

Title: Noradrenaline in MPTP parkinsonism: quantitation of locus coeruleus neurons and thalamic axons in macaque monkeys

Authors: M. CARRILLO[1], N. HERNANDEZ-PINEDO[1], J. ZALDIVAR-DIEZ[2], I. PÉREZ-SANTOS[3], J. A. OBESO[1], J. BLESA[1], ***C. CAVADA**[4];
[1]Fundación de Investigación HM Hospitales, Madrid, Spain; [2]Univ. Carlos III, Getafe, Madrid, Spain; [3]Univ. Autónoma de Madrid, Madrid, Spain; [4]Univ. Autonoma de Madrid, Madrid, Spain

Abstract: The involvement of the noradrenergic system in parkinsonism is much debated. Here we have used stereological quantification of *locus coeruleus* neurons and thalamic axons immunostained for dopamine-ß-hydroxylase in 4 control and 16 MPTP-treated *Macaca fascicularis* monkeys (MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). The treated monkeys were in the presymptomatic (n= 4), recovered (n= 4), moderate (n= 4), and severe (n= 4) parkinsonian stages. Importantly, the brains from this same monkey cohort had been used previously to characterize the dopamine denervation in the basal ganglia and thalamus; this permitted a direct comparison of the noradrenaline and dopamine systems in the same brains. No significant differences in the numbers of *locus coeruleus* noradrenergic neurons were found between the control and MPTP-treated groups. This is in contrast with the progressive and marked reduction of mesencephalic dopaminergic neurons in the same monkeys, which correlated with parkinsonism severity. Also, no significant differences in noradrenergic axonal densities were detected in the thalamus (anterior, ventral, mediodorsal, centromedian-parafascicular, and reticular nuclei). Note that the dopamine innervation is unequally affected in the same thalamic nuclei analyzed here. These findings highlight the differential vulnerability of the noradrenaline and dopamine systems in the MPTP monkey model of Parkinson's disease.

Disclosures: M. Carrillo: None. **N. Hernandez-Pinedo:** None. **J. Zaldivar-Diez:** None. **I. Pérez-Santos:** None. **J.A. Obeso:** None. **J. Blesa:** None. **C. Cavada:** None.

Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR017.03/Z10

Topic: F.03. Basal Ganglia

Support: the Collier and McGurn families Fund

Title: Electrophysiology Marker for Adaptive Deep Brain Stimulation in Patients with Parkinson's Disease

Authors: *J. CAGLE[1], D. VUDDANDAM[2], J. WONG[2], C. DE HEMPTINNE[2];
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Abstract: Introduction: Parkinson's disease (PD) is a movement disorder characterized by abnormal neural oscillations in basal ganglia circuitry. While conventional deep brain stimulation (DBS) delivers continuous stimulation independent of patient state, growing evidence suggests that adaptive DBS (aDBS), which aims to tailor stimulation in real time based on underlying neural activity, can achieve better therapeutic outcomes and less medication

fluctuation by adjusting therapeutic level accordingly. Understanding how electrophysiological signals evolve during medication transitions is therefore critical for the development of aDBS. **Methods:** We enrolled and consented 40 patients into a prospective observational study designed to acquire electrophysiology during DBS programming workflows on and off medications. Participants in the study underwent a standardized recording protocol while receiving a standardized monopolar thresholding procedure, in which the stimulation amplitude was increased from 0 mA to the individual side-effect threshold in increments of 0.5 mA. Each stimulation level was held for a minimum of 20 seconds to ensure sufficient time for stabilization of neural activity. For patients with bilateral DBS implants, the contralateral electrode was set to 0 mA to isolate unilateral stimulation effects during the assessment, and this monopolar thresholding procedure was repeated for each implanted electrode. **Results:** A total of 71 unique hemispheres/electrodes were collected from 40 patients, with 25 patients with GPi electrodes and 13 patients with STN electrodes. Two patients have dual targets (STN/GPi or STN/VIM). Beta modulations are identified in the majority of the electrodes (90.1%) with varying strengths of modulations. The baseline Beta power and Beta reduction magnitude are significantly impacted by medication, but not the amplitude at which Beta initially reduced. Finely-tuned Gamma (FTG) was detected in 22 electrodes (31.0%) with more STN detection than GPi detection (42% vs 23%). Medication has a significant impact on the amplitude at which FTG is initially detected. The FTG amplitude is associated with side effect threshold and match more closely with the chronic adaptive DBS amplitude more than Beta modulation. **Conclusions:** Medications have a significant impact on electrophysiology in patients with PD. The electrophysiology is closely related to aDBS programming, and better understanding on the signal collected from DBS device may improve the programming strategy of aDBS.

Disclosures: J. Cagle: None. **D. Vuddandam:** None. **J. Wong:** None. **C. de Hemptinne:** None.

Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.04/Z11

Topic: F.04. Voluntary Movements

Title: Evaluating speech featuresin deep brain stimulation for essential tremor

Authors: *A. BURGESS[1], A. GUNDUZ[2];
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Abstract: Deep Brain Stimulation (DBS) targeting the ventral intermediate nucleus (VIM) of the thalamus is an established therapy for patients with medication-refractory essential tremor (ET). However, speech-related off-target effects (i.e. dysarthria) can arise presumably from electrical current spreading into adjacent thalamic nuclei or cerebellothalamocortical tracts involved in speech coordination. Dysarthria is characterized by reduced intelligibility, articulation, precision, slurring, etc. with an upwards of twenty-nine percent of observed dysarthria following DBS

surgery. After DBS surgery, it has been estimated that seventy-five percent of ET patients experience a disruption in quality of life due to off-target speech effects. High-frequency, continuous DBS is hypothesized to reduce tremor severity. However, the relationship between how DBS affects speech is relatively unknown. The objective of this study is to investigate whether DBS impacts speech outcomes across and without the presence of stimulation. A total of five ET patients were implanted with the Medtronic Percept RC device and measures from pre- and post-DBS. Subjects were instructed to repeat vowels, sentences, and words across the stimulation conditions. Stimulation was modulated in real-time based on neural biomarkers from local field potentials (LFPs) recorded from the thalamus. Speech was assessed using diadochokinesis (DDK) tasks that evaluate articulatory precision while tremor severity was independently rated by a blinded neurologist using the Fahn-Tolosa-Marin Rating Scale (TRS). The results indicated a significant statistical significance across time with pre- and post-DBS surgery. There were minimal differences between DBS ON and DBS OFF within the group-cohort analysis, but there were significant distinctive features at the individual-level. ET patients preferred DBS OFF qualitivatiely for speech despite the introduction of tremors, which suggests the tradeoffs with optimizing DBS parameters. The significance of this work demonstrates the need to optimize DBS settings for speech to improve quality of life for ET patients.

Disclosures: A. Burgess: None. **A. Gunduz:** None.

Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.05/Z12

Topic: F.03. Basal Ganglia

Support: R01NS097782
RF1MH121373

Title: Electrophysiological Biomarkers for Predicting Clinically Selected DBS Contacts in Parkinsons Disease

Authors: *L. DHAHER, K. MIRPOUR, A. ALIJANPOUROTAGHSARA, S. CHILUKURI, N. POURATIAN;
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Abstract: Selection of optimal Deep Brain Stimulation (DBS) contacts for Parkinson's Disease (PD) is a lengthy, trial-and-error process highlighting the inefficiency of the current programming method. This challenge stems from an incomplete understanding of the neural mechanisms that make specific contacts therapeutically superior, a knowledge gap that impedes the development of more targeted programming strategies. This study aims to identify electrophysiological biomarkers from intraoperative Local Field Potentials (LFPs) that distinguish clinically effective DBS contacts from unselected ones. Intraoperative LFPs were

collected from 13 patients with Sub-Thalamic Nucleus (STN) DBS implants who underwent DBS surgery. The clinically selected contacts, identified postoperatively, were compared to all other contacts. Analyses included power spectral density, burst characteristics, cortico-subcortical coherence with group-level comparisons via Wilcoxon signed-rank tests. A linear mixed-effects model (LME) incorporating 17 biomarker predictors across low-beta, high-beta, and gamma bands was used to predict contact selection and cross-validated using leave one subject out. Power analysis showed no significant differences between selected and unselected contacts. Coherence analysis revealed that selected contacts demonstrated higher coherence with M1 and S1, while unselected contacts exhibited higher premotor coherence at 34 Hz ($p < 0.05$) with a similar trend across 30-35 Hz. The LME prediction model was overall significant with $F(21,58) = 3.224$ and $p = 0.00022$. Model accuracy reached approximately 73% under leave-one-subject-out cross-validation. Most individual biomarker coefficients were not independently significant, underscoring the value of a combined approach. Selected STN contacts showed distinct cortico-subcortical coherence patterns with M1 and S1, and a multimodal biomarker prediction model achieved approximately 73% accuracy in classifying contact selection. These findings support the feasibility of biomarker-informed DBS programming and suggest that specific patterns of network engagement underlie therapeutic efficacy. These electrophysiological features offer promising, albeit preliminary, insight for developing more objective and efficient DBS programming strategies, improving our understanding of the neural mechanisms of effective stimulation.

Disclosures: L. Dhaher: None. **K. Mirpour:** None. **A. Alijanpourotaghsara:** None. **S. Chilukuri:** None. **N. Pouratian:** F. Consulting Fees (e.g., advisory boards); Medtronic, Abbott, Boston Scientific, Brainlab.

Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.06/Z13

Topic: F.03. Basal Ganglia

Support: This poster has emanated from research conducted with the financial support of Taighde Éireann – Research Ireland under Grant number 22/FFP-A/10954

Title: In silico analysis of the impact of electrode design and stimulation setting on network oscillations during deep brain stimulation for Parkinson's disease

Authors: *T. MCGUIRE, C. BYRNE, J. ORLOWSKI, M. LOWERY;
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Abstract: Exaggerated beta oscillations are recorded in local field potentials (LFPs) throughout the cortico-basal ganglia-thalamus network (CBGT) in patients with Parkinson's disease (PD). Suppression of these oscillations is correlated with relief of motor symptoms during deep brain

stimulation (DBS) [1] and has been shown to be an effective biomarker for adaptive DBS. The mechanisms by which DBS modulates pathological network activity, however, are incompletely understood. The effect of DBS is influenced by many factors including stimulation parameters, electrode geometry, and network dynamics. Recently, computational models have enabled analysis of the effects of electrode arrangement and geometry on the response of individual neurons, and of stimulation parameters on network activity [2,3]. Yet, the combined effects of electrode design, stimulation parameters, and network properties on the suppression of pathological oscillations in PD remain unexplored. To address this, by coupling a network model of the CBGT [4] with biophysically detailed finite element (FE) simulations of electric fields generated by different electrodes, we investigated the impact of DBS lead design and stimulation parameters on network dynamics and STN beta-band activity. Extracellular potentials were simulated using FE models of different types of Medtronic leads before being applied to branching collaterals projecting to the subthalamic nucleus (STN) in the CBGT network. Afterward, the resulting STN synaptic currents recorded in the CBGT network were coupled to the FE models to simulate STN LFP signals recorded at the DBS electrode. STN beta power decreased non-linearly with increasing DBS amplitude, analogous to the relationship observed in clinical data. We also showed that beta-band suppression varied with the electrode used, with some configurations producing greater attenuation of pathological oscillations. This model provides a physiologically realistic computational framework whose outputs can be directly validated against patient data and can be used to provide insights into the mechanisms driving DBS-induced modulation of network dynamics.

1 Kühn et al. J. Neurosci. 2008
2 Chaturvedi et al. Brain Stimul. 2012
3 McIntyre & Hahn Neurobiol. Dis. 2010
4 Fleming et al. Front Neurosci. 2020

Disclosures: T. McGuire: None. **C. Byrne:** None. **J. Orlowski:** None. **M. Lowery:** None.

Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.07/Web Only

Topic: A.07. Development of Neural Systems

Support: 2022M3C1A3081294
RS-2025-17492968

Title: Implantable Platform for Versatile Chronic Closed-Loop Neuromodulation Studies

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Abstract: Closed-loop neuromodulation, in which stimulation is adjusted in real time according to physiological feedback, has shown promise for treating neurological disorders and probing neural circuit mechanisms. However, preclinical validation of closed-loop implants remains limited by tethered systems that restrict movement, alter natural behavior, and constrain long-term experiments in freely behaving animals. Here, we present a fully wireless implantable platform for versatile chronic closed-loop neuromodulation studies. The system integrates 16 configurable channels for electrophysiological recording and electrical stimulation, wireless data communication, and wireless power transfer, thereby eliminating tethering constraints during chronic operation. The electronics are hermetically packaged in an alumina ceramic case, which protects the implant while preserving radio-frequency transparency for wireless operation. A multipin feedthrough connects the internal electronics to external electrodes, enabling electrode exchange and adaptation to diverse anatomical targets after device assembly. The platform is further designed for broad experimental scalability through reconfigurable recording parameters, firmware reprogrammability, interchangeable electrode interfaces, and a system-on-chip architecture that provides resources for lightweight on-device algorithms. We demonstrate the utility of the platform across multiple recording and stimulation applications, including spike and local field potential recordings from the brain and spinal cord, electromyography monitoring, and deep brain stimulation paradigms relevant to epilepsy and Parkinsonian models. By combining chronic wireless operation, hermetic packaging, modular electrode connectivity, and reprogrammable closed-loop capability, this platform provides a generalizable tool for preclinical neuromodulation research and may accelerate the translation of adaptive bioelectronic therapies.

Disclosures: M. Hoang: None. **S. Park:** None.

Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.08/Z14

Topic: F.03. Basal Ganglia

Support: The Brain and Behavior Research Foundation NARSAD Young Investigator Award
Mary E. Groff Foundation
LSAMP Adelante Summer Undergraduate Research Fellowship
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Title: Anterograde and retrograde tracing of pedunculopontine tegmental nucleus inputs to substantia nigra pars compacta dopaminergic neurons

Authors: *K. PADILLA, N. FERNANDEZ, A. BALDWIN, H. ARIAS, M. NEELALA, M. RODRIGUEZ, I. KHETARPAL, D. PENNY, C. HOFFMAN, L. D. MUZYKA, G. M. BEAUDOIN, III;
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Abstract: Dopamine is a crucial neurotransmitter that plays a key role in the regulation of motivated behavior in the nigrostriatal pathway through the projections from the pedunculopontine tegmental nucleus (PPN) to the substantia nigra pars compacta (SNc). The activity of SNc dopaminergic neurons is shaped by inputs, and these firing patterns regulate signaling across target structures. A major input comes from the PPN, which uniquely sends bilateral projections to SNc dopamine neurons. However, it is unclear whether ipsilateral and contralateral PPN inputs differentially regulate SNc dopaminergic signaling.
To further investigate these bilateral connections, we examine glutamatergic and GABAergic projections from the PPN to the SNc, focusing on their synaptic properties to examine hemisphere-specific differences in their synaptic strength and directionality. Using an anterograde tracing approach, Channelrhodopsin (ChR2) tagged with either yellow or red fluorescent proteins was administered via unilateral stereotaxic surgery. This allows for selective activation of PPN projections while recording SNc dopamine neurons using electrophysiological techniques. Electrophysiological results demonstrate that excitatory inputs from the PPN project to both ipsilateral and contralateral sides of the SNc while inhibitory synapses appear to only project ipsilaterally.
Additionally, injection of retrograde tracers into the SNc were used to label neurons in the PPN and investigate the structural properties of ipsilateral and contralateral projections. Retrograde bead data revealed that PPN projections to the SNc are not strictly unilateral, but receive input from both hemispheres, suggesting that distinct PPN neurons may be projecting to both hemispheres of the SNc while others are hemisphere specific.
Immunohistochemistry and confocal microscopy are utilized to confirm neurotransmitter identity and investigate hemisphere specific inputs. Confocal microscopy of both anterograde and retrograde techniques have confirmed that the SNc receives dual innervation from PPN dopaminergic neurons.
By combining electrophysiological recordings with tracing techniques, this study clarifies how bilateral PPN inputs differentially regulate dopaminergic neuron activity. Ultimately, this contributes to our understanding of the microcircuit mechanisms underlying nigrostriatal signaling.

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PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.09/Z15

Topic: F.03. Basal Ganglia

Support: NS104089
Thomas Hartman Center

Title: Compartmental differences in striatal indirect pathway neuron intrinsic excitability and synaptic plasticity.

Authors: *T. R. BRECHBILL[1,2], Z. B. HOBEL[1,2], E. M. PRAGER[1,2], J. L. PLOTKIN[1,2]; [1]Neurobio. and Behavior, [2]Ctr. for Nervous Syst. Disorders, Stony Brook Univ., Stony Brook, NY

Abstract: Striatal output is commonly characterized as being composed of direct and indirect pathways, established by 2 classes of spiny projection neurons (SPNs). However, SPNs can be further subdivided by their spatial location, residing in either the matrix or the understudied striosome compartment. While compartment-specific differences in excitability and modulation have been described for direct pathway neurons (dSPNs), it remains unknown if analogous differences exist in indirect pathway neurons (iSPNs). Here we characterize compartment-specific differences in striosome and matrix iSPN physiology, in terms of intrinsic excitability and synaptic plasticity. Using 2-photon imaging and whole-cell patch clamp electrophysiology in transgenic mice containing compartment- and pathway- specific reporters, we demonstrate that striosome iSPNs are more intrinsically excitable than matrix iSPNs. Further, striosome iSPNs display significantly lower engagement of dendritic voltage-gated calcium channels, including L-type channels. Given the central role of L-type calcium channels in corticostriatal synaptic depression, we examined responses to intrastriatal high frequency stimulation (HFS) that is known to reliably induce endocannabinoid-mediated long-term depression in presumptive matrix iSPNs. HFS induced robust short-term synaptic depression in matrix iSPNs but failed to robustly suppress evoked EPSC amplitudes in striosome iSPNs. These results reveal that, like striosome dSPNs, striosome iSPNs are also more excitable than their matrix counterparts, demonstrating that compartment-specific difference in excitability are generalizable across SPN types. Along with a diminished capacity for corticostriatal synaptic depression, our observations suggest a model where striosome iSPNs are poised to respond to cortical inputs with high fidelity and minimal plastic adaptation, ensuring that their activity consistently transmits cortical cues. Ongoing work aims to explore the role of dopamine in establishing and modulating these compartment-specific properties.

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Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.10/Z16

Topic: F.03. Basal Ganglia

Support: NIH Grant R01NS097782

Title: Distinct cortical and subthalamic effects of apomorphine on neuronal avalanche organization in Parkinson's disease

Authors: *S. KAZEMI[1], K. MIRPOUR[2], N. POURATIAN[3];
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Abstract: Parkinson's disease (PD) is characterized by abnormal activity throughout cortico-basal ganglia networks. Although dopaminergic therapies modulate pathological neural activity and improve motor symptoms, their effects on the large-scale organization of neuronal cascades remain poorly understood. Neuronal avalanches characterize activity propagation across neural circuits and provide markers of network organization. We investigated whether apomorphine reorganizes neuronal avalanche activity across cortical and subthalamic motor circuits. Intraoperative recordings were obtained from 11 patients with PD before and after subcutaneous apomorphine administration. Beta-band (12-35 Hz) neuronal avalanches were extracted from subthalamic nucleus (STN) local field potentials and from a sensorimotor electrocorticography (ECoG) network comprising precentral, central, and postcentral cortical contacts. Avalanche size and duration distributions were evaluated across multiple bin sizes and activity thresholds. Tail organization was characterized using comparative model analysis of power-law, truncated power-law, exponential, and log-normal distributions selected using the corrected Akaike information criterion. Treatment-related effects were assessed using paired nonparametric statistics with cluster-based correction. Within the STN, treatment reduced the exponential decay rate of avalanche size distributions, increasing the probability of larger cascades. In contrast, the sensorimotor cortical network exhibited increased exponential decay rates for both avalanche size and duration distributions, indicating reduced probabilities of large and long-lasting cascades. These effects persisted across multiple thresholds and bin sizes after cluster-level correction. Notably, the dominant treatment-related changes emerged through alterations in exponential tail organization rather than through consistent shifts in classical power-law scaling. These findings demonstrate that apomorphine differentially reorganizes neuronal avalanche dynamics across cortical and subthalamic components of the motor network. The opposing effects observed in STN and sensorimotor cortex suggest that therapeutic dopaminergic stimulation does not uniformly alter network activity but instead reshapes cascade propagation in a region-specific manner, enhancing activity propagation within subthalamic circuits while constraining the spread and persistence of activity within sensorimotor cortical networks. Avalanche analyses may provide insight into how pharmacological interventions reorganize neural dynamics in PD.

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Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.11/Z17

Topic: F.03. Basal Ganglia

Support: RSNA Grant RR25-227

Title: Topographical Gradient of the Subthalamic Hyperdirect Pathway: Selective Clinical Coupling and Phenotype-Specific Structural Signatures

Authors: *R. AGRAWAL[1,2], A. ALIJANPOUROTAGHSARA[1], J. ARTURO LARCO[1], K. MIRPOUR[1], S. CHILUKURI[1], N. POURATIAN[1];
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Abstract: The hyperdirect pathway (HDP), a monosynaptic projection connecting the motor cortex to the subthalamic nucleus (STN), is a critical component of basal ganglia circuitry implicated in Parkinson's disease (PD). However, the anatomical specificity and clinical relevance of HDP structural integrity across PD motor phenotypes remain incompletely understood. We investigated whether structural properties of distinct HDP subcircuits are associated with motor symptom severity and whether these relationships differ between tremor-dominant (TD) and akinetic-rigid (AR) phenotypes. Thirty-eight patients with PD (66.2 ± 8.6 years; 29 males) underwent diffusion magnetic resonance imaging (MRI) and MDS-UPDRS Part III assessment. Deterministic tractography reconstructed STN projections to primary motor cortex (BA4) and premotor cortex (BA6). Microstructural (QA, QIR, MD) and macrostructural (streamline count, tract volume) metrics were analyzed using linear mixed-effects models to assess tract-symptom relationships. Following false discovery rate correction, tremor severity was the only motor domain associated with HDP integrity. Greater microstructural integrity within the STN-BA4 projection was associated with lower tremor severity (QIR: $\beta = -0.0122$, pFDR = 0.040), whereas the STN-BA6 projection showed no significant relationship. Interaction analyses confirmed the association between pathway integrity and tremor was significantly stronger in the primary motor than premotor HDP pathway ($p < 0.001$). QIR was more sensitive than QA, while MD and macrostructural measures were not associated with symptom severity. Phenotype analysis revealed reduced STN-BA4 integrity in TD relative to AR patients ($p = 0.047$). Stratified analyses demonstrated a phenotype-specific dissociation in structure-function relationships. In AR patients, STN-BA4 integrity correlated with tremor severity (QA: $\rho = -0.54$, $p = 0.036$), whereas no significant association was observed in TD patients. These findings may suggest that preserved hyperdirect circuitry may suppress tremor expression in AR disease, while tremor in TD patients may arise from alternative network mechanisms. These findings identify a subcircuit-specific association between HDP integrity and tremor. The results support a phenotype-specific role of the hyperdirect pathway as a structural gatekeeper in AR disease while suggesting that tremor in TD patients may reflect circuit dysfunction beyond the hyperdirect pathway.

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Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.12/Z18

Topic: F.03. Basal Ganglia

Support: CQR02630
MC_UU_00003/6
UKRI/MR/B000936/1

Title: Heterogenous Influence of Dopamine Release on Dorsal Striatal Neuronal Activity in Freely Moving Rats

Authors: *A. VERGHESE[1,5,2], C. TOSCHI[2], B. PERRY[2], S. MANOHAR[3], A. LANGDON[5], M. E. WALTON[4], A. SHAROTT[2];
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Abstract: Dopamine (DA), an important neuromodulator in the brain, is fundamental for motivation, learning, and decision making, and its signaling deficits seemingly underlie numerous neuropsychiatric and neurodegenerative disorders. Although DA signaling within cortico-striatal basal ganglia circuits has been studied for decades, its precise role remains unclear. Canonical models propose that striatal DA is shaped by regulating synaptic plasticity for learning and modulating ongoing striatal unit activity for movement. However, how moment-to-moment DA release directly affects the concurrent activity of postsynaptic striatal neurons during motivated behavior remains unknown, largely because simultaneous measurement of these signals in freely moving animals has historically been technically infeasible.To overcome these limitations, we developed a novel, composite recording probe to acquire simultaneous sub-second DA release and spiking activity from neurons in the dorsal striatum while free-moving rats engaged in a cost-benefit decision-making task, testing how these neural signals coordinate to support goal-directed action and reward pursuit. Strikingly, our results show heterogeneous modulation of neural activity by effort and reward; some neurons display strong correlated activity with concurrent DA transients, while others show no apparent modulation. Moreover, different dorsal striatal subregions display different temporal profiles of DA release to the task events, ranging from ramping activity during the reward-effort offer cue to phasic transients at action initiation, suggesting functional specialization of the dorsal striatum across subregions. Broadly, DA release increases with higher reward value but effort modulation differs by region. Overall, it is clear that moment-to-moment most striatal units are not significantly correlated with DA release, with only 15-17% of units showing coupling. Together, these findings suggest striatal DA release has a more nuanced and cell-specific influence on the concurrent activity of striatal output neurons than classical theories suggest, with important implications for our understanding of basal ganglia function in health and disease.

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Poster

PSTR017: Basal Ganglia: Transmitters and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.13/Z19

Topic: F.03. Basal Ganglia

Support: NIH Grant R01 RF1AG081767
NIH Grant R01 NS122805

Title: Striatal dopamine release increases during the initiation and pull phases of a novel string-pulling task

Authors: *A. J. MALIK[1], M. B. SCHMIT[2], R. A. CAPRAU[2], A. ARISTIETA[2], A. WHITE[2], V. PEDERSON[2], T. FALK[3,4], S. L. COWEN[2];
[1]Neurosci., [2]Dept. of Psychology, [3]Dept. Of Neurol., [4]Dept. of Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: Dopamine (DA) release in the dorsolateral striatum (DLS) is involved in the initiation and maintenance of ongoing motor function, sensorimotor integration, and motor learning. Most studies of dopamine release in the DLS have focused on gross motor function using tasks that measure locomotion and lever pressing. Consequently, less is known about dopamine's role in fine motor control and inter-limb coordination, behaviors that are compromised in disease states involving the loss of dopamine neurons such as Parkinson's Disease (PD). To investigate the role dopamine plays in fine motor control in rodents, our group developed an automated string-pulling task optimized for neural recording (Jordan et al., 2024). In this task, animals stand on their hindlimbs and pull a vertical string with their forelimbs. Paw movements are tracked using a high-speed camera (330 frames per second) and string speed is measured using a rotary encoder. This enables precise assessment of reaching, pulling, and inter-limb coordination. We utilized fiber photometry to resolve sub-second to seconds long dopamine release in the DLS. Adult male Sprague-Dawley rats (n = 3) were trained on the task as previously described (Jordan et al., 2024). Virus (AAV2/9-hSyn-GRAB-DA2h) was injected in the right DLS (AP 0.5, ML 3.4, DV 4.8 mm). Rats received a sham injection in the medial forebrain bundle (AP -1.8 to -2.8, ML 1.8 to 2.8, DV 8.2). Following a 3-week recovery, fiber photometry measures of dopamine release were acquired during 3 30-minute string-pulling sessions. Analysis was performed via DeepLabCut and custom MATLAB code. Preliminary analyses indicate that dopamine release correlates with the overall speed of the string which is associated with the 'vigor' of the pulling response. Dopamine levels also started to increase prior to each string-pulling bout. Analysis of the movement of the contralateral paw revealed that dopamine levels peaked during the slower downward string pull/push phase. Interestingly, dopamine release during this phase was positively correlated with subsequent reach height and speed, potentially indicating a role in

enhancing the vigor of subsequent movements. Taken together, these data suggest that dopamine is not only involved in the initiation and vigor of movement but also plays a role in shaping movements within a sequence of fine-motor actions. In ongoing studies, we are using this novel string-pulling task to assess fine-motor deficits in unilateral 6-hydroxydopamine (6-OHDA) lesioned rats, a standard preclinical model of PD. Given our observations, we expect that these animals will express reduced string speed, reach height, and reach velocity.

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Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.01/Z20

Topic: F.07. Rhythmic Pattern Generation

Title: A multilevel analysis of myoinhibitory peptide signaling in the motor system of Medauroidea extradentata

Authors: *E. DIRKSEN, G. DI CRISTINA, C. GUSCHLBAUER, T. BOCKEMÜHL, A. BUSCHGES;
Univ. of Cologne, Cologne, Germany

Abstract: Neuromodulation is essential for shaping locomotor circuit output and enabling flexible motor behavior in changing environments. In invertebrates, this regulation has often been considered complex. Yet in the stick insect *Carausius morosus*'s leg modulatory system, it has been linked to a single neuronal peptide modulator, the myoinhibitory peptide (MIP), which reduces extensor tibiae (ExtTi) slow fiber force and thereby enhances the contraction dynamics of the entire muscle (Liessem et al. 2021). Here, we investigate the role of MIP in the closely related stick insect *Medauroidea extradentata* using recently established genetic tools (Di Cristina et al. 2025). We combine CRISPR/Cas9-mediated gene knock-outs (KO), behavioral analyses, immunohistochemistry, and electrophysiology to assess MIP expression in the nervous system and its contribution to walking kinematics and muscle force generation. Knock-outs of *mip* and its putative receptor (*mipR*) caused developmental arrest during the first molting cycle. To bypass this lethality, we analyzed free walking in first-instar larvae before the first molt and found reduced inter-leg coordination, whereas other kinematic parameters were largely unchanged. Immunohistochemistry revealed MIP expression in dorsal unpaired median and common inhibitor neurons, as previously described in *C. morosus*, as well as in two additional cell bodies per side in the anterolateral region of the ganglion. Neuronal tracing has identified one of these newly observed cell bodies as contralaterally-projecting neuron which extends its axon into the nervus cruris and suggesting it to be efferent. With a combination of tracing, staining, and in-situ hybridization experiments we aim to unravel the neuronal identity of these newly found MIP expressing cells. Moreover, RNA-seq of KO larvae during their first molting

cycle will be used to identify differentially expressed genes and test whether the molting failure is driven by hormonal or neuromuscular alterations. Additionally, electrophysiological experiments will be conducted to investigate the effect of MIP on ExtTi slow fiber force generation in wild-type and *mipR* knockdown animals. Together, these approaches allow to further specify the role MIP plays for modulation of muscle forces in phasmid leg muscle control.

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Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR018.02/Z21

Topic: F.07. Rhythmic Pattern Generation

Support: NIH Maine INBRE P20 GM103423

Title: Modulation of the crustacean cardiac neuromuscular system by the SLY neuropeptide family

Authors: *A. SEN[1], D. J. POWELL[2];
[2]Neurosci., [1]Bowdoin Col., Brunswick, ME

Abstract: Modulation of neuronal circuits generates flexible output patterns and maintains circuit stability, allowing animals to perform complex behaviors. Decapod crustaceans utilize diverse neuromodulators, including neuropeptides, to modulate their heartbeat. Neuropeptides can modulate the heart by acting on the cardiac ganglion (CG, a central pattern generator circuit that generates rhythmic heartbeats), the cardiac muscles, or both. Both the heart and the isolated CG (dissected from the heart) of the Jonah crab (*C. borealis*) and American lobster (*H. americanus*) are valuable models for studying neuromodulation because both preparations generate rhythmic activity in vitro, the CG contains only a few neurons with known connectivity, and both tissues are regulated by numerous modulators. The SLY peptide family of modulators appears to be highly expressed based on repeat sequences in crab and lobster transcriptomes. The SLY neuropeptide exists as a crab isoform (Cab-SLY; HIGSLYRamide) and a lobster isoform (Hoa-SLY; HLASLYKPR), but its physiological function was previously uncharacterized. To investigate the physiological effects of SLY neuropeptides and assess cross-species reactivity, dose-response experiments were performed on whole hearts and isolated CG preparations from *C. borealis* and *H. americanus*. Cab-SLY modulated cardiac activity in *C. borealis* at low concentrations (as low as 10^{-13}M) and in the lobster heart at a higher threshold of 10^{-9}M. These peptides decreased the cycle period, and increased the contraction force. Whereas the lobster isoform, Hoa-SLY, produced considerably weaker effects, affecting only the contraction period of the lobster heart at a threshold of 10^{-8}M. In future experiments, we will apply Hoa-SLY to the

crab heart. In contrast, application of either Cab-SLY or Hoa-SLY to isolated CG preparations produced effectively no changes in activity, suggesting that the relevant receptors may be located primarily on the cardiac muscle rather than within the ganglion. Since changes in the whole heart contraction period are usually mediated directly by the CG pacemaker neurons, this effect could be due to indirect modulation of the CG bursting activity. Specifically, the SLY neuropeptide may modulate the feedback that the CG receives from the cardiac neuromuscular system. Ongoing immunohistochemical experiments aim to identify sites of SLY peptide expression in the CG of each species. Together, these findings provide insight into the role of SLY neuropeptides in crustacean cardiac modulation and suggest conserved mechanisms of peptidergic signaling that contribute to flexible motor pattern generation in neural circuits.

Disclosures: A. Sen: None. **D.J. Powell:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.03/Z22

Topic: F.07. Rhythmic Pattern Generation

Support: GSU Brains & Behavior Seed Grants Program

Title: Coexistence of Functional and Dysfunctional Activity in Leech Heartbeat Interneurons Under Neuromodulation

Authors: *Y. O. SHAMS[1,2], R. L. CALABRESE[3], G. S. CYMBALYUK[1,2];
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Abstract: Central pattern generators (CPGs) control rhythmic motor behaviors. Neuromodulation tunes these circuits by altering dynamics of ionic channels and synapses. Such changes can position circuit dynamics near boundaries of dysfunctional activity where functional activity can co-exist with dysfunctional. In this case, a short perturbation can switch the system from one activity to the other. This multistability raises the risk of abrupt transitions. The leech heartbeat CPG is comprised of pairs of interneurons (HNs) connected by inhibitory synapses, with each pair forming a half-center oscillator (HCO). Myomodulin, an endogenous leech neuromodulator, speeds up HCO by increase of h-current and decrease of Na^+/K^+ pump current. Activity of biophysical models were mapped under variation of maximal h-current conductance (G_h) and maximal pump current ($I_{PumpMax}$). Our HCO model recapitulates myomodulin effect by describing a functional coregulation path along which $I_{PumpMax}$ decreases as G_h increases. This path navigates the HCO within domains of functional regimes, high- and low- spike frequency bursting (HFB, LFB) located between two dysfunctional regimes, asymmetric and plateau-containing bursting (PCB). On the map of the single HN, these parameter domains correspond to dysfunctional PCB, which spans most of the path. We used our single HN and HCO models to investigate regime transitions under variation of G_h and $I_{PumpMax}$, applying two protocols:

sweeping $I_{PumpMax}$ upward in one and downward in the other. In the HCO, the upward sweep detected the HFB-to-PCB transition at higher $I_{PumpMax}$ values than the PCB-to-HFB border detected by the downward sweep. This gap between borders marks a domain where the two regimes coexist. A comparable border difference appeared in the single HN, this time between LFB and PCB regimes, marking a domain where the two coexist. We investigated how perturbations switch the system between HFB/LFB and PCB. Short inhibitory or excitatory pulses were applied, with varied pulse magnitude and its delivery phase within a cycle of the starting regime. We mapped magnitude and phase, marking which combinations triggered a switch for each case. In the single HN, inhibitory pulses triggered switches from PCB to LFB more often (~60%) than from LFB to PCB (~29%). Excitatory pulses showed the opposite trend, producing more switches from LFB to PCB (~55%) than from PCB to LFB (~11%). Neuromodulation can give rise to coexistence of functional and dysfunctional regimes. Identifying the perturbations that can switch the system from a pathological regime to a functional one could lead to novel treatments for pathological rhythms such as seizure activity.

Disclosures: Y.O. Shams: None. **R.L. Calabrese:** None. **G.S. Cymbalyuk:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.04/Z23

Topic: F.07. Rhythmic Pattern Generation

Support: Maine INBRE (NIH) 2P20GM103423

Title: Modulator-driven stability despite seasonal differences in cardiac physiology of the lobster H. americanus

Authors: *E. M. SICILIANO[1], D. J. POWELL[2];
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Abstract: Temperature directly influences all biological processes, and temperature changes pose a significant challenge to nervous systems, as temperature fluctuations alter ion channel kinetics and the precise coordination of synaptic currents within a circuit. Despite ion channels exhibiting distinct temperature dependencies, neural circuits in poikilothermic (“cold-blooded”) organisms are still able to maintain function and rhythmic output in environments with daily and seasonal temperature fluctuations. The American lobster (Homarus americanus), a poikilotherm, exhibits greater temperature tolerance in vivo than its isolated cardiac neuromuscular system in vitro. Thus, the American lobster must have evolved cellular and/or systems-level processes that enable its nervous system to maintain function within permissive temperature ranges. One proposed mechanism of temperature compensation is neuromodulation. Neuromodulators are chemicals that can alter a neuron’s intrinsic excitability or synaptic dynamics. Therefore, this project aimed to investigate the effects of temperature on the modulation of nervous systems by

exposing the whole heart of the American lobster to three endogenous neuropeptides: SGRNFLRFamide (SGRN), GYSDRNYLRFamide (GYS), and myosuppressin at 7°C, 10°C, 13°C, and 16°C; this range of temperatures is realistic to what these organisms naturally experience. Without modulation by these peptides, as temperature increased, the contraction force of the lobster heartbeat decreased, while frequency increased. We hypothesized that the application of these peptides would stabilize heartbeat parameters, providing temperature compensation as temperature increased from 7°C to 16°C. Application of SGRN and GYS provided temperature compensation for the lobster heartbeat, whereas myosuppressin modulation was temperature-dependent. Myosuppressin allowed the cardiac muscles to increase contraction force in proportion to temperature increases. This project also examined the seasonal dependence of modulation patterns by comparing responses in animals caught in the summer versus the winter. Preliminary data indicated that modulation provided by the three peptides would be seasonally distinct. However, we did not observe differences in modulatory responses across seasons. Interestingly, the baseline cardiac physiology, without modulation, differed seasonally. Although the exact temperature dependencies of each modulator varied based on season, the application of the peptides seemed to compensate for underlying differences in cardiac physiology across seasons.

Disclosures: E.M. Siciliano: None. **D.J. Powell:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.05/Z24

Topic: F.07. Rhythmic Pattern Generation

Support: Kavli Foundation

Title: Acute and chronic heat stress alters neuropeptide signaling in pattern generating networks

Authors: *M. SEYMOUR[1], W. STEIN[2];
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Abstract: Acute and chronic heat stress strongly influences nervous system activity, with detrimental consequences for neuronal function that can threaten survival when vital circuit activity fails. Yet, some neural circuits display a remarkable robustness across a broad range of acute temperature changes. Studies using chronic heat stress have further shown that this temperature robustness can shift and expand to higher temperatures, suggesting that neural circuits undergo acclimatory-induced plasticity. While the mechanisms underlying this long-term plasticity remain largely unknown, increasing evidence supports the role of neuropeptide modulators in neuronal temperature robustness and acclimatory processes during prolonged heat stress. Here, we test the hypothesis that changes in neuropeptide signaling contribute to stabilizing neural circuit function during prolonged heat stress. To test this hypothesis, we use

the central pattern generating circuits (CPGs) in the stomatogastric nervous system of green crabs (*Carcinus maenas*) and Jonah crabs (*Cancer borealis*) acclimated for two months to 20°C (warm-acclimated) and 10°C (cold-acclimated). Previous studies have shown that CPG temperature robustness differs between these two species, with *C. maenas* showing a larger robustness. We assessed changes in neuropeptide signaling by recording 1) the activity of modulatory projection neurons known to release tachykinin-related peptide modulators important for temperature robustness in stomatogastric CPGs and 2) the synaptic currents elicited by peptide release in CPG pacemaker and half-center oscillator neurons using two-electrode voltage clamp. Our data indicate that modulatory projection neuron activity differs between species and acclimation conditions, with higher activity in *C. maenas* and an increase in warm-acclimated animals compared to cold-acclimated animals. In addition, synaptic currents show species-dependent differences, with *C. borealis* exhibiting larger currents than *C. maenas*. Overall, this suggests that long-term temperature exposure is associated with changes in neuromodulatory signaling and that these changes may be organized differently in homolog neurons of related species.

Disclosures: M. Seymour: None. **W. Stein:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.06/AA1

Topic: F.07. Rhythmic Pattern Generation

Support: R35NS142987

Title: The substrates for robustness tuning: thermal acclimation driven plasticity in the pyloric network of lobster, Homarus americanus

Authors: *S. KEDIA[1], M. KENNGOTT[2], E. E. MARDER[3];
[2]Physics, [1]Brandeis Univ., Somerville, MA; [3]Biol., Brandeis Univ., WALTHAM, MA

Abstract: Plasticity mechanisms allow neurons to change themselves and their connections to facilitate learning and memory and to keep network output stable. We describe the mechanisms underlying robustness tuning- the network wide changes previously reported to occur upon thermal acclimation in various decapod crustaceans in *H. Americanus*. This form of plasticity shifts the robustness range of a network in accordance to environmental features and is a complicated feat of engineering given the non-linearity of the interactions of various conductances and the differences in their individual responses to acute temperature. We studied underlying changes in the pyloric network of the stomatogastric nervous system (STNS) which continuously produce rhythmic motor outputs over a wide range of temperatures with distinct ‘crash’ points. Animals were acclimated to ‘cold’ and ‘hot’ temperatures (4 and 18°C) for a period of >3 weeks. Hot acclimation extended crash temperatures by ~7°C increase over which

the network produces a triphasic pyloric rhythm. Intrinsic conductance expression shifts after acclimation to make preparations from hot acclimated animals have higher endogenous activity in the absence of neuromodulators, both at 10 and 20°C. Neuromodulator dose responses of Crustacean Cardioactive Peptide (CCAP) were tested at both temperatures and there are temperature and acclimation dependent differences in the dose responses. High doses of CCAP fail to restore rhythmicity after cold-acclimation of the animals. High doses of CCAP produce a greater impact on isolated Lateral Pyloric neuron (LP) firing in hot-acclimated animals suggesting that modulatory responses are larger after hot-acclimation which interact with other intrinsic changes promoting excitability to give greater thermal robustness. Computational models demonstrate the effects of a neuromodulatory current on neuronal excitability and how these difference may emerge.

Disclosures: S. Kedia: None. **M. Kenngott:** None. **E.E. Marder:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.07/AA2

Topic: F.07. Rhythmic Pattern Generation

Support: Kavli Foundation Exploration Award

Title: Acute and long-term temperature exposure modulates membrane resonance in pattern generating neurons

Authors: *C. STEIGER, W. STEIN;
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Abstract: Oscillatory neural networks such as central pattern generators (CPG) produce rhythmic activities that drive many vital behaviors. Their preferred (resonant) frequency of oscillation is determined by the biophysical membrane properties and synaptic inputs of the CPG pacemaker neurons, suggesting that modulatory influences may target these properties to alter network frequency. Here we test whether acute and long-term temperature exposure act as modulators of membrane resonance in pacemaker neurons of the crustacean stomatogastric nervous system. Sinusoidal currents were injected at the animals' acclimation temperature (cold acclimation: 10°C; warm acclimation: 20°C), as well as 5°C below and 5°C above. In intact circuits, resonance frequency increased with temperature, but only after long-term acclimation ($P=0.001$, RM Anova, $N=9$, $F(2,16)=10.57$; 15°C vs 20°C and 25°C, SNK posthoc test, $P<0.05$). To determine the contribution that network feedback has on temperature-induced changes in membrane resonance, we blocked synaptic input to the pacemakers with Picrotoxin (10^{-5}M). In this case, resonance frequency increased with temperature after cold acclimation ($P=0.003$, RM Anova, $5 \leq N \leq 8$, $F(2,11)=10.587$; 15°C vs 5°C vs 10°C, SNK posthoc test, $P<0.05$) and warm-acclimation ($P=0.014$, RM Anova, $8 \leq N \leq 9$, $F(2,15)=5.794$, 25°C vs 15°C vs 20°C, SNK

posthoc test, $P<0.05$). Finally, to determine the contribution of the subthreshold responses of the pacemaker neurons to the temperature-induced shifts in resonance properties, we suppressed action potentials with Tetrodotoxin (10^{-6}M). Here, resonance frequency increased with temperature in both acclimation conditions (cold: $P=0.014$, RM Anova, $5 \leq N \leq 8$, $F(2,11)= 6.505$, 15°C vs 5°C vs 10°C, SNK posthoc test, $P<0.05$; warm: $P=0.043$, RM Anova, $7 \leq N \leq 8$, $F(2,13)=4.059$, 15°C vs 25°C, SNK posthoc test, $P<0.05$), indicating that intrinsic membrane properties are sufficient for temperature-induced shifts in membrane resonance to occur. To determine whether long-term acclimation modulates membrane resonance, we compared resonance frequencies at 15°C between acclimation conditions. Resonance frequencies only differed when action potentials were suppressed ($P=0.01$, Mann-Whitney U-Test, $8 \leq N \leq 11$), suggesting that long-term acclimation induced changes to the subthreshold responses of pacemaker neurons, while suprathreshold and synaptic inputs aided to stabilize membrane resonance. Overall, our results suggest that acute and long-term temperature exposure act as modulators of membrane resonance, but with distinct actions on subthreshold, suprathreshold, and synaptic pacemaker properties.

Disclosures: C. Steiger: None. **W. Stein:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.08/AA3

Topic: F.07. Rhythmic Pattern Generation

Support: NIH NINDS R15-NS128619 (DMB)
NIH NINDS R01-NS029436 (MPN)
The Crustacean Society (HTB)

Title: Sensory Neuron Cotransmitter Modulation of Central Pattern Generator Inputs

Authors: H. T. BISHOP[1], C. M. NAYLON[1], M. P. NUSBAUM[2], ***D. M. BLITZ**[1]; [1]Miami Univ., Oxford, OH; [2]Dept. of Neurosci., Perelman SOM, Univ. Pennsylvania, Philadelphia, PA

Abstract: Sensory neurons can provide metabotropic as well as ionotropic influences on neural circuits via direct actions and/or actions on their modulatory projection neuron inputs (Blitz & Nusbaum, CONEUR, 2011). Many sensory neurons contain cotransmitters (Gatto et al, CONEUR, 2019), but little is known about their individual and collective actions. Here we study how multi-transmitter proprioceptor neurons (GPR: 2 bilateral copies) act on two identified commissural ganglion (CoG) modulatory projection neurons (MCN1, CPN2) to regulate a well-described central pattern generator circuit in the Jonah crab (*Cancer borealis*) stomatogastric ganglion (STG). Directly stimulating GPR triggers long-lasting activity in MCN1 & CPN2, which drives a gastric mill (chewing) rhythm in the STG. GPR neurons respond to stretch of

gastric mill muscles with a low frequency (~5 Hz) tonic mode or a high frequency (~30 Hz) bursting mode (Birmingham et al, J Neurophysiol 1999). We are testing the hypothesis that different sensory encoding modes use different cotransmitters at the level of circuit inputs. GPR cotransmitters include 5HT, ACh and the peptide allatostatin (AST), with its known STG actions limited to 5HT and ACh (Nusbaum et al, Nat Rev Neurosci 2017). We first tested the firing rate dependence of brief (6 s) GPR stimulations, finding it increased both MCN1 and CPN2 firing rates in 30 s windows after 5 Hz or 30 Hz stimulation (MCN1: p= 0.93, n=10; CPN2: p=0.77, n=10). We then found that bath applied 5-HT (10 μM) also increased the MCN1 (p=0.002, n=6) and CPN2 (p=0.02, n=6) firing rate vs saline, thereby activating a gastric mill rhythm (n=5/6). In a pilot experiment using 0.1X Ca^{2+} saline, 5HT excited MCN1 (saline: 1.3 Hz, 5HT: 13.7 Hz) and CPN2 (saline: 3.9 Hz, 5HT: 6.0 Hz), suggesting direct effects. Bath applied 5HT also altered GPR actions in the CoG. Stimulating GPR at 5 Hz changed the MCN1/CPN2 response from excitatory in saline (n=5/5) to no effect in 5HT (Pre- vs Post-GPR: MCN1: p=0.49, CPN2: p=0.51); 30 Hz GPR stimulations in 5HT weakened (2/5) or briefly silenced (3/5) MCN1 (p=0.04) and did not affect CPN2 (n=5, p=0.19), delaying onset of the next gastric mill protractor phase. This suggests applied 5HT occludes the GPR 5HT excitation and, at 30 Hz GPR stimulation, unmasks inhibition on MCN1, which may occur via AST. Bath applied AST (1 μM) inhibits STG circuit neurons (Skiebe & Schneider, 1984 J Exp Biol). We next aim to determine the source of the unmasked inhibition, and examine the impact of rhythmic GPR stimulation, as would occur in vivo, to further explore how GPR cotransmitters mediate the tonic proprioceptive and intrinsic bursting functions of a multi-transmitter sensory neuron.

Disclosures: H.T. Bishop: None. **C.M. Naylon:** None. **M.P. Nusbaum:** None. **D.M. Blitz:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.09/AA4

Topic: F.07. Rhythmic Pattern Generation

Support: NINDS R35NS142987

Title: Differential inhibitory effects of allatostatin classes in on pyloric activity in Homarus americanus

Authors: *K. SCHAPIRO[1], E. MARDER[2];
[1]Brandeis Univ., Waltham, MA; [2]Biol., Brandeis Univ., WALTHAM, MA

Abstract: Neuromodulation enables the modification of neural activity, which is especially relevant to rhythmic pattern generation. In the well studied pyloric circuit of crustaceans, the vast majority of characterized neuropeptides have excitatory effects on the cells that participate in the rhythm. Many of these modulators converge on the same ionic current. However, a number of

inhibitory neuromodulators have been identified, and it is unclear if they similarly converge on a molecular mode of action. This work investigates the effects of three classes of allatostatins (AST) on the activity of pyloric cells in *Homarus americanus* both in the presence and absence of intrinsic neuromodulation. ASTC1 exposure causes a transient decrease in the spikes per burst of the lateral pyloric (LP) neuron and a persistent decrease in the overall pyloric frequency in the presence of intrinsic neuromodulation. ASTA exposure causes a sustained suppression of both LP activity and pyloric frequency. ASTB does not appear to have a strong effect except in the absence of intrinsic neuromodulation in cases where pyloric dilator activity is tonic, in which case ASTB restored bursting. Continued experimentation aims to determine the molecular mechanisms by which these varied effects are achieved.

Disclosures: K. Schapiro: None. **E. Marder:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.10/AA5

Topic: F.07. Rhythmic Pattern Generation

Support: NIH Grant MH060605

Title: Neuropeptides directly modulate gap junction-mediated electrical coupling and spike synchrony

Authors: N. DAUR[1], X. LI[2], F. NADIM[1], ***D. M. BUCHER**[1];
[1]New Jersey Inst. of Technol., Newark, NJ; [2]Princeton Univ., Princeton, NJ

Abstract: Neuromodulators tune circuit dynamics through effects on intrinsic neuronal excitability and synaptic function. While there are plenty of cases where the effects on target ion channels and components of chemical synapses have been characterized, direct modulation of electrical synapses is less well understood. In most cases, it has not been determined whether modulation of electrical coupling strength is due to effects on neuronal impedance or on the coupling conductance itself. We examined this problem in the pyloric central pattern generator (CPG) of the crab, *Cancer borealis*, stomatogastric ganglion (STG). Pyloric oscillations (~1 Hz) are driven by a pacemaker circuit which includes two pyloric dilator (PD) neurons. The PD neurons are strongly electrically coupled and produce near-synchronous parabolic bursting activity. We examined the effects of three endogenous neuropeptides known to have convergent effects in pyloric neurons, where they target their respective GPCRs to activate the same voltage-gated inward current. 1 μM bath application of either red pigment concentrating hormone (RPCH) or crustacean cardioactive peptide (CCAP) increased PD-PD coupling conductance (measured by voltage clamping both neurons) by ~50%, while proctolin (PROC) decreased it by ~25%. Co-applications of two or three peptides suggested that these effects were roughly linearly additive.We then tested whether the neuromodulation of electrical coupling conductance had any

functional effects on the activity of the PD neurons. The slow waveform oscillations of the two PD neurons remained highly synchronous under all conditions, and the peptides had no significant effects on waveform correlations or phase offset. However, the spiking activity during the burst phase of the oscillations showed limited synchrony between the PD neurons and was significantly affected by the neuropeptides. We performed extracellular recordings of the PD spiking activity from motor nerves close to the target and determined their spike time tiling coefficient (STTC, Cutts & Eglen, J Neurosci, 2014) as a measure of spike synchrony. CCAP, which increased coupling conductance, also significantly increased spike synchrony between the two PD neurons. PROC, which decreased coupling conductance, also significantly decreased spike synchrony. Therefore, direct neuromodulation of electrical coupling differentially influences the temporal coordination between circuit neurons. Additionally, neuromodulators that converge on their actions on target ion channels can have opposite actions on gap junction-mediated electrical coupling.

Disclosures: N. Daur: None. **X. Li:** None. **F. Nadim:** None. **D.M. Bucher:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.11/AA6

Topic: F.07. Rhythmic Pattern Generation

Support: NSF DBI2015317

Title: A computational model for the biting-swallowing transition in Aplysia Californica

Authors: *Y. LI[1], M. BENNINGTON[3], V. A. WEBSTER-WOOD[4], H. J. CHIEL[5], R. D. QUINN[2];
[1]Case Western Reserve Univ., Cleveland, OH; [2]Mechanical Engin., Case Western Reserve Univ., Akron, OH; [3]Dept. of Mechanical Engin., [4]Mechanical Engin., Carnegie Mellon Univ., Pittsburgh, PA; [5]Biol., Case Western Res. Univ., University Heights, OH

Abstract: *Aplysia californica* uses multifunctional feeding control to generate smooth transitions between feeding behaviors. For example, the marine mollusk generates little or no force for pulling food into the buccal cavity during the attempt to grasp food (biting). Although motor neuronal activity to the retractor muscle (I3) generates very little force, the neural activation enhance I3's ability to generate force once the same motor neurons are activated more intensely during swallowing (Lu et al., 2015). How does *Aplysia* achieve such sophisticated control through a relatively small neural circuit (around 20,000 neurons for the whole nervous system)? Researchers have developed neuromechanical models with different levels of accuracy and complexity to investigate the mechanisms underlying *Aplysia*'s feeding control. Our previous work demonstrated that the modulatory mechanisms could be incorporated into a bioinspired artificial neural network model, Synthetic Nervous Systems (SNSs), to generate animal-like

force enhancement (Li et al., 2024) *in vitro*. Whether the integration of modulatory SNSs and a biomechanical model of *Aplysia* will lead to the biting-to-swallowing transition observed in animals, however, has not been studied. In this work, we developed an SNS model of *Apylisa*'s feeding circuitry with modulatory mechanisms in the B3/B6/B9 motor neuron pool. We tested that, when integrated with a high-fidelity model of *Aplysia*'s feeding apparatus (Bennington et al., 2025), the SNS circuitry could generate feeding control for biting, swallowing, and rejection. Furthermore, the modulatory mechanism allows the neuromechanical model to produce minimal force during biting while preparing the I3 muscle to generate large force during subsequent swallowing. These results, similar to those observed in animals, suggest that neuromodulation can play an important role in the adaptive, multifunctional motion control of animals.

Disclosures: Y. Li: None. **M. Bennington:** None. **V.A. Webster-Wood:** None. **H.J. Chiel:** None. **R.D. Quinn:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.12/AA7

Topic: F.07. Rhythmic Pattern Generation

Title: Coexistence of Episodic and Continuous Bursting in a Conductance-Based Model of a neuron

Authors: O. KOVALENKO[1], A. GRINSHPON[2], ***G. S. CYMBALYUK**[3];
[1]Univ. Laval, Quebec City, QC, Canada; [2]Georgia Inst. of Technol., Atlanta, GA; [3]Neurosci. Inst., Georgia State Univ., Atlanta, GA

Abstract: Rhythmic motor behaviors such as breathing, walking, and swimming are produced by central pattern generators (CPGs), neural circuits that generate patterned output without rhythmic input. Classically, CPG activity has been described through two fundamental regimes: continuous bursting, underlying sustained behaviors, and silence, corresponding to rest. Recent recordings from isolated spinal cords of larval zebrafish and neonatal mice reveal a third fundamental pattern—episodic bursting—in which trains of bursts are grouped into discrete episodes separated by prolonged quiescence. How a neuron or circuit generates episodic bursting and switches among these regimes remains poorly understood. Here we characterize episodic bursting and propose it as a novel dynamical scenario for central pattern generation. We develop a single-neuron Hodgkin-Huxley-type conductance-based model that reproduces complex dynamics, with multiple bursts grouped within individual episodes; its slow-fast structure arises from a slowly inactivating persistent sodium current that forms individual bursts, and from a slowly activating potassium current (I_{K2}) and h-current that control episode and inter-episode durations, respectively. The half-activation voltage of this potassium current ($-\theta_{K2}$) acts as a master control parameter. Decreasing θ_{K2} prolongs episodes and, below −9.0 mV, drives a transition to continuous bursting from episodes of more than 34 bursts; increasing θ_{K2} shortens

episodes, lengthens inter-episode intervals, and, above −2.2 mV, drives a transition to silence from episodes of five bursts. Episode duration grows in discrete, stepwise increments, adding three bursts at a time, and becomes irregular near transitions. Within a θ_{K2} range, continuous and episodic bursting coexist as robust attractors, with the number of bursts per episode ranging from 14 at θ_{K2} = -8.965 mV to 34 at θ_{K2} = -8.996 mV. Brief perturbations can produce a permanent switch from one regime to the other. These results identify potassium-channel activation as a critical determinant of episodic rhythms and reveal how a single neuron can generate multiple rhythmic outputs.

Disclosures: O. Kovalenko: None. **A. Grinshpon:** None. **G.S. Cymbalyuk:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

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Program #/Poster #: PSTR018.13/AA8

Topic: F.07. Rhythmic Pattern Generation

Support: NS45248

Title: Central Pattern Generator-diven primary afferent depolarisation (CPG-PAD) in the neonatal rat in vitro spinal cord

Authors: *E. SALCEDO[1], A. SALCEDO-CARRILLO[2], J. N. QUEVEDO[3];
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Abstract: The integration of sensory information within the spinal cord dynamically recruits and reorganises spinal circuits, enabling organisms to respond to a myriad array of diverse environmental perturbations. During locomotion, Central Pattern Generators (CPGs) modulate flexor-extensor activity as a function of stimulus modality -cutaneous, proprioceptive, or interoceptive-, and locomotor phase. CPGs also regulate the efficacy of sensory transmission through phase-dependent modulation of primary afferent depolarisation (PAD). This process involves oscillations of afferent membrane potential coupled to the locomotor cycle (CPG-PAD; CPG-mediated PAD). Depolarisation amplitude is typically maximal during flexion, followed by a repolarisation trough at the onset, and a subsequent, lower-amplitude depolarisation. Whether this modulation is produced by the disynaptic pathway mediating classical PAD, hijacked by the CPG, or by distinct circuit mechanisms remains unresolved. In neonatal rats, PAD evoked by low-threshold afferent stimulation reduces monosynaptic reflex (MSR) latency and increases peak amplitude without altering overall duration or halfwidth. These findings are consistent with enhanced synaptic efficacy due to facilitation of action potential propagation, rather than increased or diversified recruitment of afferent populations. Computational modelling further suggests that this facilitation extends to CPG-PAD, supporting the existence of a feedback mechanism that enhances the reliability of stimuli-driven reflexes in a locomotor phase-dependent manner.

Disclosures: E. Salcedo: None. **A. Salcedo-Carrillo:** None. **J.N. Quevedo:** None.

Poster

PSTR018: Rhythmic Pattern Generation: Cellular Properties and Neuromodulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.14/AA9

Topic: F.07. Rhythmic Pattern Generation

Support: NIH Grant 5R01NS133694

Title: Subnucleus-specific ablation of caudal raphespinal neurons reveals serotonergic contributions to sensorimotor function in Tph2-iCre rats

Authors: *A. ENGLAND[1], G. M. SMITH[2];
[1]Temple Univ. Lewis Katz Sch. of Med., Philadelphia, PA; [2]Dept of Neurosci., Temple Univ., Philadelphia, PA

Abstract: Serotonin (5-HT) has long been implicated in motor control, with pioneering work by Rossignol and colleagues demonstrating that 5-HT or serotonin receptor agonists could reinstate fictive locomotion in cats with a complete spinal transection. Anatomical studies revealed that spinal 5-HT is released from raphespinal neurons originating in the caudal raphe nuclei (CRN), with three subnuclei projecting to distinct spinal laminae. Nucleus raphe magnus (RMg) preferentially innervates the dorsal horn, while the nucleus raphe obscurus (ROb) and pallidus (RPa) tend to innervate the ventral laminae and densely surround motoneurons. Recently, gain-of-function studies in transgenic mice have shown that activity of the ROb and RPa correlates with increased locomotor bouts, and that the activity of these nuclei increases the probability of maintaining an active locomotor state, despite observable differences in locomotion patterning. However, **the discrete contribution of each CRN subnucleus to sensorimotor function in intact animals remains unresolved**, a gap directly relevant to the design of serotonergic restoration strategies following spinal cord injury. In the present study, we employ two complementary approaches to elucidate these contributions. **First**, using diphtheria toxin subunit A-mediated ablation of spinal-projecting 5-HT neurons in Tph2-iCre rats, we characterize the sensorimotor consequences of CRN 5-HT loss across behavioral assays including rotarod and plantar heat test. Second, we employ a bimodal chemogenetic strategy using subnucleus-targeted KORD and hM3Dq DREADDs to bidirectionally modulate the activity of discrete CRN populations, assessing locomotor output via **quantitative video kinematics** using a four-camera high-speed acquisition system. We anticipate that bidirectional modulation of ROb and RPa will produce dissociable kinematic signatures, and that subnucleus-specific perturbations will reveal functional distinctions not captured by lesion alone. **Together, these findings are expected to establish a subnucleus-resolved map of CRN contributions to spinal sensorimotor function, providing a mechanistic foundation for targeted serotonergic circuit interventions aimed at locomotor recovery after SCI.**

Disclosures: A. England: None. **G.M. Smith:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.01/AA10

Topic: F.08. Respiratory Regulation

Title: Operant Conditioning of Respiratory Rate in Rats

Authors: *M. KAWAMURA[1], N. MATSUMOTO[2,3], Y. IKEGAYA[2,3];
[1]the Univ. of Tokyo, Komae city, Tokyo, Japan; [2]Grad. Sch. of Pharmaceut. Sci., [3]Inst. for AI and Beyond, The Univ. of Tokyo, Tokyo, Japan

Abstract: Breathing is unique among physiological functions because it is indispensable for survival yet also subject to voluntary control. Although respiratory rhythm is generated automatically by distributed brainstem circuits, higher-order brain regions can adaptively modulate or override this activity to support behaviors such as vocalization and deliberate breath control. However, the neural mechanisms that enable such top-down regulation of an essential autonomic function remain largely unresolved.
To examine the neural basis of voluntary breathing, we established an operant conditioning paradigm in which rats learned to intentionally regulate their breathing rate. In this task, rats were trained to increase their respiratory rate in response to an auditory cue and received a reward only when the change in breathing occurred immediately after cue onset. Using this paradigm, rats consistently acquired the task and achieved success rates above 80%, demonstrating that rodents can learn to regulate breathing in a goal-directed manner.
This work establishes a robust rodent model for investigating how cortical motor planning interacts with evolutionarily conserved respiratory rhythm generators, and positions breathing as a powerful model system for understanding the interface between voluntary action and autonomic regulation.

Disclosures: M. Kawamura: None. **N. Matsumoto:** None. **Y. Ikegaya:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.03/AA12

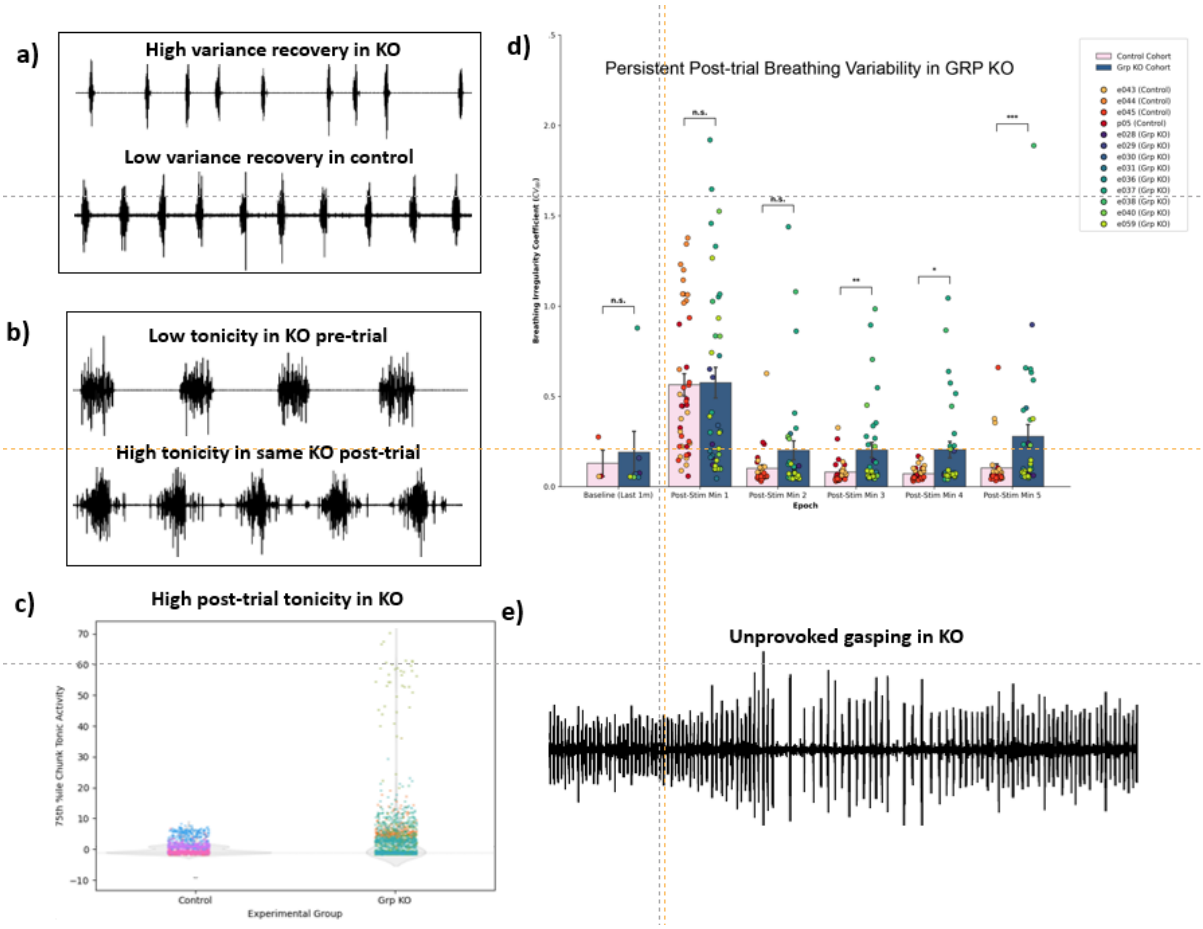
Topic: F.08. Respiratory Regulation

Support: R01HL126523
R01HL144801
F32NS143860

Title: The role of Grp in gasping and autoresuscitation

Authors: *R. B. BUDDE, L. PASCUAL, J. M. RAMIREZ;
Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA

Abstract: Rationale: The respiratory medulla represents a large dynamic neural network which must reconfigure between different rhythmic states to accomplish different behaviors. Gasping is a fundamental life saving reflex in response to extreme hypoxia and represents a dramatic reconfiguration of medullary dynamics. In this study we explore the role of the neuromodulator Grp in gasping dynamics.
Methods: We anesthetize mice with urethane and subject them to gasping trials. We compare healthy controls (n=6) and global Grp knockout (n=8). Here we report cardiorespiratory metrics. We have collected but not yet analyzed Neuropixel data from medullary respiratory sites.
Results: Baseline cardiorespiratory metrics are not different between controls and Grp KO prior to the first respiratory trial. Controls recover easily from respiratory trials never die from them. Conversely, all Grp KO show significant respiratory impairment after a gasping trial, and 6/8 of these animals die following a trial which should be survived. 4/8 Grp KO show gradual dramatic diaphragm reduction after the trial, ending in fatal gasping. 4/8 Grp KO show periods of significant respiratory rate instability, including de novo apnea and gasping with no stimulus. 5/8 Grp KO show high diaphragm tonicity after the trials. In fatal trials, the time from trial to death was 14.9 ± 19.8 minutes - suggesting, for some animals, a distinct gap between stimulus and death. We also observed arrhythmia in 5/8 Grp KO which are never observed in controls. Our preliminary data suggest focal Grp blockage can produce similar effects to the global knockout.
Conclusions: These data suggest that Grp KO does not obviously impact baseline eupnea, possibly has a minor effect on the acute gasping and recovery phase (1-2 minutes), and has a dramatic role in the extended recovery phase (3 minutes and beyond).
Figure 1: a) Grp KO respiration is high variance after trials b) Grp KO acquire diaphragm tonicity after trials c) all animals comparison of variance, d) all animals comparison of tonicity e) example de novo gasping period in KO (no stimulus)



Disclosures: R.B. Budde: None. **L. Pascual:** None. **J.M. Ramirez:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.04/AA13

Topic: F.08. Respiratory Regulation

Support: International Rett Syndrome Foundation

Title: Role of Glutamatergic Mecp2 Deficiency in Swallow-breathing Dysfunction in a Mouse Model of Rett Syndrome

Authors: *A. C. SWEENEY[1], P. NOGUERA GOMEZ[2], A. HUFF[3];
[1]Anesthesiol. and Critical Care Med., [3]Anesthesiol. and CCM, [2]The George Washington Univ., Washington, DC

Abstract: Swallowing, both for nutrition and airway protection, is profoundly impaired in children with Rett Syndrome (RTT), an x-linked neurodevelopmental disorder caused by mutations in the methyl-CpG-binding protein 2 (MECP2) gene. Difficulty swallowing (dysphagia) has been reported in approximately 43% of individuals with RTT, while aspiration of food, liquid, or mucus—often leading to recurrent aspiration pneumonia—occurs in 67-94% of affected children. Oliveira et al. demonstrated that Mecp2-deficient mice exhibit impaired submental muscle activity and reduced cholinergic immunoreactivity in the brainstem, contributing to deficits in swallowing, breathing, and swallow-breathing coordination that likely underlie premature mortality. These findings suggest that Mecp2-deficient mice on a C57Bl/6 background recapitulate key features of RTT-related swallow-breathing dysfunction. The swallow pattern generator has historically been localized to glutamatergic neurons within the Nucleus of the Solitary Tract. Meng et al. reported that Mecp2-deficiency in glutamatergic neurons results in tremors, anxiety-like, and seizure-like activity; however, its effect on swallow generation and breathing coordination remains unknown. We hypothesize that Mecp2 deficiency in Vglut2-expressing neurons impairs swallow generation and disrupts swallow-breathing coordination. To test this, both male and female Mecp2 Vglut2 conditional knockout (Vglut2cKO) mice were studied. Swallows were elicited in freely breathing, urethane-anesthetized mice via oral water delivery. Swallow and breathing activity were recorded using monopolar suction electrodes placed on the hypoglossal (XII) and vagus (X) nerves, along with bipolar hook wire electrodes in the submental complex, laryngeal complex, and costal diaphragm muscles. Post-hoc histological analysis, including Vglut2 immunostaining, will be used to verify targeting and assess glutamatergic neuron integrity in the brainstem. This study will define the contribution of glutamatergic Mecp2 deficiency to swallow-breathing dysfunction and provide mechanistic insight into the neural circuit disruptions underlying dysphagia in RTT.

Disclosures: A.C. Sweeney: None. **P. Noguera Gomez:** None. **A. Huff:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.05/AA14

Topic: F.08. Respiratory Regulation

Support: International Rett Syndrome Foundation

Title: Influence of Genetic Background on Swallow-Breathing Activity in Mecp2-deficient mice.

Authors: *P. NOGUERA GOMEZ, A. SWEENEY, A. HUFF;
Anesthesiol. and Critical Care Med., The George Washington Univ., Washington, DC

Abstract: Genetic background significantly influences phenotypic presentation in *Mecp2*-deficient mice. Guy et al. demonstrated that male Mecp2 knockout (KO) mice on a C57Bl/6

background exhibit rapid weight loss prior to death, whereas males on a 129 background are significantly heavier than wild-type controls. Oliveira et al. further showed that both male and female Mecp2-deficient mice on a C57Bl/6 background display impaired submental muscle activity and reduced cholinergic immunoreactivity in the brainstem, contributing to deficits in swallowing, breathing, and swallow-breathing coordination that likely underlie premature death. These findings suggest that Mecp2-deficient mice on a C57Bl/6 background recapitulate key features of swallow-breathing dysfunction observed in Rett Syndrome. However, whether similar impairments occur in Mecp2-deficient mice on a 129 background remains unknown. We hypothesize that Mecp2-deficient mice on a 129 background do not exhibit swallow-breathing impairments comparable to those seen on the C57Bl/6 background, and therefore may not model Rett Syndrome-related dysphagia effectively. To test this, both male and female Mecp2-deficient mice on a 129 background and their wild-type littermates were studied. Swallows were elicited in freely breathing, urethane-anesthetized mice via oral water delivery. Swallow and breathing activity were recorded using monopolar suction electrodes placed on the hypoglossal (XII) and vagus (X) nerves, along with bipolar hook wire electrodes in the submental complex, thyrohyoid, laryngeal complex, and costal diaphragm muscles. Post-hoc histological analysis, including choline acetyltransferase (ChAT) immunostaining, will be used to assess cholinergic neuron integrity in the brainstem.

Disclosures: P. Noguera Gomez: None. **A. Sweeney:** None. **A. Huff:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.06/AA15

Topic: F.08. Respiratory Regulation

Support: R01HL169679
R01DA061412
R01HL163965

Title: Fentanyl Disrupts Respiratory Motor Coordination Beyond Ventilatory Depression

Authors: *J. SOTO[1], B. M. BROWE[1], A. J. GARCIA, III[2], S. WEE[1], G. FISHER[3], W. SHARP[1], Y. FANG[1];
[1]Univ. of Chicago, Chicago, IL; [2]Emergency Med., The Univ. of Chicago, Chicago, IL; [3]Novartis, Berkeley, CA

Abstract: Fentanyl overdose mortality is widely attributed to ventilatory depression, yet its impact on respiratory motor dysfunction is not fully defined. Fentanyl overdose also produces tonic diaphragmatic activation manifesting as elevated expiratory-phase EMG activity. This represents a departure from the normal restriction of diaphragmatic activity to inspiration and may reflect phase-specific dysregulation that produces disordered respiratory activity. Here, we

sought to resolve whether phasic changes in diaphragm EMG correspond with hemi-diaphragmatic discoordination dissociable from generalized muscle tonicity. In urethane-anesthetized adult mice, diaphragm EMG and ventilatory flow were recorded at baseline, during fentanyl, and following naloxone reversal. Fentanyl produced two temporally distinct phases: an early phase of maximal ventilatory depression with preserved phasic diaphragm activity, and a late phase of increased respiratory variability with partial rebound in ventilation, diaphragm activation in the expiratory phase, and reduced bilateral diaphragm coordination. Aberrant diaphragm activity, both expiratory EMG elevation and hemi-diaphragm discoordination, was abolished during gasping evoked by severe hypoxia. Furthermore, carotid body denervation eliminated expiratory phase EMG elevation but did not prevent hemi-diaphragm discoordination or respiratory instability. Consistent with a loss in respiratory motor coordination, bilateral preBötzinger complex burst-amplitude coordination was disrupted by μ-OPR agonism. Fiber photometry further revealed that locus coeruleus activity paralleled changes in ventilation, with discrete bursts transiently stimulating breathing without altering diaphragm tonicity. These data dissociate two mechanistically distinct components of fentanyl-induced respiratory dysfunction beyond depression: 1) tonic diaphragm activation requiring carotid body afferent input, and 2) bilateral diaphragm discoordination driven by μ-OPR mediated premotor disruption. Based on these findings, we propose fentanyl overdose is a multidimensional syndrome extending beyond canonically described respiratory depression to encompass active disruption of respiratory motor coordination.

Disclosures: J. Soto: None. **B.M. Browe:** None. **A.J. Garcia:** None. **S. Wee:** None. **G. Fisher:** None. **W. Sharp:** None. **Y. Fang:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.07/AA16

Topic: F.08. Respiratory Regulation

Support: International Rett Syndrome Foundation

Title: Breathing and Drinking Behavior in a Mecp2-deficient Mouse Model of Rett Syndrome.

Authors: *F. ALDOUSARI, A. SWEENEY, A. HUFF;
Anesthesiol. and Critical Care Med., The George Washington Univ., Washington, DC

Abstract: Rett Syndrome (RTT) is a rare x-linked neurological disorder primarily caused by MECP2 gene mutations and is characterized by disruption in breathing and feeding. Difficulty swallowing (dysphagia) arises from impaired muscle function and/or poor coordination with breathing, increasing the risk of aspiration pneumonia—a leading cause of mortality. *Mecp2*-deficient male and female mice on a C57Bl/6 background exhibit swallowing impairments similar to those observed in humans, likely due to deficits in cholinergic swallow-related

motoneurons that weaken muscles and compromise airway protection. However, because prior studies primarily assessed swallow activity under anesthesia, feeding and drinking behaviors in awake RTT mice remain poorly understood. Approximately 62% of children with RTT experience prolonged feeding times, often due to impaired drinking and chewing associated with poor tongue control and ineffective bolus formation. Although human-like neuromuscular deficits have been characterized in *Mecp2*-deficient mice, it remains unclear whether these mice exhibit comparable feeding and drinking phenotypes or how these behaviors interact with breathing. We hypothesize that Mecp2-deficient mice on a C57Bl/6 background display altered breathing and licking patterns during drinking, leading to increased occurrence of aspiration-related reflexes compared to wild-type (WT) littermates. To test this, freely behaving male and female *Mecp2*-deficient and WT littermates were evaluated during 10-minute drinking sessions in a whole-body plethysmography chamber. Breathing patterns were assessed in conjunction with licking behavior. Post-hoc histological analysis, including choline acetyltransferase (ChAT) immunostaining, will be used to assess hypoglossal motoneuron integrity. This study will define the extent to which this RTT mouse model recapitulates feeding-related dysfunction and will inform its utility for future mechanistic and translational investigation of airway protection.

Disclosures: F. Aldousari: None. **A. Sweeney:** None. **A. Huff:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.08/AA17

Topic: F.08. Respiratory Regulation

Support: F31 HL176159
R01 HL108609
T32 GM148379
R01 HL148004

Title: The Retrotrapezoid nucleus undergoes reversible remodeling in response to chronic hypercapnic exposure

Authors: *R. CLEMENTS[1], A. PEREIRA[1], K. LI[1], G. SOUZA[2,1], M. PARANDEH[1], S. SAOUD[1], T. J. HOLT[3], S. M. BACA[1], S. B. ABBOTT[1], D. A. BAYLISS[1];
[1]Pharmacol., [3]Biol., [2]Univ. of Virginia, Charlottesville, VA

Abstract: The retrotrapezoid nucleus (RTN) functions as the principal central respiratory chemoreceptor and provides excitatory drive to increase ventilation in response to arterial CO_2 (hypercapnia), a response known as the hypercapnic ventilatory response (HCVR). The HCVR is critical for maintaining proper blood gas homeostasis. Chronic hypercapnia is a feature of several respiratory disorders. Clinical reports indicate that patients with chronic hypercapnia have a diminished HCVR and worsened clinical outcomes, yet the effects of sustained hypercapnia on

RTN function remain unclear. We hypothesized that chronic hypercapnia induces adaptive changes within RTN neurons. To test this hypothesis, adult C57BL6-J mice were exposed to chronic CO_2 (8-10%) for two to four weeks and the HCVR was assessed pre- and post-exposure using whole-body plethysmography. RTN activation during acute CO_2 challenge was determined using RNAScope to label cells expressing c-Fos mRNA. The functional contribution of RTN neurons to the HCVR was examined in real time using loss of function optogenetics. Chronic hypercapnia produced a significant attenuation of the HCVR, resulting in an approximately 50% reduction in ventilatory responsiveness to acute CO_2 challenge compared with normocapnic controls. Consistent with this physiological adaptation, chronic hypercapnia significantly reduced CO_2-induced c-Fos expression within the RTN, indicating diminished RTN recruitment during acute CO_2 stimulation. Despite this loss of RTN activation to acute CO_2, optogenetic inhibition of RTN neurons further suppressed ventilation during acute CO_2 demonstrating that RTN neurons continue to contribute to the residual HCVR following chronic hypercapnic exposure. Importantly, both the HCVR and RTN activation in response to CO_2 recovered to control levels by one week following return to room air. These data indicate that the observed adaptations are reversible and do not reflect permanent loss of RTN function. These significant findings demonstrate that chronic hypercapnia induces robust but reversible adaptive changes within central respiratory chemoreceptor networks. While prolonged CO_2 exposure decreases RTN responsiveness and blunts the HCVR, RTN neurons remain functionally engaged in mediating residual chemoreflex responses. Ongoing studies are using whole-cell electrophysiology and RNA sequencing to determine the cellular and molecular mechanisms underlying this plasticity. **These results identify the RTN as a key site of dynamic central chemoreceptor adaptation** and provide new insight into the neural mechanisms that regulate breathing during chronic hypercapnic states.

Disclosures: R. Clements: None. **A. Pereira:** None. **G. Souza:** None. **M. Parandeh:** None. **S. Saoud:** None. **T.J. Holt:** None. **S.M. Baca:** None. **S.B. Abbott:** None. **D.A. Bayliss:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.09/AA18

Topic: F.08. Respiratory Regulation

Support: NIH HL108609

Title: Molecular Determinants for TASK-2 Channel Contributions to CO2/H+ Regulation of Retrotrapezoid Nucleus Neurons and Breathing

Authors: *A. BUDZYNSKA[1], K. LI[2], R. CLEMENTS[1], E. GONYE[3], D. A. BAYLISS[2]; [2]Pharmacol., [1]Univ. of Virginia, Charlottesville, VA; [3]Univ. of Richmond, Richmond, VA

Abstract: Brainstem retrotrapezoid nucleus (RTN) neurons are crucial chemosensors of CO2/H+ for breathing regulation. RTN dysfunction may contribute to impaired CO2 regulation of breathing in many respiratory disorders (e.g., congenital central hypoventilation syndrome, sudden infant death syndrome, chronic obstructive pulmonary disease). RTN neurons are defined by expression of Phox2b and Neuromedin B, along with the proton-activated G protein coupled receptor, GPR4, and the proton-inhibited background potassium channel, TASK-2, which are implicated as the likely intrinsic proton detectors in RTN neurons.
The goal of this project is to establish a molecular mechanism for TASK-2 contributions to RTN neuron chemosensitivity and CO2-regulated breathing; specifically, we test if the extracellular proton sensor (R224) and/or an intracellular proton sensor (K245) of TASK-2 is involved. To this end, we generated novel CRISPR-modified mouse models in which engineered point mutants (R224A, K245A) have disabled one of the proton sensing mechanisms. For in vivo physiology from conscious mice, we performed whole body plethysmography and blood gas measurements and use CO2-stimulated c-Fos expression as a surrogate for RTN activation in vivo. Our in vivo data suggest a possible role for both extracellular and intracellular proton sensing by TASK-2 since mice with either R224A or K245A mutations show blunted CO2-stimulated breathing, with little change in systemic acid-base status. Surprisingly, we find that CO2-stimulated c-Fos expression is preserved in both mouse lines, despite the blunted respiratory chemoreflex. In addition, by using in vitro patch clamp electrophysiology from RTN neurons in acute brainstem slices, we find a preeminent role for changes in extracellular pH on CO2 sensitivity. We are currently assessing CO2/H+ effects on mutated or wild type TASK-2 channel currents and RTN neuron excitability, while clamping extracellular or intracellular pH. Collectively, our data currently suggest that changes in both CO2/H+ sensing and excitability of RTN neurons may contribute to the blunted CO2-stimulated breathing in these TASK-2 mutant mouse lines.

Disclosures: A. Budzynska: None. **K. Li:** None. **R. Clements:** None. **E. Gonye:** None. **D.A. Bayliss:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.10/AA19

Topic: F.08. Respiratory Regulation

Support: R01 HL128970
R01 HL133100
R01 HL138932
AHA 24CDA1270910

Title: The effect of setmelanotide on opioid-induced respiratory depression in mice and rats

Authors: *N. WILLIAMS[1], M. ALEXIS RUIZ[3], O. AUNG[4], O. DERGACHEVA[5], J. ESCOBAR[6], D. S. MENDELOWITZ[5], V. POLOTSKY[5], M. R. AMORIM[2,7];
[2]Med., [1]The George Washington Univ., Washington, DC; [3]The George Washington Univ. Sch. of Med. and Hlth. Sci., Washington, DC; [4]Med. Col. of Wisconsin, Milwaukee, WI; [5]George Washington Univ., Washington, DC; [6]George Washington Univ., Washington D. C., DC; [7]Med. Sch. of Ribeirão Preto, Sao Paulo, Brazil

Abstract: The primary cause of death associated with opioids is opioid-induced respiratory depression (OIRD) and obesity is a major risk factor that increases mortality. Naloxone is used to reverse OIRD, but this drug is a competitive antagonist of μ-opioid receptor (MOR) and reverses analgesia, which limits its therapeutic use. Alternative non-opioid receptor antagonist-based approaches to OIRD treatment and prevention are needed. Previous studies suggest that melanocortin 4 receptor pathway (MC4R), which is implicated in body weight regulation, may impact control of breathing. An MC4R agonist, setmelanotide (SET), is approved by FDA to treat genetic obesity caused by abnormal melanocortin and leptin signaling. We hypothesized that SET can treat OIRD in mice. C57BL/6J male mice with diet-induced obesity were treated with IP morphine (10 mg/kg) and then 15 min later with either SET (1 mg/kg IP) or vehicle VEH (IP) in a random order. Breathing was recorded by barometric plethysmography, and pain sensitivity was measured by the tail-flick test. In mice with OIRD, SET induced a 3-fold reduction of the apnea index, from 67 ± 7 to 22 ± 4 events per hour ($p < 0.001$), and decreased apnea duration as compared to the VEH treatment. SET increased respiratory rate from 102 ± 4.5 to 130 ± 5.6 breaths per minute ($p < 0.05$). SET did not affect opioid analgesia. Photostimulation of MC4R+ ChR2-expressing fibers in the parafacial region elicited short-latency postsynaptic current in pre-motoneurons projecting to the phrenic motoneurons in the C3-C4 ventral horns of the spinal cord. In conclusion, SET effectively treated OIRD by increasing respiratory rate and inducing a significant decrease in the number of apneas without decreasing analgesia. Parafacial MC4R (+) neurons are a likely site of respiratory effects of SET.

Disclosures: N. Williams: None. **M. Alexis Ruiz:** None. **O. Aung:** None. **O. Dergacheva:** None. **J. Escobar:** None. **D.S. Mendelowitz:** None. **V. Polotsky:** None. **M.R. Amorim:** None.

Poster

PSTR019: Respiratory Control

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.11/AA20

Topic: F.08. Respiratory Regulation

Support: NIH HL149630
HMS Deans Postdoctoral Research Fellowship

Title: Orexin neuron chemoactivation improves the ventilatory response to hypercapnia in a mouse model of obesity hypoventilation syndrome

Authors: *B. M. MILLA, T. E. SCAMMELL;
Neurol., Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: Obesity Hypoventilation Syndrome (OHS) is characterized by impaired respiratory mechanics due to increased upper airway resistance, decreased chest wall compliance, and impaired central ventilatory drive to CO2. Consequently, OHS patients develop chronic daytime hypercapnia that worsens during sleep when ventilatory drive is reduced. Current treatments for OHS are limited, warranting investigation of new therapies. Orexin neurons control wake/sleep behavior and project to brainstem respiratory centers to regulate breathing. We hypothesized that chemoactivation of orexin neurons would improve the hypercapnic ventilatory response (HCVR) in diet induced obesity (DIO) mice, a model of OHS. We studied DIO orexin-cre mice which were fed a 60% high fat diet and lean orexin-cre mice which were fed normal chow. We stereotaxically injected the orexin field with AAV8-hsyn-DIO-hM3Dq-mCherry and surgically implanted EEG/EMG headstages. We measured respiratory activity across quiet wake and NREM sleep using whole body plethysmography chambers integrated with EEG/EMG. We exposed mice to ascending hypercapnia mixtures of 0, 3, 5, 8% CO2, with 50% oxygen, balanced with nitrogen (one hour of each gas). Treatment with CNO (0.3 mg/kg IP) increased the latency to enter REM sleep. With saline, DIO mice showed a blunted HCVR compared to lean mice. In lean mice, chemoactivation of the orexin neurons increased the frequency, tidal volume, and minute ventilation at moderate to high levels of CO2 during quiet wakefulness and NREM sleep. Importantly, in DIO mice, chemoactivation increased tidal volume and minute ventilation across high CO2 levels during quiet wake and NREM sleep. These findings demonstrate that activation of the orexin neurons improves the hypercapnic ventilatory response in a mouse model of OHS. These results suggest that enhancing orexin signaling may improve hypoventilation in Obesity Hypoventilation Syndrome.

Disclosures: B.M. Milla: None. **T.E. Scammell:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.01/AA21

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NSF Grant NSF2336906
NSF Grant NSF2336907

Title: Neuroplasticity of motherhood: insular cortex perineuronal net expression levels across pregnancy and postpartum

Authors: *B. HAMMOND[1], H. DOBSON[2], M. GOSSARD[3], D. NAREDO[3], K. KRISHNAN[3], J. S. LONSTEIN[2,1];

[1]Neurosci. Program, [2]Psychology, Michigan State Univ., East Lansing, MI; [3]Biochem. & Cell. and Mol. Biol., Univ. of Tennessee At Knoxville, Knoxville, TN

Abstract: For female mammals, the transition to parenthood requires tremendous physiological and behavioral changes. Arising during pregnancy and continuing through the postpartum period, one such change is the widespread neuroplasticity that occurs as macro-anatomical and micro-architectural modifications that cause critical alterations in females' behavior necessary for infant caregiving. The insular cortex, known for roles in social communication, integrative sensory processing, salience processing, and interoception, exhibits neuroplastic changes during pregnancy and the postpartum period in both humans and rodents. Perineuronal nets (PNNs)—which are extracellular matrix structures composed of proteoglycans such as brevican, aggrecan, and phosphacan—encompass the soma and proximal dendrites of neurons and restrict synaptic connections. PNN expression in the insula is sensitive to the hormonal shifts across the estrous cycle; however, insular PNN fluctuations across pregnancy and postpartum have never been investigated. In this study, real-time quantitative polymerase chain reaction (RT-qPCR) and immunohistochemistry were used to examine the expression of three PNN proteoglycans, as well as full PNNs, in the insula across six reproductive timepoints (diestrus virgin; pregnancy days 10 and 20; postpartum days 0, 7/8, and 19/20) in female rats. Results from the RT-qPCR analysis showed that mRNA expression of brevican, but not phosphacan or aggrecan, was significantly higher in the posterior (but not anterior) insula in all the pregnant and postpartum groups relative to the virgin females. However, immunohistochemical staining of PNNs collapsed across the entire insula showed more high-intensity PNNs at parturition and postpartum day 19 when compared to other time points, with specific changes occurring in the granular, dysgranular, and agranular insular cortices. These differences between PNN mRNAs and proteins across reproduction may be due to changes in other PNN components not yet investigated here. These and other neuroplastic changes in the insula may be essential for the adaptation required for maternal sensory processing of pup cues and thus, mother-infant interactions.

Disclosures: B. Hammond: None. **H. Dobson:** None. **M. Gossard:** None. **D. Naredo:** None. **K. Krishnan:** None. **J.S. Lonstein:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.02/AA22

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NSF Grant NSF2336906
NSF Grant NSF2336907

Title: Motherhood alters perineuronal net levels in the primary somatosensory cortex

Authors: *H. R. DOBSON[1], B. V. HAMMOND[2], D. NAREDO[3], M. GOSSARD[3], K. KRISHNAN[3], J. S. LONSTEIN[1];
[1]Psychology, [2]Michigan State Univ., East Lansing, MI; [3]Biochem. & Cell. and Mol. Biol., Univ. of Tennessee At Knoxville, Knoxville, TN

Abstract: Pregnancy and motherhood induce widespread plasticity in the female brain that is imperative for the initiation and maintenance of maternal caregiving behaviors. These changes are known to occur in cortical regions responsible for processing sensory cues from young, including the somatosensory cortex (S1). Although maternal caregiving is typically a multisensory experience, somatosensation is the only sensory modality singularly indispensable for normal maternal behavior toward pups in laboratory rats. However, the mechanisms underlying motherhood-associated neuroplasticity in the S1 have rarely been studied. Perineuronal nets (PNNs) are extracellular matrix structures that surround neuronal cell bodies and have been demonstrated to modulate neuroplasticity in various contexts, including in some brain regions involved in maternal caregiving. We used real-time quantitative polymerase chain reaction (RT-qPCR) to examine the gene expression of three PNN proteoglycan components (brevican, phosphacan, aggrecan) and immunohistochemistry with *Wisteria floribunda* agglutinin (WFA) to visualize the number of high-intensity PNNs in the S1 across female reproduction in rats. We focused on the S1 representations of the mystacial pads (barrel field) and trunk of female rats sacrificed across six reproductive timepoints (diestrous virgin [DV]; pregnancy [P] days 10 and 20; postpartum [PP] days 0, 7/8, and 19/20). The RT-qPCR analyses revealed that *brevican* mRNA levels were higher in all pregnant and postpartum rat groups compared to DVs in the S1 barrel field, but higher only in the postpartum groups in the S1 trunk. In contrast, *phosphacan* mRNA levels were lower in pregnant and recently parturient rats relative to DVs, returning to virgin-like levels in the PP19/20 group, and only in the barrel field. Immunohistochemistry demonstrated that the numbers of high-intensity PNNs in both S1 regions were lowest in late pregnancy (P20) and returned to levels comparable to DVs in late postpartum (PP19/20). Notably, this pattern resembled that observed for *phosphacan* mRNA in the S1 barrel field, suggesting that S1 barrel field PNNs transiently degrade to support plasticity in response to the hormonal and sensory experiences of motherhood, then reform late postpartum to stabilize S1 barrel field circuit remodeling. Thus, PNNs may be vital regulators of somatosensory plasticity across female reproduction and motherhood, with implications for better understanding the tactile regulation of maternal caregiving behaviors in both animals and women.

Disclosures: H.R. Dobson: None. **B.V. Hammond:** None. **D. Naredo:** None. **M. Gossard:** None. **K. Krishnan:** None. **J.S. Lonstein:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.03/AA23

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Keck Undergraduate Research Experience (KURE Incubator)
NIH T34 U-RISE
CSULB ORED SFG/MG

Title: Dopamine and Orphanin FQ/nociceptin co-transmission in the arcuate nucleus of the hypothalamus may act on β-endorphin neurons to facilitate sexual receptivity in female rats

Authors: *C. KARR, K. SINCHAK;
Biol Sci., California State University, Long Beach, Long Beach, CA

Abstract: We hypothesize that progesterone acts in multiple types of neurons in the arcuate nucleus of the hypothalamus (ARH) to rapidly to facilitate lordosis in ovariectomized (OVX) rats primed with 2ug of 17β-estradiol benzoate (EB). The actions of progesterone inhibit the output of ARH β-endorphin (β-END) neurons that project to the medial preoptic nucleus (MPN) through direct and presynaptic actions. Progesterone acts directly on ARH β-END neurons through an interdependent signaling complex composed of dopamine receptor 1 (D1), Src family kinase (SRC), and progesterone receptors (PR). Presynaptically, progesterone receptors are located in ARH dopaminergic and orphanin FQ/nociceptin (OFQ/N) ARH neurons. Both dopamine, a small molecule neurotransmitter, and OFQ/N, a neuropeptide, facilitate sexual receptivity by inhibiting ARH β-END neurons, suggesting OFQ/N and dopamine may be expressed in the same neuron regulated by progesterone. Thus, we tested the hypothesis that OFQ/N and dopamine are colocalized in a subpopulation of ARH neurons using double label immunohistochemistry. Brain sections containing ARH from EB and oil treated OVX rats were double labeled for OFQ/N and tyrosine hydroxylase (TH: a biomarker for dopaminergic ARH neurons) using FITC and TRITC conjugated secondary antibodies. A subpopulation of ARH neurons was observed to have colocalized immunopositive extranuclear staining for OFQ/N and TH. These results indicate that progesterone regulates ARH neurons that express and release both OFQ/N and dopamine to inhibit β-END release and facilitate lordosis. It is unclear whether this population of dopamine-OFQ/N neurons are solely responsible for progesterone actions or in combination with individual populations of OFQ/N and dopaminergic neurons.

Disclosures: C. Karr: None. **K. Sinchak:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.04/AA24

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Keck Undergraduate Research Experience (KURE Incubator)
CSULB ORED SFG/MG

Title: β-arrestin-mediated dopamine receptor-1 (D1) signaling acts through Src kinase in the ARH to regulate sexual receptivity in female rats.

Authors: *M. TAO, G. LOMELI, K. SINCHAK;
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Abstract: Progesterone rapidly facilitates lordosis in ovariectomized rats primed with 17β-estradiol benzoate (EB; 2 μg) via activation of progesterone receptor-B (PR-B) in the arcuate nucleus of the hypothalamus (ARH). Progesterone inhibits ARH β-endorphin neurons that project to the medial preoptic nucleus (MPN) to facilitate lordosis. Although PR-B are nuclear transcription factors, membrane-associated PR-B mediate progesterone rapid facilitation of lordosis. Like progesterone, activation of either Src kinase (Src) or dopamine receptor-1 (D1) in the ARH facilitates lordosis. Antagonism of either PR-B, Src, or D1 blocks the facilitation of lordosis by the other two. Previous studies from our laboratory demonstrated that PR-B, Src, and D1 signaling converge in ARH β-endorphin neurons that project to the MPN. Co-immunoprecipitation findings indicate that PR-B forms complexes with Src. However, we failed to detect direct interactions between D1 receptors and PR-Src complexes, suggesting the involvement of an intermediary protein. The D1 being a GPCR suggested a G-protein mediated D1 receptor interaction with Src. Yet, double-label immunohistochemistry revealed minimal Src and Gαs-protein colocalization. D1 can also signal through β-Arrestin 2, and β-Arrestin 2 can activate Src. Therefore, we tested the hypothesis that β-Arrestin 2 mediates D1 receptor signaling with PR-Src complexes to regulate sexual receptivity. Double-label immunohistochemistry was used to assess colocalization of Src and β-Arrestin 2, and D1 and β-Arrestin 2 in the ARH. We observed subpopulations of ARH neurons that were immunopositive for Src and β-Arrestin 2 as well as D1 and β-Arrestin 2, indicating the potential of D1, β-Arrestin 2, Src interactions and complex formation. Additionally, EB-primed ovariectomized rats received sequential ARH infusions of the β-Arrestin inhibitor, barbadin, followed 15 min later by a Src activator (47.5 h after EB priming). Sexual receptivity was assessed 30 min later by lordosis quotient (LQ). Barbadin significantly attenuated Src activator-induced sexual receptivity (LQ = 18.8 +/- 8.7) compared with saline-treated controls (70.0 +/- 10.8; $p = 0.035$, paired t-test). These findings support the hypothesis that D1 signaling through β-Arrestin 2 associates with the D1-PR-Src signaling complex in ARH β-endorphin neurons to facilitate sexual receptivity.

Disclosures: M. Tao: None. **G. Lomeli:** None. **K. Sinchak:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR020.05/AA25

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH P51 OD011107
NIH R01 MH125411
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Good Nature Institute

Title: Interplays between daytime activity patterns, sleep quality, and neurotrophins in a pair bonding primate

Authors: *L. A. MECKLER[1], M. SOSNOWSKI[2], K. L. BALES[2];
[1]Biol. Psychology, [2]California Natl. Primate Res. Ctr., Univ. of California, Davis, Davis, CA

Abstract: Pair bonds are uniquely strong, selective social bonds that are relatively rare in mammals. Their formation and maintenance in dynamic environmental and social environments require substantial neural flexibility. Brain-derived neurotrophic factor (BDNF) is a promising modulating candidate for flexibility. Recently, we demonstrated that serum BDNF is measurable in coppery titi monkeys (*Plecturocebus cupreus*), an established, non-traditional, pair bonding non-human primate model. Serum BDNF concentrations were higher in the morning than the evening ($\beta = 0.28$, $p = 0.045$) and declined with age ($\beta = -0.45$, $p = 0.027$), mirroring patterns seen in humans and rodents. These findings provided a foundation for investigating BDNF's role in the behavioral endocrinology of pair bonding. Using triaxial accelerometry, we next characterized daytime activity and nighttime sleep architecture in pair-housed titi monkeys. Mixed effects models revealed a strong effect of between-pair variation in correlated daytime activity (CDA) on individual nighttime sleep quality, whereas neither sex nor daily pair-level fluctuations in CDA predicted sleep outcomes. This finding suggests that stable, pair-level activity correlation, rather than transient activity fluctuations, provides specific benefits to sleep quality. Although prior work in humans has independently linked being in a committed romantic relationship and sleep to peripheral BDNF, neither CDA ($\beta = -0.18$, $p = 0.91$) nor sleep quality ($\beta = -0.01$, $p = 0.63$) significantly predicted serum BDNF in titi monkeys. The absence of effects may reflect species' differences in BDNF expression, that bond relevant BDNF dynamics operate over different timescales, or that bonding relevant BDNF expression fluctuates centrally, rather than peripherally. Further longitudinal and neurobiological studies will clarify the directional relationships between bonding dynamics, sleep quality, and BDNF expression in this model.

Disclosures: L.A. Meckler: None. **M. Sosnowski:** None. **K.L. Bales:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.06/AA26

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Howard Hughes Medical Institute
Howard Hughes Medical Institute Cech Fellowship
Harvard College Research Program
Tan Yang Center for Autism Research at Harvard funding the project "Neural control of instinctive social drive in wildtype and ASD mice"

Title: Family Matters: Probing the Functional Role of Cholinergic Inputs to the Hypothalamic Preoptic Area in Mouse Parenting Behavior

Authors: *L. L. LOEB, X. M. HAN, M. RAHMAN, H. KAPLAN, C. G. DULAC;
Mol. & Cell. Biol., Harvard Univ., Cambridge, MA

Abstract: Parenting is an instinctual mammalian behavior crucial for offspring survival, yet its molecular and circuit-level mechanisms remain incompletely understood. Previous work from our lab identified transcriptionally defined neuronal populations in the hypothalamic preoptic area (POA) regulating parenting and other innate behaviors in mice. One population, POAGal+/CalcR+ neurons, is activated in male and female parenting. Recent findings show maternal upregulation of the excitatory muscarinic acetylcholine receptor M3 (Chrm3) in POAGal+/CalcR+ neurons relative to virgin females, suggesting that cholinergic inputs may regulate parenting. This possibility is supported by pharmacological disruption of cholinergic signaling impairing paternal care in mice, genetic studies of postpartum depression implicating cholinergic neuronal populations, and acetylcholine regulating attention, sensory processing, and arousal—processes critical for parenting. However, the role of POA cholinergic inputs in parenting remains unknown. We investigated POA cholinergic signaling using anatomical mapping, pharmacological modulation of muscarinic signaling, and targeted chemogenetic inhibition of cholinergic projections during parenting assays. We detected cholinergic projections to the POA, primarily from the brainstem system, and found that inhibition enhanced parenting by shortening pup retrieval latency and increasing crouching and grooming (n=4). These findings suggest that cholinergic signaling exerts a net inhibitory influence on POA parenting circuits, potentially through local inhibitory mechanisms. Ongoing studies are defining the temporal dynamics and specific POA cell types recruited by cholinergic inputs during parenting. First, we are using genetically encoded acetylcholine sensors and in vivo fiber photometry in the POA (n=6) to monitor acetylcholine release during parenting. Second, we are combining microendoscopic imaging, spatial MERFISH, and pharmacological inhibition to identify parenting-related POA cell types recruited by cholinergic signaling. Third, to test these target candidates of cholinergic inputs, we are performing in situ hybridization for c-Fos and relevant cell markers in the POA following chemogenetic inhibition (n=3). Finally, to assess the broader relevance of this pathway, we are examining parenting in autism spectrum disorder and bipolar disorder models under pharmacological inhibition of acetylcholine signaling. Together, these ongoing studies aim to define how cholinergic signaling modulates parental behavior, advancing understanding of the neuromodulatory control of parenting.

Disclosures: L.L. Loeb: None. **X.M. Han:** None. **M. Rahman:** None. **H. Kaplan:** None. **C.G. Dulac:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.07/AA27

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: JSPS KAKENHI 22K06322

Title: Reproductive state and natural genetic variation regulate mating avoidance of C. elegans hermaphrodites

Authors: *S. SUO;
Dept. of Pharmacol., Saitama Med. Univ., Saitama, Japan

Abstract: In many animals, females modulate mate acceptance according to their reproductive state, yet the internal physiological signals that regulate such behaviors remain incompletely understood. In *Caenorhabditis elegans*, self-fertilizing hermaphrodites produce a limited number of self-sperm and can reproduce either by self-fertilization or by mating with males. Males actively seek hermaphrodites, whereas hermaphrodites display male-avoidance behavior and increase their speed upon contact with males. I previously showed that male-avoidance behavior is regulated by sperm status. Hermaphrodites of the standard wild-type strain N2 increased their locomotor speed upon contact with males, whereas sperm-deficient mutant hermaphrodites instead reduced their speed. This sperm-dependent behavioral regulation may allow hermaphrodites to prioritize self-reproduction when self-sperm are available, while promoting outcrossing when self-sperm are depleted. Interestingly, hermaphrodites that had already mated exhibited reduced male-avoidance. Male sperm are known to outcompete self-sperm within the reproductive tract. This post-mating suppression of avoidance may reflect a shift in reproductive priorities after acquisition of male-derived sperm. To examine the effect of natural genetic variation, I analyzed another wild isolate CB4856 (Hw). Unlike N2, unmated Hw hermaphrodites did not exhibit increased locomotor speed upon male contact. After mating with males, Hw hermaphrodites decreased speed upon male contact rather than increasing it. These results suggest that Hw hermaphrodites have a lower level of male avoidance and natural genetic variation affects the plasticity of male-avoidance behavior. Furthermore, cross-strain tests suggest that male-avoidance behavior is influenced by the genetic backgrounds of both males and hermaphrodites. Together, these results reveal natural variation in male-avoidance behavior, providing a tractable system to study the genetic mechanisms underlying reproductive-state-dependent behavioral plasticity.

Disclosures: S. Suo: None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.08/AA28

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: The Science and Technology Innovation (STI) 2030-Major Projects (2025ZD0214900- 02)
The National Natural Science Foundation of China (82130032)

Title: A neural basis for maternal cleaning at birth

Authors: *G. LI;
Fudan university, Shanghai, China

Abstract: Mammalian birth triggers highly conserved maternal cleaning behaviors, including neonate licking and afterbirth ingestion, that clean, stimulate, and revive the newborn. Yet the neural mechanisms underlying these life-sustaining behaviors remain poorly understood. Here, we show that corticotropin-releasing hormone (CRH)-expressing neurons in the central amygdala (CeA^{CRH} neurons) differentially encode neonate licking and afterbirth ingestion. Single-unit recordings further reveal dynamic remapping of CeA^{CRH} neuronal ensembles across sequential components of maternal cleaning. Silencing CeA^{CRH} neurons disrupted maternal cleaning, delayed neonatal thoracic movement, and compromised offspring survival. Conversely, activation of CeA^{CRH} neurons in virgin females was sufficient to elicit licking of cesarean-delivered newborns and ingestion of afterbirth tissues, enhancing neonatal recovery while conferring positive reinforcing properties on maternal cleaning. Notably, dams persisted in rescuing and cleaning their newborns despite physical restraint, while maternal cleaning remained largely preserved in *Oxt* knockout dams. Together, our findings reveal an amygdalar hub that orchestrates a critical suite of maternal behaviors at birth, ensuring neonatal survival during the transition to extrauterine life.

Disclosures: G. Li: None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR020.09/AA29

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Vermont Biomedical Research Network P20RR16462
Middlebury College

Title: Effects of sexual experience on adult neurogenesis, learning, and memory among adult male rats.

Authors: *M. D. SPRITZER[1], L. D. MILLIGAN[2], H. WANG[2], L. M. SHULMAN[2];
[1]Biol., [2]Program in Neurosci., Middlebury Col., Middlebury, VT

Abstract: Past evidence suggests that sexual interactions can enhance adult neurogenesis and improve some forms of cognition. We assessed the potential effects of sexual interactions upon

spatial memory, reversal learning, and different stages of adult neurogenesis. In our first experiment, male Long-Evans rats (N = 12/group) were separated into three treatment groups that received 30 min sexual interactions with estrus females on the first day of the experiment, on the final twelve days of the experiment, or on all sixteen days of the experiment, while control males never engaged in sexual interactions. BrdU injections were given on the first day of the experiment, and animals were euthanized on day 17, one day after the final sexual interaction. BrdU-labeled cells were counted in the granule cell layer and subgranular zone to quantify the survival of newly proliferated cells. Repeated sexual interactions (12 or 16 days) caused a significant decrease in the number of BrdU-labeled cells in the ventral, but not dorsal, portion of the dentate gyrus relative to the control group. Fluorescent double-labeling of tissue (BrdU and NeuN) followed by confocal microscopy was used to assess neuronal development, and preliminary analysis indicates that sexual interactions had no effect on the percentage new cells that developed into neurons. We next compared the effects of a single sexual interaction on cell proliferation (24 h after BrdU injection) among both Sprague-Dawley and Long-Evans rats (n = 12/group). There was a nearly significant increase in cell proliferation among rats that engaged in a single sexual interaction but no effect of rat strain. Subsequent experiments were conducted to test spatial memory and reversal learning in male Long-Evans rats (n = 12/group) exposed to sexually receptive females for 30 min periods daily for two weeks. During the last week of sexual interactions, memory testing was conducted on the same day that sexual interactions occurred. Sexual experience had no effect on acquisition or retention on the Morris water maze but did cause a significant increase in perseverative behavior during a reversal learning trial in the water maze. In contrast, sexual experience had no significant effect on reversal learning assessed using a plus maze task. Overall, the results indicate that sexual interaction caused a modest increase in cell proliferation in the hippocampus, but this did not lead to a later increase in neurogenesis and that repeated daily sexual interactions actually decreased neurogenesis in the ventral hippocampus. Additionally, sexual experience had no effect on spatial learning or reversal learning but did increase perseverative behavior.

Disclosures: M.D. Spritzer: None. **L.D. Milligan:** None. **H. Wang:** None. **L.M. Shulman:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR020.10/AA30

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: R-2025-1602-007

Title: Gestational hyperglycemia disrupts hypothalamic neuropeptide expression associated with maternal and emotional behaviors in Sprague-Dawley rats

Authors: *C. GONZÁLEZ GARCÍA[1], R. MERCADO[2], L. TORNER[3];
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Abstract: Maternal behavior is a complex set of caregiving actions that promote offspring survival and development and is regulated, in part, by the hypothalamic neuropeptides oxytocin (OXT), vasopressin (AVP), and corticotropin releasing hormone (CRH). Metabolic disorders such as gestational hyperglycemia may disrupt maternal care and alter the neuroendocrine mechanisms underlying maternal responsiveness. This study examined the effects of different levels of gestational hyperglycemia on maternal behavior and hypothalamic neuropeptide expression. Pregnant Sprague-Dawley rats (n=8/group) were assigned to five experimental groups: control (vehicle), streptozotocin (STZ) 25 mg/kg, 30 mg/kg, 40 mg/kg, and STZ 30 mg/kg followed by daily insulin treatment (1 IU) during the postpartum period. STZ was administered on gestational day 9. Glucose levels were monitored during gestation and postpartum. Maternal behavior was assessed on postpartum days 1-3 using six (30 min) daily observation sessions (five during the light phase and one during the dark phase). Additionally, behavioral tests included the elevated plus maze, open field, and forced swim tests. Hypothalamic OXT, AVP, and CRH levels were quantified by qPCR. STZ administration produced significant dose dependent increases in glucose concentrations compared with controls. Hyperglycemic dams showed dose-dependent impairments in maternal behavior, including reduced nursing, maternal care, arched-back nursing, and anogenital licking. Conversely, non-maternal behaviors increased. The STZ 30 and 40 mg/kg groups also showed increased anxiety- and depressive-like behaviors in the elevated plus maze, open field, and forced swim tests. In parallel, hypothalamic OXT and AVP levels were significantly reduced in STZ-treated dams, whereas CRH levels remained unchanged. Importantly, postpartum insulin treatment normalized glycemic levels, prevented maternal behavioral deficits, and restored OXT and AVP levels to control-like levels. These findings demonstrate that gestational hyperglycemia disrupts maternal behavior and decreases hypothalamic OXT and AVP expression in proportion to the severity of the metabolic disturbance. Furthermore, the recovery of maternal behavior and neuropeptide expression following insulin treatment suggests that alterations in OXT- and AVP-mediated signaling may contribute to the maternal deficits induced by gestational hyperglycemia.

Disclosures: C. González García: None. **R. Mercado:** None. **L. Torner:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR020.11/AA31

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: R01 HD088411
U19 NS107616

U01 DA063565
R34 NS138066

Title: Mouse midwives: behavioral mechanisms that greatly improve maternal-infant survival

Authors: *V. J. IVAN[1], L. SCHUSTER[2], D. GILLY SUAREZ[3], A. CASLIN[1], S. WINOKUR[1], A. OSTLUND[1], R. J. HENDERSON[1], A. C. MAR[4], R. C. FROEMKE[5];
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[5]Otolaryngology, NYU Grossman Sch. of Med., New York, NY

Abstract: Oxytocin (OT) is an evolutionarily conserved neuropeptide that regulates mammalian reproduction and parental care, including uterine contractions during labor (Gimpl & Fahrenholz, 2001; Dulac et al., 2014; Froemke & Young, 2021). Mice lacking oxytocin receptors (OXTR KOs) exhibit impaired uterine contractility yet remain fertile (Takayanagi et al., 2005), raising questions about how disrupted OT signaling affects reproductive behavior (Berendzen et al., 2022). Given increasing rates of and disparities in maternal and infant mortality (CDC, 2025), it is critical to identify the physiological, behavioral, and social factors that promote successful childbirth.

Using a system we built for continuous monitoring of mouse family life (Schuster, Ivan et al., bioRxiv 2025), we compared maternal and pup survival outcomes of first-time pregnant OXTR KO females co-housed with wild-type (WT) dams vs outcomes of singly-housed pregnant OXTR KO females. When co-housed, WT dams actively assisted in labor, performing 'midwife' behaviors such as extracting stuck pups with their mouth or paws and cleaning newborn pups of amniotic sacs. Solitary OXTR KOs had low survival rates (1/7 surviving labor; 0% pup survival). Assistance from WT midwives resulted in a 9/10 survival rate for OXTR KOs and a 90.2% pup survival rate. Co-housing with the paternal male or a virgin female was less effective with ~50% of dams surviving but 0% pup survival. Further, males and virgins spent less time attending to the dam in labor and these dams experienced longer labor durations. Midwifery behaviors were also observed in WT dams paired with WT females in labor (N=6) and were associated with improved litter survival rates.

To investigate the neural basis of midwifery behavior, we suppressed parvocellular PVN OT neurons in dams using inhibitory chemogenetics in Ntng1-Cre × Oxt-Flp mice (N=4). Chronic suppression of OT release reduced the proportion of time midwives spent attending to laboring females and was associated with prolonged pup birth durations. We next expressed GCaMP8s in PVN OT neurons of OT-Cre dams (N=6) and performed fiber photometry during labor assistance. PVN OT activity increased around the onset of early midwifery bouts, suggesting recruitment of OT neurons during initial engagement with labor-related events. Across cohorts, greater proportions of attentive midwife behavior were associated with shorter individual pup birth durations. These findings identify cooperative maternal assistance as a powerful determinant of successful labor outcomes and suggest that PVN OT signaling is recruited during early midwifery experience to increase salience and sustain attentiveness.

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Poster

PSTR020: Sexual and Parental Circuits and Behaviors

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.12/AA32

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Carleton College

Title: Adult sexual motivation is not affected by pubertal suppression, but is altered by adult cross-sex hormone treatment in female Long-Evans rats

Authors: M. ITEGHETE[1], A. MENDEZ[1], M. FROST[1], T. R. BEASLEY[1], F. A. GUARRACI[2], *S. H. MEERTS[1];
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Abstract: Gonadotropin-releasing hormone agonist (GnRHa) prescriptions to delay puberty are increasing in an effort to prevent adverse effects on mental health in youth experiencing gender dysphoria. Some, but not all, individuals go on to take gender affirming hormone therapy (GAHT). Effects of pubertal suppression on adult sexual behavior, both when the GnRHa is discontinued and when GAHT follows the GnRHa, are poorly understood. Here, pubertal onset and adult sexual behavior was observed in gonadally intact female Long-Evans rats that were assigned to pubertal suppression or control with or without adult cross-sex hormone. Specifically, rats received one i.m. injection of leuprolide acetate for depot suspension (Lupron-Depot Ped 0.372 mg) or vehicle peripubertally (postnatal day (PD) 22-24). Four weeks after Lupron or vehicle rats received 0.45 mg testosterone enanthate (TE) or oil s.c. twice weekly. Final groups: Vehicle + Oil, Vehicle + TE, Lupron + Oil, Lupron + TE. Pubertal onset was measured by monitoring vaginal opening (VO) beginning 7 days after Lupron. Once VO occurred, vaginal cytology was observed daily to assess estrous cyclicity. At the end of the four week TE treatment, rats were tested for sexual motivation and behavior using the partner preference paradigm. Vehicle + Oil and Lupron + Oil rats exhibited estrous cyclicity, so were tested in proestrus. Vehicle + TE and Lupron + TE rats were tested on the afternoon of the final TE injection. The first phase of the test limited physical contact between the subject and the stimulus animals, allowing for only the transmission of auditory, visual, and olfactory cues (No Contact). The second phase of the test provided unlimited physical contact between the subject and the stimulus animals (Contact). Lupron significantly delayed VO, but all behavioral effects were due to adult TE. During No Contact the oil groups preferred the male, spending significantly more time with the stimulus male than the stimulus female. In contrast, the TE groups preferred the female, spending significantly more time with the stimulus female than the stimulus male. Both oil groups were fully receptive and received intromissions during the Contact phase. The Vehicle + TE group was fully receptive but the Lupron + TE group showed reduced receptivity. Of the TE rats that were receptive, 57% received intromissions during the contact phase. No differences in sensitivity to sexual stimulation were observed (i.e., contact-return latencies) but TE rats spent less time with the male, and exhibited more rejection behaviors and fewer proceptive behaviors. These results indicate that pausing puberty does not affect adult sexual motivation.

Disclosures: M. Iteghete: None. **A. Mendez:** None. **M. Frost:** None. **T.R. Beasley:** None. **F.A. Guarraci:** None. **S.H. Meerts:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.13/BB1

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Carleton College

Title: Effects of pubertal suppression with or without adult cross-sex hormone treatment on reproductive tissue in male and female Long-Evans rats.

Authors: *T. R. BEASLEY[1], L. M. SOILLIS[1], M. ITEGHETE[1], A. MENDEZ[1], Y. LOPEZ[1], J. CIESLOWSKI[1], J. M. WEN[1], M. FROST[1], L. WATNE[1], F. A. GUARRACI[2], S. H. MEERTS[1]; [1]Carleton Col., Northfield, MN; [2]Psychology, Southwestern Univ., Georgetown, TX

Abstract: Gonadotropin-releasing hormone agonists (GnRHa), such as leuprolide acetate, suppress endogenous gonadal hormone production and are widely used to delay puberty. The present study aimed to better understand the effects of delaying puberty followed by cross-sex hormones on development of reproductive organs. Gonadally intact Long-Evans rats received one i.m. injection of 0.372 mg LUPRON DEPOT-PED® (Lupron) or vehicle prepubertally (PD 22-24). Vaginal opening (VO) or preputial separation (PPS) was monitored daily as markers of pubertal onset. Female rats were monitored for estrous cyclicity following VO. Beginning on PD 50, rats received cross-sex hormone treatment or oil for four weeks. Natal females received 0.45 mg testosterone enanthate or oil twice weekly, whereas natal males received 2 µg estradiol benzoate and 200 µg cyproterone acetate daily, with 500 µg progesterone or oil administered every fourth day. A two-week washout period followed the cross-sex treatment, at which point reproductive tissue was collected. Effects of pubertal suppression with or without cross-sex hormone treatment were analyzed with a 2 (Lupron/vehicle) x 2 (cross-sex hormone/oil) ANOVA. There was a significant main effect of Lupron on pubertal onset, such that VO was delayed in female rats and PPS was delayed in male rats. There was also a main effect of Lupron in female rats, indicating reduced ovarian, uterine, and vaginal weights relative to vehicle, but there was no main effect of Lupron on male tissue. The main effect of cross-sex hormone was reflected in lighter ovaries and heavier clitoral glands, and lighter penis, testes, ventral and dorsal prostate relative to oil. Additionally, a Lupron x cross-sex hormone interaction was observed in male tissue, such that cross-sex hormone was less effective at reducing the weight of testes, seminal vesicles, ventral prostate, and penis in rats that received Lupron than vehicle prepubertally. The effects of Lupron in female rats may be related to the delay in puberty and, consequently, less time exposed to endogenous gonadal hormones. Adult cross-sex hormone treatment more robustly affected reproductive tissue, consistent with known activational effects

of gonadal hormones. These findings provide a foundation to build on for future peripubertal endocrine research.

Disclosures: T.R. Beasley: None. **L.M. Soillis:** None. **M. Iteghete:** None. **A. Mendez:** None. **Y. Lopez:** None. **J. Cieslowski:** None. **J.M. Wen:** None. **M. Frost:** None. **L. Watne:** None. **F.A. Guarraci:** None. **S.H. Meerts:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.14/BB2

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Carleton College

Title: A single LUPRON DEPOT-PED® injection suppresses puberty for longer and more robustly than daily leuprolide acetate in female and male Long-Evans rats.

Authors: *L. SOILLIS[1], T. R. BEASLEY[1], J. M. WEN[1], Y. D. LOPEZ[1], D. APPEL[1], J. B. CIESLOWSKI[1], F. A. GUARRACI[2], S. H. MEERTS[1];
[1]Carleton Col., Northfield, MN; [2]Psychology, Southwestern Univ., Georgetown, TX

Abstract: The transgender, non-binary, and gender diverse (TNG) community has called for establishing guidelines for preclinical animal models for gender-affirming care. Incongruent pubertal development can exacerbate the distressing psychological effects of gender dysphoria. TNG youth often pause pubertal development by administration of gonadotropin-releasing hormone receptor agonists (GnRHa). To establish the most effective treatment to delay puberty in rats, we compared multiple doses of daily leuprolide acetate (LEU) injections or multiple doses of a single LUPRON DEPOT-PED® (LUPRON) injection relative to vehicle (VEH) on markers of pubertal onset. Male rats received LEU 50 or 100 µg/kg or VEH, and female rats received 50, 100, or 200 µg/kg or VEH injections (s.c.) daily from postnatal day (PD) 25-50. Rats received a single LUPRON or VEH injection (i.m.) on PD 23. In initial studies, male rats were more sensitive than female rats to LEU; therefore, females received 0.372 or 0.186 mg LUPRON, whereas males received 0.186 or 0.093 mg LUPRON. For all groups, vaginal opening (VO) or preputial separation (PPS), and body weight were monitored from PD 30-50. On PD 50 rats were euthanized, and size of reproductive organs (ovaries, vagina, uterus, and clitoral gland or testes, penis, seminal vesicle, and prostate) was measured. LEU delayed VO by 5 days and PPS by 8 days vs VEH, whereas LUPRON delayed VO by 9 days and PPS by 2 days vs VEH. Weight was not affected by LEU in rats of either sex. In contrast, LUPRON led to significantly higher body weight in female rats and significantly lower body weight in male rats vs VEH at the end of the observation period. Ovaries were heavier in 100 µg/kg LEU but lighter in 200 µg/kg LEU vs VEH. Vagina, uterus, and clitoral gland weights were significantly lighter for both 100 and 200 µg/kg LEU vs VEH. Both doses of LUPRON also significantly reduced the weight of all

female reproductive organs. Testes, penis, seminal vesicle, and prostate were significantly lighter with both doses of LEU and both doses of LUPRON vs VEH. A single LUPRON injection was more effective than daily LEU in terms of suppressing pubertal onset, inhibiting development of reproductive tissues, and altering weight gain in female rats. Although LEU delayed PPS longer than LUPRON in male rats, both treatment approaches significantly reduced reproductive tissue weights, but only LUPRON affected body weight. The specific research question, i.e., pubertal onset or reproductive tissue development, should determine which treatment is selected to suppress puberty in studies using animal models.

Disclosures: L. Soillis: None. **T.R. Beasley:** None. **J.M. Wen:** None. **Y.D. Lopez:** None. **D. Appel:** None. **J.B. Cieslowski:** None. **F.A. Guarraci:** None. **S.H. Meerts:** None.

Poster

PSTR020: Sexual and Parental Circuits and Behaviors

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.15/BB3

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NSF IOS-2118607

Title: Characterization of perineuronal nets and behavioral correlates across gestation in expectant California mouse (Peromyscus californicus) fathers

Authors: *I. WARREN[1], W. SALTZMAN[2], K. A. RAZAK[3];
[1]Neurosci., [2]Evolution Ecology & Organismal Biol., Univ. of California, Riverside, Riverside, CA; [3]Psychology, Univ. California, Riverside, Riverside, CA

Abstract: Mammalian fathers in biparental species, like mothers, undergo numerous neural and hormonal changes leading up to and with the birth of their first offspring. One such species is the California mouse (*Peromyscus californicus*), in which the father provides extensive parental care to the young, along with the mother. Typically, males show little motivation to care for pups until the birth of their own offspring. However, the onset of paternal responsiveness can also occur in virgin male California mice following repeated exposure to novel pups. This sensitization to pups is associated with a reduction of perineuronal nets (PNNs), extracellular matrix structures that play a key role in regulating neural plasticity, in the infralimbic cortex (IL) of the medial prefrontal cortex, a brain region implicated in parental behavior. Whether a comparable change in PNNs is seen with the onset of fatherhood in male California mice, or any other species, is not known. We characterized behavioral responses to unfamiliar pups and changes in PNNs in first-time, expectant California mouse fathers across their mate's gestation. Specifically, we performed histochemical staining for *Wisteria floribunda agglutinin* (WFA) in the IL, as well as the medial preoptic area (MPOA), medial amygdala (MeA), and primary auditory cortex (AC). Affiliative behavior toward unfamiliar pups, such as grooming and huddling, increased in frequency and duration across the mate's gestation, while latency to

initiate parental care decreased. Staining for WFA is expected to show a decrease in PNNs in the IL across gestation, fathers to have less PNNs in the MeA than virgins, and a transient increase in PNNs in the MPOA late in gestation. We further predict that males will show increasing lateralization of PNNs in the AC as gestation progresses, as suggested by a pilot study. Thus, we anticipate that the onset of paternal behavior in new fathers will be accompanied by remodeling of PNNs in several brain regions associated with paternal care and processing of pup vocalizations, Ultimately, we hypothesize that dynamic changes in PNNs during the mate's gestation facilitate changes in both behavior and neuronal function as males transition into fatherhood.

Disclosures: I. Warren: None. **W. Saltzman:** None. **K.A. Razak:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.01/BB4

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Hippocampus-synthesized estrogen and androgen modulate dendritic spines and LTP in non-genomic manner

Authors: *S. KAWATO;
Univ. of Tokyo, Tokyo, Japan

Abstract: We have demonstrated (1) hippocampal synthesis of estrogen and androgen, and (2) non-genomic synaptic modulation by these sex-steroids. [Synthesis] We showed expression as well as neuronal/synaptic localization of essential enzymes in the adult male rat hippocampus. Mass-spectrometric analysis demonstrated that hippocampal levels of estradiol (E2), testosterone (T) and dihydrotestosterone (DHT) are about 8 nM, 17 nM and 7 nM, higher than those in plasma. Rapid E2 synthesis with in the hippocampus can be measured via blocking of LTP (long-term potentiation) by 20 min perfusion of Aromatase inhibitor in hippocampal slices. Castration did not decrease male hippocampal E2, because E2 is synthesized from hippocampal T. Castration, however, significantly decreased T and DHT in the hippocampus, indicating a transport of T via the blood circulation. Female hippocampal levels of E2 (0.5-4 nM), and T (1 nM) are less than male, but much higher than those in plasma. [Synaptic Modulation] E2-induced rapid non-genomic modulation (1 h) was demonstrated by analysis of dendritic spines and LTP of adult rat hippocampal 'acute' slices (steroid-depleted slices). Dendritic spine analysis was performed for CA1 pyramidal neurons in hippocampal slices. Spine density and spine head diameters were obtained by mathematical software Spiso-3D which identifies spines by calculating geometrical parameters. E2 at 1 nM rapidly increased the density of small-head spines. T and DHT at 10 nM increased the density of small-head and large-head spines. Signaling pathways are: synaptic ERalpha or AR → LIMK, MAPK, PKA, PKC, Src → cofilin or cortactin → actin polymerization→ new spine formation. LTP analysis showed that 1 nM E2

induced full-LTP (E2-LTP) upon sub-threshold stimulation, although without E2 the sub-threshold stimulation could not induce full-LTP. Kinase inhibitors against MAPK, PKA, PKC, LIMK, Src blocked E2-LTP. References: Kimoto et al., 2001 Endocrinol, Hojo et al., 2004 PNAS, Mukai et al., 2007 J. Neurochem, Hojo et al., 2009 Endocrinol, Mukai et al. 2011 Cereb Cortex, Ooishi et al. 2011 Cereb Cortex, Okamoto et al., 2012, PNAS, Kato et al., 2013, Frontiers Neurosci. Hasegawa et al., 2015 Brain Res., Hatanaka et al., 2015 Brain Res., Murakami et al., 2015 Brain Res., Soma et al., 2018 Frontiers Neurosci., Hojo and Kawato 2018 Frontiers Neurosci., Kawato et al.2026 Frontiers Cellular Neurosci.

Disclosures: S. Kawato: None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.02/BB5

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Max Planck Society

Title: Systemic testosterone signal, specific response: Brain and peripheral transcriptomic profiling of seasonal vocal behavior in canaries

Authors: *F. HU[1,2], L. TROST[1], C. FRANKL-VILCHES[1], M. L. GAHR[1,2];
[1]Max Planck Inst. for Biol. Intelligence, Seewiesen, Germany; [2]Fac. of Biol., Ludwig Maximilian Univ. of Munich, Martinsried, Germany

Abstract: Seasonal changes in vocal behaviors of songbirds provide a model for understanding how internal states regulate social communication. In canaries (*Serinus canaria*), the transition from the non-breeding to the breeding season brings pronounced changes in song pattern and singing behavior, closely linked to rising circulating testosterone levels. Here, we investigated coordinated transcriptional responses across brain regions and peripheral tissues to this systemic endocrine signal in parallel with seasonal changes in singing behavior.
We combined behavioral analysis in a semi-natural environment, endocrine profiling, and multi-organ transcriptomics to investigate this seasonal regulation. Specifically, bulk RNA sequencing was performed across multiple peripheral tissues (liver, heart, spleen, intestine, syrinx muscle, kidney, gonad, pectoral muscle) and brain regions (hyperpallium, cerebellum, preoptic area) as well as spatial transcriptomics of song-control brain areas.
Seasonal differences were observed in both song structure and singing performance, including body posture. Transcriptional responses were highly tissue-specific. Gonads showed extensive molecular remodeling, with ~4,500 differentially expressed genes (DEGs), whereas the liver and heart exhibited only tens of DEGs. All other peripheral tissues showed remarkably limited transcriptional responses, with only a handful of DEGs detected despite expressing androgen receptor (*AR*). RNAscope analyses revealed that *AR* mRNA expression remained largely stable

across tissues but was specifically reduced in breeding gonads, suggesting local negative feedback regulation. In contrast, the heart maintained stable *AR* expression while upregulating *SRD5A1*, encoding 5α-reductase, which converts testosterone into the more potent androgen dihydrotestosterone.
In the brain, bulk transcriptomic analyses identified 11 DEGs in the hyperpallium, 5 DEGs in the cerebellum, and no significant DEGs in the preoptic area, suggesting that seasonal neural responses may be region specific. Ongoing spatial transcriptomic analyses will provide higher resolution characterization of seasonal molecular changes within key song control brain circuits. These findings demonstrate highly tissue-specific molecular responses to seasonal increases in endogenous testosterone. While some tissues undergo extensive transcriptional remodeling, most peripheral organs and brain regions exhibit comparatively limited changes, highlighting substantial heterogeneity in seasonal endocrine responsiveness across the organism.

Disclosures: F. Hu: None. **L. Trost:** None. **C. Frankl-Vilches:** None. **M.L. Gahr:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.03/BB6

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIGMS-5R35GM150979-03-NIH

Title: Dose Response Effect of a Selective Estrogen Receptor Modulator (SERM) on Pain Behaviors in Female Mice

Authors: *B. OJO[1], K. FRIMPONG-MANSON[2], L. KHODAVIRDILOU[2], J. WILKERSON[3]; [1]Anestesiology and Perioperative Med., Rutgers Univ., Newark, NJ; [2]Anesthesiol. and Perioperative Med., Rutgers, The State Univ. of New Jersey, Newark, NJ; [3]Anesthesiol. and Perioperative Med., Rutgers New Jersey Med. Sch., Newark, NJ

Abstract: In women, estrogen depletion or fluctuations has been linked to a higher prevalence of certain pain conditions. Fulvestrant® (ICI 182,780) is clinically used to deplete estrogen receptors in hormone receptor positive breast cancer and can be used to model the depletion of estrogen receptors in animals. We sought to investigate whether ICI 182,780 would produce pain-related behaviors in female mice. Female (10 to 12 week) C57Bl/6J mice received daily subcutaneous ICI 182,780 injections (56, 100, 178 μg) in 0.1 ml vehicle (ethanol, emulphor, saline in a 1:1:18 ratio) for 7 days. Estrus cycle monitoring was carried out daily via vaginal lavage. Starting on injection day 4 ICI 182,780 (100 μg, 178 μg) halted the estrus cycle at the diestrus phase. To investigate mechanical allodynia, cold allodynia, and thermal hyperalgesia, mice were tested at baseline before injections commenced and then on injection day 3 and day 7 using the von Frey, acetone evaporation, and 52ºC hot plate assays, respectively. No dose of ICI 182,780 produced mechanical allodynia. On day 3 of administration, ICI 182,780 (178 μg)

produced transient thermal hyperalgesia. On day 7 these same mice displayed decreased responding to acetone. To investigate the effects on locomotion as well as the development of anxiety-like behaviors, the open field and light dark box assays were carried out at baseline and injection day 7. ICI 182,780 did not alter locomotion or produce anxiety-like behaviors. Mice were euthanized after behavioral testing and the hippocampus, prefrontal cortex (PFC), hypothalamus, spinal cord (SC), and plasma were collected and assayed using the Luminex multiplex assay to quantify immune and inflammatory markers. There was upregulation of innate immune and interferon-associated signaling markers in the plasma and SC mostly at 56µg and plasma-specific reduction in adaptive immunity and metabolic-immune markers at 100µg. In the hippocampus and PFC pro- and anti-inflammatory cytokines, chemokines and growth factors were downregulated across the doses particularly with the two highest doses. These findings demonstrate that ICI 182,780 disrupted the estrus cycle of female mice and differentially affected pathways involved in thermal hyperalgesia and cold allodynia. Estrogen receptor downregulation in the PFC and hippocampus may indicate immune suppression or reduced neuroimmune tone affecting basal immune homeostasis. In contrast, estrogen receptor suppression in the SC and periphery appears to promote innate immune activation and inflammatory signaling, highlighting region-specific effects of estrogen receptor loss.

Disclosures: B. Ojo: None. **K. Frimpong-Manson:** None. **L. Khodavirdilou:** None. **J. Wilkerson:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.04/BB7

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: HAIR STEROID HORMONES ARE ASSOCIATED WITH COGNITIVE PERFORMANCE AND SOCIAL BEHAVIOR IN INFANT RHESUS MACAQUES

Authors: *S. MUWANIKA[1], A. M. DETTMER ERARD[2];
[1]St Edward's Univ., Austin, TX; [2]Yale Child Study Ctr., Yale Sch. Of Med., New Haven, CT

Abstract: Hair concentrations of cortisol (HCC) and dehydroepiandrosterone (HDHEA) provide indices of chronic hypothalamic-pituitary-adrenal (HPA) axis activity, with DHEA acting as an antiglucocorticoid that may buffer some effects of prolonged cortisol exposure. Despite increasing interest in developmental neuroendocrinology, chronic HPA-axis activity is rarely examined in relation to both cognitive and social development early in life. We hypothesized that HCC, HDHEA, the cortisol:DHEA ratio (CDR) would associate with cognitive performance and social behavior in infant rhesus macaques (Macaca mulatta; N=19) between four and eight months of age. Infants participated in cognitive testing assessing associative learning, cognitive flexibility, and impulsivity during rule-switching, including simple discrimination and object detour reach paradigms. Social behavior was quantified using twice-weekly focal observations.

Hormone concentrations were assayed from hair samples collected during infancy. Spearman correlations revealed that higher HDHEA was associated with greater accuracy on a simple discrimination task (ρ=0.762, p=0.028), whereas higher CDR was associated with lower accuracy (ρ=-0.762, p=0.028). During the object detour reach task, higher HDHEA was associated with more side-errors (ρ=0.833, p=0.005) and straight-reach errors (ρ=0.767, p=0.016), whereas higher CDR was negatively associated with these outcomes (ρ=-0.850, p=0.004 and ρ=-0.783, p=0.013, respectively). Lower HDHEA and higher CDR were also associated with greater social play behavior (ρ=-0.573, p=0.016 and ρ=0.533, p=0.027, respectively). Finally, infants exhibiting higher levels of social play demonstrated fewer errors on the impulsivity task. Together, these findings suggest that chronic HPA-axis activity, particularly DHEA-related signaling, is associated with distinct aspects of early neurobehavioral development, including associative learning, inhibitory control, impulsive responding, and social play behavior in infant rhesus macaques.

Disclosures: S. Muwanika: None. **A.M. Dettmer Erard:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.05/BB8

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIMH Grant R01MH101518
NIMH Grant R21MH106924
Brain and Behavoir Research Foundation Independent Scientist Award

Title: Epigenetic Regulation and Sex-Differentiation of Neuroactive Steroid Genes in an Adolescent Twin Cohort

Authors: *R. FRYE, R. ROBERSON-NAY;
Dept. of Psychiatry and Neurobehavoiral Sci., Univ. of Virginia, Charlottesville, VA

Abstract: Neuroactive steroids (NAS) are fast-acting, sex-differentiated modulators of GABA-A inhibitory activity in the central nervous system. GABA-A receptors play a critical role in hormone-sensitive conditions such as premenstrual dysphoric disorder and postpartum depression. Understanding the development and integration of these systems may inform the etiology behind these conditions. DNA methylation (DNAm) is one such epigenetic regulatory mechanism by which methylation of promoter CpG sites can suppress transcription. In a human adolescent monozygotic twin cohort (N = 137, ages 15.6 - 20.8 years; 54 complete pairs), we examined whether NAS-pathway methylation predicted expression of the same gene and whether NAS-pathway transcript abundance and methylation status differ by sex in adolescence. Gene-mean DNAm predicted transcript abundance for the HPA-related loci TSPO (M = −0.75, p = .003, FDR = .036) and FKBP5 (M = −1.06, p = .017, FDR = .093), indicating an inverse

association between methylation and gene expression. Within MZ pairs, these associations were directionally consistent but attenuated, consistent with heritability of methylation at these loci. Sex differences in mean DNAm (FDR < .10) were observed at GABA-A receptor (GABRA5) and HPA/catecholamine-regulatory (NR3C1, COMT) loci, with direction varying by gene, higher methylation in females at NR3C1 and higher methylation in males at GABRA5 and COMT, indicating sex-differentiated epigenetic regulation across GABA-A and HPA components of the NAS system by late adolescence. Together, these data suggest that regulatory machinery linking GABA-A signaling and the HPA axis has begun to differentiate by sex during adolescence, potentially shaping responses to periods of hormonal flux later in life.

Disclosures: R. Frye: None. **R. Roberson-Nay:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.06/BB9

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: HAWK-IDDRC, NIH P50 HD103556
NIH R01 DA056113
Roy J. Carver Directorship of the Iowa Neuroscience Institute
BBRF 2024NARSAD Young Investigator Grant 32261

Title: Cell type-specific profiling reveals distinct estradiol-regulated transcriptomes in striatal D1R- and D2R-spiny projection neurons

Authors: *J. KIM[1,2], B. KELVINGTON[2], K. L. BLACKWELL[3], T. ABEL[2];
[2]Neurosci. and Pharmacol., [3]Biomed. engineering, [1]Univ. of Iowa, Iowa City, IA

Abstract: 17β-Estradiol (E2), the most abundant and potent estrogen during adulthood, has been a major focus of research on estrogenic regulation of the nervous system. The striatum, a principal input structure of the basal ganglia, is highly sensitive to E2 and plays critical roles in motor function and multiple forms of learning, including reward-based and instrumental learning. Approximately 95% of striatal neurons are spiny projection neurons (SPNs), which are primarily divided into dopamine D1 receptor-expressing (D1R) SPNs and dopamine D2 receptor-expressing (D2R) SPNs. Previous studies have demonstrated that E2 modulates dopamine receptor expression, neuronal excitability, and synaptic transmission within the striatum. However, underlying molecular mechanisms mediating the effects of E2 in the striatum, particularly in specific SPN populations, remain poorly understood. In this study, we examined the effects of E2 treatment on striatal gene expression in ovariectomized mice using RNA sequencing (RNA-seq). To determine cell type-specific transcriptional responses, we performed translating ribosome affinity purification followed by RNA sequencing (TRAP-seq) in D1R- and D2R-SPNs using Drd1-bacTRAP and Drd2-bacTRAP mice. Bulk RNA-seq

analysis revealed only three differentially expressed genes (DEGs) in E2-treated mice compared with vehicle-treated controls. In contrast, D1R-SPN TRAP-seq identified 1,465 DEGs, whereas D2R-SPN TRAP-seq identified 110 DEGs following E2 treatment. Notably, there was minimal overlap between the DEG profiles of D1R- and D2R-SPNs, indicating distinct transcriptional responses to E2 in these two neuronal populations. Together, these findings demonstrate that E2 exerts robust and highly cell type-specific effects on striatal gene expression that are largely obscured in bulk tissue analyses. Our results highlight the importance of cell type-specific transcriptomic approaches for understanding estrogen signaling in the striatum and provide new insight into the molecular mechanisms through which E2 regulates striatal function.

Disclosures: J. Kim: None. **B. Kelvington:** None. **K.L. Blackwell:** None. **T. Abel:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.07/BB10

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIDA Grant DA061028

Title: Thyroid Hormone Signaling Mediates Cocaine Reward in a Sex- and Region-Specific Manner

Authors: T. N. VU, M. A. BELL, *D. M. WALKER;
Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Cocaine use disorder is a chronic relapsing psychiatric ailment characterized by maladaptive learning, behavioral, cognitive, and psychosocial impairments, and is was responsible for nearly 1 in 5 drug overdose deaths in 2023 (NCDAS). However, no FDA-approved pharmacological treatment exists. While many neuroendocrine axes are dysregulated by cocaine, the thyroid hormone axis is a likely target given that cocaine's behavioral effects mirror hyperthyroidism symptoms. We recently showed that manipulation of thyroid hormone signaling in the brain can influence the preference for drugs of abuse, and these behavioral changes are associated with transcriptional changes within the reward circuitry. Like all nuclear hormone receptors, thyroid hormone receptors, when bound to their ligand, act as transcription factors and epigenetic regulators, but little is known about how cocaine affects thyroid hormone-mediated transcription in the brain. Therefore, we hypothesize that cocaine disrupts the thyroid hormone axis and thyroid-mediated transcription within the brain. To assess how cocaine dysregulates the thyroid hormone axis, adult male and female C57BL/6 mice received 9 daily injections of saline, followed by a tenth injection of saline or cocaine (7.5 mg/kg). Serum and brain punches from the prefrontal cortex (PFC), nucleus accumbens, medial amygdala, and basolateral amygdala were collected one hour post-injection for a thyroid hormone panel and RT-qPCR. Acute cocaine decreased thyroid-stimulating hormone (TSH) in males, but not in

females. Generalized linear model analysis (GLM) showed that acute cocaine altered thyroid hormone receptor genes (Thra & Thrb), and deiodinase-2 (Dio2), the enzyme that converts thyroid hormone to its active form, in a brain region- and sex-specific manner. To functionally link the changes in gene expression to the behavioral consequences of cocaine, mice were given the thyroid hormone antagonist propylthiouracil (PTU) in food for three weeks and underwent cocaine CPP at 7.5 and 10 mg/kg (N = 8 per sex, treatment, and dose). GLM revealed that blocking thyroid hormone signaling resulted in an enhanced preference for cocaine, particularly in females. We are currently analyzing transcriptome-wide effects of PTU within the PFC to identify potential thyroid hormone-sensitive targets associated with changes in cocaine CPP. These findings suggest a bidirectional relationship in which cocaine dysregulates the thyroid hormone axis, which, in turn, alters cocaine reward. Together, thyroid-related gene expression and behavioral outcomes point to a novel therapeutic target to treat cocaine use disorder.

Disclosures: T.N. Vu: None. **M.A. Bell:** None. **D.M. Walker:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.08/BB11

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Sexual dimorphism in hippocampal citrullination is associated with differential peptidylarginine deiminase expression

Authors: *K. MOYTE[1], B. CATLIN[1], L. QUIGLEY[1], A. SEQUOIA[1], W. BONDS[1], J. EDWARDS[1], W. D. TODD, III[2], B. CHERRINGTON[1];
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Abstract: Citrullination is a post-translational modification in which arginine residues within target proteins are converted to the non-coded amino acid citrulline. This process is catalyzed by peptidylarginine deiminase (PAD) enzymes. Elevated PAD activity and the resulting accumulation of citrullinated proteins is reported in several neurodegenerative disorders including Alzheimer's disease (AD). PADs are expressed in female reproductive tissues, where their expression is regulated by estrogen throughout the reproductive cycle. In the brain, PADs are expressed in the hippocampus and can citrullinate amyloid-β (Aβ) peptides, promoting their aggregation into amyloid plaques that contribute to neurodegeneration and AD pathology. Notably, women account for nearly two-thirds of AD cases, suggesting a potential hormonal contribution to disease susceptibility; however, the underlying mechanisms remain poorly understood. We hypothesized that sex specific regulation of PAD expression leads to differential accumulation of cit-proteins in the female hippocampus, thereby increasing vulnerability to AD related pathology during aging. To test this hypothesis, we examined age related changes in PAD expression in male and female wild type and 3xTg-AD mice at 3, 7, and 14 months of age. Our results demonstrate that PAD2 expression is sexually dimorphic, with higher levels in the

hippocampal CA1 region of females compared with males. In female 3xTg-AD mice, PAD2 colocalized with Aβ plaques and citrullinated histones within the CA1 region. Furthermore, mass spectrometry analysis revealed a substantially greater number of citrullinated proteins in the female hippocampus compared with males. Collectively, these findings suggest that PAD mediated protein citrullination may contribute to the development and progression of AD pathology in females during aging. Ongoing studies are focused on characterizing the hippocampal citrullinome across age groups in 3xTg-AD mice and extending these analyses to 14-month-old animals to further define age and sex dependent changes in protein citrullination associated with AD.

Disclosures: K. Moyte: None. **B. Catlin:** None. **L. Quigley:** None. **A. Sequoia:** None. **W. Bonds:** None. **J. Edwards:** None. **W.D. Todd:** None. **B. Cherrington:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.09/BB12

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant 1K01HL145339-01A1

Title: Interactive Effects of Biological Sex and Age on Perineuronal Nets and Spatial Memory in Syrian Hamsters and Relevance to Estrogen-dependent Mechanisms in Brain Health.

Authors: *L. GARCIA[1], E. I. ALANIZ[2], J. LUNA[1], M. GIL[3];
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Abstract: Memory impairment is a hallmark of Alzheimer's Disease, and aging and hormonal status are critical risk factors for Alzheimer's Disease and related dementias (ADRD). Syrian hamsters (*Mesocricetus auratus*) were used to examine the effects of age and biological sex on spatial memory and perineuronal nets (PNNs), which are involved in memory formation. The hole-board task was used to assess exploration and cognitive function in males (n=28) and females (n=36). Seven subjects were transcardially perfused; brains were collected and fixed with 4% paraformaldehyde, sliced at 35 μm, and tissue was processed via immunohistochemistry to stain for estrogen receptors (ER), PNNs, and PNNs+ERs. Results of a repeated-measures ANOVA showed that both sexes across all age cohorts (young, middle, and old) demonstrated more overall nose pokes during stimulus exposure trials for the experimental group compared to controls ($F(3,156) = 4.535$, $p < .01$), confirming memory formation. There was a trend for the interaction between memory trials, sex, and age ($F(4,104) = 2.400$, $p = .05$), suggesting that age and sex influence spatial memory in hamsters. ERs were quantified in the hypothalamus and amygdala (number of ER-ir cells per 2500 μm2), and the results of an independent samples t-test confirmed that females had more ER-ir cells compared to males ($t(6)=.773$, $p<.05$), consistent

with prior literature. The results of a repeated-measures ANOVA with brain area, sex, and age as factors showed significant interactions between sex and brain area ($F(7,17.466) = 2.495$, $p = 0.017$) and between age and brain area ($F(7, 18.519) = 2.646$, $p = 0.012$). A significant difference in PNN size was observed, with younger adults showing larger PNNs than older adults ($t(13.351) = 4.202$, $p = .001$). And finally, the three-way interaction between sex, age, and brain area was also significant ($F(6, 16.746) = 2.791$, $p = 0.012$). Preliminary results showed co-localization of ERs and PNNs in the hypothalamus, hippocampus, and amygdala, suggesting that PNNs surround ER-ir cells. These results provide insight into the relationship between PNNs, synaptic plasticity, and memory, and underscore the significance of the *Mesocricetus auratus* as a model for neurodegenerative disorders, brain health, and aging. We are currently conducting additional studies to test whether the female estrous cycle influences PNNs in Syrian hamsters.

Disclosures: L. Garcia: None. **E.I. Alaniz:** None. **J. Luna:** None. **M. Gil:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.10/BB13

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant R15MH140275

Title: Effects of Synthetic Hormones on Fear Behavior in Female Rats

Authors: *M. R. CARRINGTON[1], C. E. HARTSGROVE[4], A. S. TRAN[2], R. MANIANI[3], D. SANCHEZ VARGAS[5], L. Y. MAENG[6];
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Abstract: Women are twice as likely to be diagnosed with post-traumatic stress disorder (PTSD). A key feature of PTSD is impaired fear extinction, the ability to reduce fear responses to a no longer threatening stimulus. Increasing evidence demonstrates that 17β-Estradiol (E2) influences fear extinction processes, enhancing extinction memory in both women and female rodents. However, less is known about how hormonal contraceptives (HCs), which reduce endogenous E2 levels, impact fear behavior and the underlying neurocircuitry. Specifically, there have been mixed findings on how HCs impact fear extinction. These conflicting results may be partly due to the various formulations of synthetic estrogen and progestins administered. The current study aims to compare the effects of three commonly used components of HCs: ethinyl estradiol (EE), levonorgestrel (LNG), and the combination (EE+LNG). We hypothesized that these formulations would have differential effects on fear behavior and neural activation. Adult female Sprague Dawley rats (N=24, n=6/group) received daily vehicle (sesame oil + 0.5% ethanol) or HC injections for 25 days, including three days of a cued auditory fear conditioning

paradigm. Blood was collected once a week for serum E2 analysis, and brains were extracted to assess changes in recent neural activation within the medial prefrontal cortex, amygdala, and hippocampus with c-fos immunofluorescence. Serum E2 levels were significantly reduced in the HC-treated group compared to the vehicle-treated animals ($p<0.01$); however, the LNG-treated rats exhibited a slower decline. Ovarian weights were also significantly decreased in the HC-treated animals ($p<0.01$), paralleling the serum changes. There was a pattern of reduced extinction retention in the HC-treated groups compared to the vehicle group, although these differences did not reach statistical significance. These preliminary findings suggest that synthetic hormones may differentially influence fear-related behavior. Investigating the effects of hormonal contraceptives on fear behavior and the associated neural mechanisms may enhance our understanding of how ovarian hormones modulate fear processes.

Disclosures: M.R. Carrington: None. **C.E. Hartsgrove:** None. **A.S. Tran:** None. **R. Maniani:** None. **D. Sanchez Vargas:** None. **L.Y. Maeng:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.11/BB14

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: UVA Brain Institute Transformative Neuroscience Pilot Grant

Title: In-Vivo Estrogen Regulation of Inceptor Expression in the Brain

Authors: *C. HARVEY-STOLTZ, H. A. FERRIS;
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Abstract: Inceptor has been identified as a novel regulator of insulin biology in multiple tissues. Furthermore, the Inceptor encoding gene (EIG_121) has been identified as an estrogen-induced gene with roles in autophagy, cell survival, and cancers. Previous studies have identified it as a regulator of insulin sensitivity in the brain, with significant sex differences in expression. Therefore, we are investigating the physiological regulation of Inceptor by estrogen (E2) in the brain. We hypothesize that Inceptor expression differs based on fluctuating E2 levels in murine neurons and could contribute to insulin-resistance observed during pregnancy. Female C57Bl/6J mice were used during the experiments. Tissues were collected from females at different E2 circulation phases, pregnancy, and ovariectomy. Inceptor protein expression in brain regions was analyzed using Western blot. Serum was collected for E2 assays. Primary neurons were collected from timed pregnant females and qPCR was performed following E2 treatments. Data were analyzed using one-way ANOVA. There was a significant increase in Inceptor mRNA expression with E2 treatment of primary neurons. To investigate the relationship between Inceptor and in vivo E2 fluctuations, Inceptor was measured in hypothalamic and cortical tissue from wild-type female mice across estrous cycle stages (proestrus, estrus, metestrus, and

diestrus), and at P0, E10.5, E16.5, and E17.5 of pregnancy. We did not observe significant differences in Inceptor expression with physiologic changes in estrogen. Ovariectomy surgeries were performed using sham, OVX, and OVX with E2-rescue groups. There were no significant differences between groups after vehicle/E2 administration. The role of estrogen as a regulator of Inceptor in the brain is not supported in the context of baseline and pregnancy E2 states. These data contradict previous findings supporting increased Inceptor expression in E2-dependent cancers. The sex differences in Inceptor suggest some mechanism of insulin signaling and estrogen regulation that is currently unknown. Further investigation into mechanisms connecting estrogen regulation and insulin resistance could lead to a better understanding of diseases such as PCOS and gestational diabetes.

Disclosures: C. Harvey-Stoltz: None. **H.A. Ferris:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.12/BB15

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NSF IOS 1655626
Department of Veteran Affairs I21 BX002085
Department of Veteran Affairs I01 BX001804

Title: Hippocampal-specific insulin resistance elicits structural and functional deficits in hippocampal plasticity

Authors: J. L. WOODRUFF[1], D. M. COLEMAN[2], N. D. MAXWELL[3], D. M. GILES[2], V. GLASS[2], L. P. REAGAN[4], *C. A. GRILLO[5];
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Abstract: Metabolic disorders such as type 2 diabetes mellitus (T2DM), metabolic syndrome and obesity are associated with increased risk of a variety of neurological deficits. Insulin resistance is a common feature of these metabolic disorders and has been implicated in the development of central structural and functional deficits that result in decreases in hippocampal synaptic plasticity. The current study examined the causal relationship between brain insulin resistance and cognitive dysfunction using a lentivirus that expresses an insulin receptor antisense sequence (LV-IRAS) to specifically downregulate hippocampal insulin receptors and thereby elicit hippocampal specific insulin resistance compared to rats that received the control lentivirus (LV-Con). Immunohistochemistry for doublecortin combined with non-biased stereological approaches determined that LV-IRAS rats exhibited dendritic atrophy of immature

granular neurons in the dentate gyrus. Golgi impregnation analysis determined that LV-IRAS rats also exhibited dendritic atrophy of CA1 pyramidal neurons, demonstrating that hippocampal-specific insulin resistance elicits structural changes in the hippocampus independent of peripheral complications of metabolic disorders. To determine the potential functional consequences of these structural deficits, hippocampal-dependent learning and memory was assessed using the novel object recognition test. Compared to rats that received LV-Con, rats that received bilateral injections of the LV-IRAS construct spent ess time with a novel object resulting in a significant decrease in the Preference Index without changes in locomotor activity or time of exploration. Collectively, the results of the current study demonstrate that insulin resistance restricted to the hippocampus elicits structural and functional synaptic plasticity deficits independent of peripheral insulin resistance or insulin resistance in other brain regions such as the hypothalamus. Such observations provide important insight into the role of brain insulin resistance in the cognitive dysfunction in T2DM, as well as the cognitive deficits in age-related cognitive decline and Alzheimer's disease.

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Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.13/BB16

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Department of Veterans Affairs Grant 121 BX002085
Department of Veterans Affairs Grant IO1 BX001804
National Science Foundation Grant IOS-1655626

Title: Identifying a novel circuit that modulates leptin-mediated learning and memory.

Authors: *K. S. CALAMUSA[1], J. L. WOODRUFF[2], N. MACIEJEWSKA[3], M. FRICK[4], C. E. SMILEY[3], S. K. WOOD[7], J. R. FADEL[5], C. A. GRILLO[6], L. P. REAGAN[7];
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Abstract: In addition to regulating peripheral metabolism, leptin also facilitates hippocampal synaptic plasticity. While it is well known that locally expressed leptin receptors (LepRs) facilitate hippocampal plasticity, less is known regarding the potential role of lateral hypothalamus (LH) LepRs in hippocampal function. We hypothesize that activation of a leptin-

mediated pathway from the LH to the locus coeruleus (LC) to the hippocampus enhances hippocampal neuroplasticity and cognition. To test this hypothesis, we developed a lentiviral vector that expresses the activating DREADD hM3Dq and mCherry under the control of the LepR promoter. We then injected this viral construct bilaterally into the LH of adult male Sprague-Dawley rats to specifically activate our hypothesized LepR-driven circuit. Immunofluorescence identified mCherry expression in the LH, validating the accuracy of the viral injections and the successful expression of the construct. Administration of the DREADD ligand JHU37160 (J60; 0.3 mg/kg) increased fos expression in the LC that was colocalized with tyrosine hydroxylase (TH) positive neurons, demonstrating that activation of LepR-positive neurons in the LH stimulates norepinephrine (NE) synthesizing neurons in the LC. J60 administration increased hippocampal NE levels, as determined by in vivo microdialysis and high-performance liquid chromatography. Activation of this circuit through J60 administration also enhanced performance of a hippocampal-dependent learning and memory task, namely the novel object recognition test. Collectively, these results support our hypothesis that stimulation of LepR-positive neurons in the LH activates a LH→LC^{NE}→hippocampus circuit that facilitates hippocampal-dependent behavior.

Disclosures: K.S. Calamusa: None. **J.L. Woodruff:** None. **N. Maciejewska:** None. **M. Frick:** None. **C.E. Smiley:** None. **S.K. Wood:** None. **J.R. Fadel:** None. **C.A. Grillo:** None. **L.P. Reagan:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.14/BB17

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant R01NS128123
NIH Grant R01AG074041
NIH Grant T32GM152354

Title: Estradiol-Induced Suppression of Acan, Encoding a Major Perineuronal Net Proteoglycan, Promotes Hippocampal Memory Consolidation

Authors: *J. XU[1], H. BOYD[2], S. B. BEAMISH[4], A. FLEISCHER[6], I. ALBERT[3], A. SEBASTIAN[3], J. L. KWAPIS[7,8], K. M. FRICK[5];
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Abstract: The potent estrogen 17β-estradiol (E2) facilitates the consolidation of hippocampus-dependent object memoriesin part by altering hippocampal gene expression. However, it remains unclear how exogenous E2 influences learning-induced hippocampal gene expression to promote memory formation. To determine how E2 drives gene expression and how gene expression pattern induced by E2 is changed following learning, ovariectomized female C57BL/6NTac mice were trained in an object recognition task and immediately treated with vehicle or E2 (0.2 mg/kg, i.p.). Dorsal hippocampal tissue was collected 60 min lateralong with homecage (HC) controls for RNA sequencing.Differential gene expression analyses compared HC+E2 versus HC+vehicle and trained+E2 versus HC+E2, followed by GO and KEGG functional enrichment analyses. We found that E2 treatment activated pathways associated with immunoglobulin superfamily cell adhesion molecules (IgSF CAMs signaling) and myelination. In contrast, E2 on the basis of training preferentially engaged genes involved in endoplasmic reticulum protein processing, cellular stress responses, and thyroid hormone synthesis. Gene set enrichment analysis of coordinated transcriptomic responses revealed that learning in the presence of E2 downregulated pathways related to cell adhesion molecule interactions and synaptic vesicle priming, while upregulating pathways involved in endoplasmic reticulum protein processing and RNA splicing. Among the differentially expressed genes, *Acan*, which encodes the major perineuronal net (PNN) proteoglycan aggrecan, was selectively downregulated by E2 only in trained mice, and this effect was confirmed by qPCR. In addition, prolonged ovarian hormone deprivation promoted hippocampal *Acan* build-up, suggesting that E2 normally suppresses aggrecan accumulation. Functional enrichment analysis of postmortem human hippocampal transcriptomic datasets further revealed increased expression of extracellular matrix structural genes and decreased expression of extracellular matrix degradation pathways in Alzheimer's disease. Given that PNNs are a condensed form of extracellular matrix in the nervous system, these findings identify *Acan*/aggrecan as a novel downstream target of E2 signaling and suggest that E2-mediated remodeling of hippocampal extracellular matrix/PNN composition may contribute to memory consolidation. Ongoing studies are testing this hypothesis by testing effects of *Acan* up- and down-regulation on estrogenic spatial memory consolidation.

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Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.15/BB18

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant R01NS128123

Title: Aging effects on estrogenic modulation of aggrecan-positive perineuronal nets surrounding parvalbumin neurons in female mice

Authors: *S. K. MORIARTY[1], J. XU[2], K. M. FRICK[2];
[1]Univ. of Wisconsin Milwaukee, Milwaukee, WI; [2]Psychological and Brain Sci., Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: Women represent two thirds of Americans diagnosed with Alzheimer's disease (AD). Menopause, a transitional period in aging women characterized by massive loss of circulating estrogens, is considered a risk factor for AD. The potent estrogen 17β-estradiol (E2) has long been shown to improve memory consolidation, therefore the loss of estrogens during menopause likely contributes to this increased risk. However, the mechanisms behind estrogenic modulation of memory are not fully understood. The dorsal hippocampus (DH) and retrosplenial cortex (RSC) are reciprocally connected and have important roles in mnemonic processes. Both the DH and RSC show aging-related changes in activity, including early dysfunction in the onset of neurodegenerative conditions. Both regions have abundant parvalbumin (PV)-containing inhibitory interneurons, which modulate the balance between excitatory and inhibitory neuronal activity and are key regulators of neural plasticity. Perineuronal nets (PNNs), a specialized, condensed form of extracellular matrix, surround PV neurons and stabilize synaptic connections formed during critical periods of learning. Abnormal expression of PNNs has been linked to various pathologies impacting cognition, including AD. One way that abnormal PNNs contribute to disease may be through the accumulation of aggrecan, the proteoglycan primarily responsible for PNN structure. Interestingly, many PV neurons co-express estrogen receptors (ERs), particularly ERβ. Recent work has suggested that both naturally circulating estrogens and exogenous E2 modulate PNNs on PV neurons, although reports of impact are mixed. To examine the effect of hormone loss during aging on aggrecan-positive PNNs around PV neurons, brains were collected from young adult (4-month-old) and aged (21-month-old) female mice. The DH and anterior RSC were mounted on slides and RNAscope combined with immunohistochemistry was performed to identify PV-containing neurons, ERβ, and aggrecan, which was quantified via fluorescent labeling intensity. We hypothesize that estrogen loss in females due to aging changes activity of PV/ Erβ+ neurons, which correlates with accumulation of aggrecan.

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Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.16/BB19

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: R01NS128123
R01MH122414

Title: Estrogen Receptor Subtype-Specific Regulation of the Ubiquitin-Proteasome System in the Dorsal Hippocampus of Male and Female Mice

Authors: *P. MOHAMMADI[1], S. B. BEAMISH[2], T. J. JAROME[4], K. M. FRICK[3]; [1]UWM, Milwaukee, WI; [2]Psychology Dept., [3]Psychological and Brain Sci., Univ. of Wisconsin-Milwaukee, Milwaukee, WI; [4]Virginia Tech., Blacksburg, VA

Abstract: 17β-estradiol (E2) enhances hippocampal function and long-term memory formation, but the molecular mechanisms remain unclear. E2 regulates hippocampus-dependent memory by activating cell-signaling cascades in the dorsal hippocampus (DH) to promote the synthesis of proteins that support structural changes at DH synapses. However, this work has overlooked the potentially important role of protein degradation by the ubiquitin proteasome system (UPS) in E2's effects on hippocampal function. Our lab's previous data indicate that proteasome activity is necessary for E2 to increase CA1 dendritic spine density and memory consolidation in ovariectomized (OVX) female mice. Yet E2 acts through three estrogen receptors (ERα, ERβ, and the G-protein-coupled estrogen receptor, GPER) that engage distinct downstream cascades, and it remains unclear which receptor subtypes mediate E2's regulation of the UPS and whether this regulation differs between males and females. Thus, this work examined the extent to which estrogen receptor subtypes regulate UPS activity in the DH of male and female mice. Adult male and female C57BL/6J mice were gonadectomized, implanted with bilateral guide cannulae targeting the DH, and then assigned to receive a bilateral DH infusion of vehicle, E2, the ERα agonist PPT, the ERβ agonist DPN, or the GPER agonist G-1. DH tissue was collected 4 h post-infusion, a timepoint at which training-induced UPS activity is influenced by E2 and at which E2 regulates K48 polyubiquitination in the DH. Homogenized tissue was analyzed for three measures of UPS-mediated degradation: 1) K48 polyubiquitination, representing protein tagging, 2) RPT6 phosphorylation, representing proteasome state, and 3) 20S proteasomal activity, representing proteasome catalysis. Because our prior work shows that both ERα and ERβ agonists enhance dorsal hippocampal memory consolidation, we predict that activation of ERα and/or ERβ, like E2, will regulate these measures of UPS function, whereas GPER activation by G-1 will produce little change. We further expect these effects to be more pronounced in females than in males. Ongoing work is determining which estrogen receptor subtype(s) regulate UPS activity in the DH and whether this regulation is sex-dependent.

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Poster

PSTR021: Hormones and Cognition

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Program #/Poster #: PSTR021.17/BB20

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant R01 AG041374

Title: Disruption of membrane estrogen signaling alters hippocampal excitatory-inhibitory balance.

Authors: P. TIRRELL[1,2], ***M. J. MAROTEAUX**[3,2], J. M. DANIEL[1,2,3];
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Abstract: Memory encoding, consolidation, and retrieval in the hippocampus rely on tightly regulated activity of excitatory pyramidal neurons, which is shaped by a diverse population of inhibitory GABAergic interneurons. Disruption of this excitatory-inhibitory (E/I) balance impairs synaptic plasticity and memory, and is a contributing factor to many cognitive disorders. Estrogens are increasingly recognized as key regulators of E/I balance in the hippocampus, modulating neuronal excitability, synaptic plasticity, and inhibitory tone. Parvalbumin-positive (PV^+) basket cells provide perisomatic inhibition onto pyramidal neurons to enable precise temporal control of firing and maintenance of E/I balance. PV^+ basket cells express estrogen receptor α (ERα), and parvalbumin expression in the dorsal hippocampus is estrogen-regulated, positioning these interneurons as key mediators of estrogen action on hippocampal circuitry. Estrogens signal via divergent genomic and non-genomic pathways. However, the relative contributions of genomic vs membrane-initiated estrogen signaling to hippocampal E/I balance remains unclear. To dissociate these mechanisms, we used nuclear-only ERα mice (NOER) carrying a C451A mutation that abolishes membrane-initiated signaling while preserving nuclear receptor function. We previously showed that loss of membrane-localized ERα impairs spatial memory and alters extracellular signal-regulated kinase (ERK), protein kinase B (AKT), and cAMP response element-binding protein (CREB) signaling. Here, we examined the impact of membrane ERα loss on hippocampal E/I balance. Proteomic analysis revealed increased excitatory and decreased inhibitory pathway proteins, leading us to hypothesize that NOER mice would show reduced hippocampal PV^+ interneuron density and elevated basal c-Fos expression in pyramidal neurons. Immunofluorescence revealed decreased PV^+ interneuron density in CA1 stratum oriens and stratum pyramidale, CA3 stratum pyramidale, and dentate gyrus, with no change in CA2. Basal c-Fos expression was selectively increased in CA1 and CA3. However, activity-dependent c-Fos induction following novel environment exposure was unchanged between NOER and wild-type mice. Together, these findings show that loss of membrane ERα reduces PV^+ interneuron density and elevates basal neuronal activity, likely contributing to E/I imbalance and hippocampus-dependent memory deficits.

Disclosures: P. Tirrell: None. **M.J. Maroteaux:** None. **J.M. Daniel:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.18/BB21

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant P01AG071746

Title: Impact of estradiol and hypertension on white matter integrity in prefrontal cortex and hippocampus of middle-age ovariectomized rats

Authors: *C. MONTANARI[1,2], B. P. PETHE[2,3], A. P. O. LEITE[2,4], S. H. LINDSEY[2,4], J. M. DANIEL[1,2,3];
[1]Psychology, [2]Tulane Brain Inst., [3]Tulane Neurosci. Program, [4]Pharmacol., Tulane Univ., New Orleans, LA

Abstract: Preclinical models of menopausal hormone therapy have demonstrated positive effects on cognitive aging, whereas clinical findings remain equivocal, and cardiometabolic health status may contribute to this discrepancy. Since age-related cognitive decline is linked to white matter shrinkage, we hypothesized that hypertension alters the effects of estradiol on brain white matter integrity in a rat model of menopause. Female Long-Evans rats arrived at 10 weeks of age. At 42 weeks of age, animals were either left normotensive or administered angiotensin II (700 ng/kg/min) via subcutaneous osmotic minipumps to induce a hypertensive state. Four weeks later, rats were ovariectomized and implanted with subcutaneous capsules containing vehicle or estradiol; at the time of ovariectomy, angiotensin pumps were replaced. Treatments resulted in the following groups: Normotensive-Vehicle, Normotensive-Estradiol, Hypertensive-Vehicle, and Hypertensive-Estradiol. Rats were euthanized four weeks after ovariectomy at 50 weeks of age. Medial prefrontal cortex and hippocampus samples were collected to measure two myelin-associated proteins, myelin basic protein (MBP) and proteolipid protein (PLP), via western blotting. In the prefrontal cortex, results revealed an overall main effect of estradiol and no main or interactive effects of hypertension for both MBP and PLP, indicating overall increased estradiol-induced levels of myelin expression in both normotensive and hypertension rats. In the hippocampus, there were no main effects of estradiol or hypertension for either MBP or PLP. However, there was a marginally significant interactive effect of estradiol and hypertension for PLP, revealing that estradiol resulted in decreased levels of white matter in hypertensive rats but not in normotensive rats. A similar, though nonsignificant pattern was observed for MBP expression in the hippocampus. Overall, our findings demonstrate that the effects of estradiol on white matter integrity vary by brain region and hypertensive status. While estradiol exerted beneficial effects in the medial prefrontal cortex regardless of hypertensive status, hypertension modified its effects in the hippocampus. In conclusion, results suggest that cardiovascular health may be an important determinant of hormone therapy outcomes during aging. This work highlights the need for further investigation of region-specific responses to estradiol under conditions of cardiovascular risk.

Disclosures: C. Montanari: None. **B.P. Pethe:** None. **A.P.O. Leite:** None. **S.H. Lindsey:** None. **J.M. Daniel:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.19/BB22

Topic: G.06. Autonomic Regulation

Title: A brain-thyroid axis mediates stress-induced hormonal change in the male mice

Authors: *C. YU[1], H. LIAN[2], X.-M. LI[3];
[1]Zhejiang Univ., HangZhou, China; [2]Zhejiang Univ. Sch. of Med., Hangzhou, China; [3]Zhejiang Univ., Inst. of Neurosci., Hangzhou, China

Abstract: Rapid energy deployment under environmental stress drives adaptive responses and optimizes survival outcomes. Faced with environmental threats, animals must rapidly mobilize energy to drive the cardiovascular, muscular, and cognitive responses necessary for "fight" or "flight" behaviors. Accordingly, to optimize this threat-response system and restore energy, any competing behavioral patterns, such as foraging or consuming food, must be suppressed. Hormonal regulation plays a critical role in adapting the balance of energy expenditure. In response to acute stress, the central nervous system quickly initiates the hypothalamus-pituitary-adrenal (HPA) axis to fuel the energy pool and facilitate "fight" or "flight" behaviors. However, little is known about how the body suppresses resting and digesting behaviors. To address this question, we used foot shock as an acute stressor and illustrated the timescale of hormonal changes. We found thyroid hormone levels significantly declined in 90 minutes, while thyroid-stimulating hormone remained unchanged. The delayed onset of the hypothalamus-pituitary-thyroid (HPT) axis indicated that there was an alternative pathway rapidly regulating thyroid hormones. Using viral tracing coupled with tissue clearing, we mapped the three-dimensional landscape of the sympathetic and vagus nerve innervation targeting the thyroid. To investigate the function of autonomic innervation, we ablated the sympathetic nerve by injecting 6-hydroxydopamine. It turned out the ablation of the sympathetic nervous system had no effect on thyroid hormone levels. On the other hand, chemogenetic manipulation of the vagus nerve bidirectionally regulated thyroid hormone levels. Chemoinhibition of the vagus nerve also restored the reduction of thyroid hormone levels induced by foot shock. In summary, we demonstrate that this central-peripheral axis actively governs thyroid hormone dynamics in response to acute environmental stressors.

Disclosures: C. yu: None. **H. Lian:** None. **X. Li:** None.

Poster

PSTR021: Hormones and Cognition

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.20/BB23

Topic: I.08. Learning and Memory

Support: Charles E Kubly Mental Health Research Center
NIH Grant R21AG095422

Title: Ovarian hormone modulation of prefrontal neural activity during trace fear conditioning

Authors: *G. SCHAMBER, R. C. TWINING, M. R. GILMARTIN;
Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: Sex hormones modulate cognitive and emotional brain function and likely contribute to sex differences in fear learning disorders such as PTSD which affect women more than men. However, much is unknown about the influence of ovarian hormones on the neural circuits of fear memory. The prefrontal cortex is an important regulator of fear memories and ovarian hormones modulate prefrontal activity and fear extinction learning (Zeidan et al., 2011; Cover et al., 2014). We have found that estrous cycle state also shapes the acquisition of fear to threat-predictive cues in trace fear conditioning. Trace conditioning requires subjects to associate a neutral cue and aversive shock that are separated in time. We have previously shown that a subset of prelimbic (PL) neurons exhibit sustained firing to the cue beyond its offset, activity that is required for learning (Gilmartin & McEchron, 2005; Gilmartin et al., 2013). More recently we have found that ovarian hormone state during training influences fear memory strength and PL cellular mechanisms that support fear learning (Kirry et al., 2019; and unpublished). Here we investigate PL activity during trace conditioning across the estrous cycle to determine how hormone state affects learning-related activity supporting memory formation. Female rats were implanted with a GRIN lens in PL targeting neurons transfected with AAV-hsyn-GCaMP8f for in vivo calcium imaging with miniscopes. The estrous cycle was tracked with daily vaginal lavage, and rats received trace fear conditioning or unpaired control training on the day they entered late diestrus/proestrus (high ovarian hormones) or metestrus/early diestrus (low ovarian hormones) (n=3-4/group). Testing occurred the following day regardless of cycle stage. We recorded activity from ~100-150 neurons per rat across training and testing sessions. Initial results show greater cue-evoked activity at test in trace vs unpaired, consistent with associative learning. In trace-conditioned females, high ovarian hormone state increased the proportion of neurons with sustained activity during the trace interval compared with females trained in a low ovarian hormone state. Interestingly, cue-inhibited neurons show greater rebound magnitude in high ovarian hormone females. Together, these findings suggest that ovarian hormone state dynamically regulates cue-shock bridging during trace conditioning. Ongoing analyses will fully characterize hormone-modulated activity patterns during different trial epochs, including cue, trace, and shock periods, and across sessions and determine how these response profiles influence the storage and expression of fear memory.

Disclosures: G. Schamber: None. **R.C. Twining:** None. **M.R. Gilmartin:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.01/BB24

Topic: G.03. Stress and the Brain

Support: University of Colorado Cancer Center Support Grant P30CA046934

Title: Social isolation stress promotes ovarian cancer metastasis through sympathetic adrenergic signaling and neuroimmune remodeling of the omentum

Authors: *E. R. WOODRUFF, N. DAVIDSON, S. TANIS;
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Abstract: Social isolation is a potent psychosocial stressor that activates the sympathetic nervous system (SNS) and is associated with poor patient outcomes in multiple cancers, including high-grade serous carcinoma of the ovary (HGSC). However, the neurobiological mechanisms linking social stress to tumor progression remain poorly understood. Because the omentum is the preferred site of HGSC metastasis and is responsive to stress-related signaling, we tested whether SNS beta-adrenergic receptor (β-AR) activity mediates the effects of social isolation on metastatic progression and the omental tumor immune microenvironment.
Methods: We used 8-week-old female C57BL/6J mice and the murine HGSC cell line, ID8 $Trp53^{-/-}$. HGSC is specific to ovary-bearing individuals; thus, we did not include male mice. Mice were housed in social isolation (SI; 1 per cage) or group housing (GH; 4 per cage) and treated daily with vehicle or the nonselective β-AR antagonist, propranolol (20 mg/kg, n=8/group) via oral gavage. To assess disease stage-specific effects, independent cohorts underwent treatment either before or after tumor engraftment (intraperitoneal injection of ID8 cells). Physiological indices of stress, tumor burden, and omental immune composition were assessed at necropsy by an investigator blinded to treatment condition using tissue phenotyping, RNA sequencing, and pseudobulk immune deconvolution. Data were analyzed by two-way ANOVA.
Results: SI increased adrenal weight and reduced body weight gain, indicating activation of stress-responsive pathways. Across both pre- and post-engraftment paradigms, SI significantly increased omental tumor burden (0.064g vs. 0.091g, $p<0.0001$; 0.056g vs. 0.08g, $p=0.0121$, respectively) and metastatic dissemination (0.067g vs. 0.09g, $p<0.0001$; 0.061g vs. 0.074g, $p = 0.0003$, respectively), effects that were normalized by propranolol treatment. Within omental tumors, SI decreased tumor-inhibiting M1-like macrophages while increasing conventional and plasmacytoid dendritic cell content; these alterations were normalized by propranolol. In contrast, SI-induced reductions in $CD8^+$ T-cell content persisted despite β-adrenergic receptor blockade.
Conclusions: These findings identify sympathetic β-AR signaling as a key neuroimmune mechanism linking social isolation stress to ovarian cancer metastasis. Convergent behavioral, physiological, transcriptomic, and pharmacological evidence supports a model in which chronic social stress engages SNS pathways that remodel the omental immune microenvironment toward a pro-tumorigenic state, thereby facilitating disease progression.

Disclosures: E.R. Woodruff: None. **N. Davidson:** None. **S. Tanis:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.02/BB25

Topic: G.03. Stress and the Brain

Support: ORWH NIMH 3U54-MH11891

Title: Impact of peripheral cytokines on cell activity in the dorsal vagal complex

Authors: *E. CASTELLANOS[1], S. A. TOBET[2];
[1]Colorado State Univ., Fort Collins, CO, CO; [2]Colorado State Univ., Loveland, CO

Abstract: A growing body of evidence indicates a subset of patients with major depressive disorder exhibit elevated peripheral levels of inflammatory cytokines, including IL-6 and TNF-α. The consistent association between inflammation and depression, along with consideration of inflammatory biomarkers in the development of the sixth edition of the Diagnostic and Statistical Manual of Mental Disorders, has created new opportunities to investigate the mechanisms through which cytokine signaling contributes to depression and stress-related pathology. Understanding how cytokines influence neuronal populations involved in immune signaling is critical for identifying the long-term consequences of chronic inflammation and developing more effective therapeutics. In this study, we examined the effects of peripheral cytokine administration on cellular activity within the dorsal vagal complex (DVC), a region involved in autonomic and immune regulation through the inflammatory reflex. The DVC contains the area postrema, a sensory circumventricular organ with fenestrated capillaries enabling direct communication with circulating immune signals. Mice received peripheral injections of IL-6 (76 μg/kg), TNF-α (63 μg/kg), or IL-10 (68 μg/kg) and were perfused 2, 4, or 6 hours later. Brainstem tissue was processed for immunohistochemical detection of c-Fos, NeuN, S100β, and IBA-1 to assess temporal patterns of cellular activation and identify potential downstream effects of cytokine signaling. We hypothesize that cytokines induce distinct, cell type-specific patterns of activation across time. Preliminary data show greater c-Fos expression in the nucleus tractus solitarius (NTS) following TNF-α compared with IL-6 treatment at all time points. At 2 hours, TNF-α induced an average of 510 c-Fos-positive cells versus 40 following IL-6 treatment (12.75-fold difference). At 4 hours, averages increased to 376 and 213 cells, respectively (1.76-fold difference). At 6 hours, TNF-α produced 554 c-Fos-positive cells compared with 78 following IL-6 treatment (7.1-fold difference). Additional findings suggest a temporal shift in cellular activation, with increased neuronal c-Fos expression at 2 hours followed by increased astrocytic c-Fos expression at 6 hours. Ongoing studies will distinguish activity driven by peripheral cytokine signaling from that mediated by the vagal inflammatory reflex, clarifying the relative contributions of central and peripheral immune signaling pathways.

Disclosures: E. Castellanos: None. **S.A. Tobet:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.03/BB26

Topic: G.03. Stress and the Brain

Support: Rutgers Camden Chancellors Grants for Independent Student Research

Title: Sphingosine-1-Phosphate Receptor 3 (S1PR3) Mitigates Neuroinflammation via Galanin Signaling

Authors: *Z. BACCHUS[1,2], B. CORBETT[1,2];
[1]Rutgers Camden, Camden, NJ; [2]Ctr. for Computat. and Integrative Biol., Camden, NJ

Abstract: Chronic stress drives neuroinflammation, in part by activating microglial tumor necrosis factor-α (TNF-α) release. TNF-α contributes to behavioral dysfunction and increases vulnerability to stress-related disorders. Our lab has previously shown that activation of sphingosine-1-phosphate receptor 3 (S1PR3) reduces anxiety-like behavior and increases sociability. However, the mechanisms by which S1PR3 reduces inflammation and increases sociability remain poorly understood. Using RNA sequencing, we found that the pharmacological activation of S1PR3 increases transcription of the neuropeptide galanin. Because galanin suppresses microglial TNF-α production and increases sociability, we hypothesize that S1PR3 reduces TNF-α and increases sociability by increasing galanin levels in the brain. To test this, we treated mice with either vehicle or the S1PR3-specific agonist CYM5541. We found that CYM5541 increased galanin protein expression within the locus coeruleus, a major source of galanin, compared to vehicle-treated controls under baseline conditions. These findings provide evidence that S1PR3 activation is sufficient to enhance galanin signaling in a key stress-responsive brain region. Together, this work provides a potential mechanism by which S1PR3 mitigates stress-induced TNF-α and increases sociability.

Disclosures: Z. Bacchus: None. **B. Corbett:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.04/BB27

Topic: G.03. Stress and the Brain

Support: JSPS KAKENHI 25K19080
JSPS KAKENHI 24K10679

Title: Neuroendocrine modulators potentially regulate hyper activity and gut microbiota composition in activity-based anorexia model

Authors: *S. SAKAMOTO[1], H. KAWAI[2], Y. OHYA[3], T. ASADA[3], A. YOKODE[3], K. HINOTSU[3], M. TAKAKI[1];
[1]Okayama Univ. Fac. of Medicine, Dent. and Pharmaceut. Sci., Okayama, Japan; [2]Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Dept. of Neuropsychiatry, Okayama Univ. Grad. Sch. of Medicine, Dent. and Pharmaceut. Sci., Okayama, Japan

Abstract: Introduction: In anorexia nervosa (AN), hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis is associated with elevated corticosterone levels and resistance to ghrelin, an orexigenic hormone, both of which are thought to contribute to reduced body weight and food intake. Gut microbiota dysbiosis has also been implicated in the endocrine pathophysiology of AN; however, no studies have investigated the effects of targeting these endocrine abnormalities on the gut microbiota. Here, we investigated the effects of a glucocorticoid-modulating agent and a traditional herbal medicine that ameliorates ghrelin resistance in an activity-based anorexia (ABA) mouse model. We evaluated behavioral phenotypes, gut microbiota composition, brain inflammation, and blood hormone levels to explore the mechanisms underlying AN from a gut-brain axis perspective.Method: Female C57BL/6J mice underwent a 5-7-day ABA paradigm, involving 3 h of daily food access and unrestricted wheel access, until they reached 25% body weight loss or the end of the experimental period. Mice were orally treated once daily with glucocorticoid-modulating agent (potent 11β-HSD1 inhibitor, DSOK-0011) or traditional herbal medicine that ameliorates ghrelin resistance (Rikkunshito), or vehicle. Body weight, food intake, and activity transitions were recorded; plasma corticosterone and ghrelin levels were measured using ELISA assay; gut microbiota was analyzed using 16S rRNA sequencing; and brain neuronal cells and glial cells were analyzed using immunohistochemistry.All procedures were approved by the Animal Care and Use Committee, Okayama University.Results: ABA mice showed decreased body weight and food intake, hyperactivity, elevated corticosterone levels, and resistance to ghrelin. DSOK-0011-treated mice exhibited suppressed food anticipatory activity compared with vehicle-treated mice. Gut microbiota analysis revealed increased gut microbial alpha diversity in ABA mice, with a specific enrichment of the Lachnospiraceae family in the DSOK-0011-treated group. However, DSOK-0011 did not significantly affect body weight, food intake, serum corticosterone levels, or hippocampal glial cell populations. Analysis of the effects of Rikkunshito is currently ongoing, and the results will be presented at the meeting.Conclusion: These findings suggest that modulation of glucocorticoid signaling may alter gut microbiota composition and food anticipatory activity in ABA mice, supporting a role for endocrine-gut-brain interactions in the pathophysiology of AN.

Disclosures: S. Sakamoto: None. **H. Kawai:** None. **Y. Ohya:** None. **T. Asada:** None. **A. Yokode:** None. **K. Hinotsu:** None. **M. Takaki:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.05/BB28

Topic: G.03. Stress and the Brain

Support: This work was supported by the ISRAEL SCIENCE FOUNDATION grant No. 2330/23

Title: ADAM10/17-Dependent Fractalkine Signaling Through Microglial CX3CR1 Regulates Early Neuroinflammation Associated with Stress-Induced Depression

Authors: *E. DINUR[1], E. ROBINSON[1], L. NAGGAN[2], R. YIRMIYA[1];
[1]Psychology, [2]Neurobio., The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Microglial activation is central to the pathophysiology of depression. Mice lacking the microglial checkpoint receptor CX3 chemokine receptor 1 (CX3CR1; Cx3cr1$^{-/-}$) exhibit resilience to chronic stress. Activation of CX3CR1 by neuronal membrane-bound fractalkine (CX3CL1) maintains microglial quiescence, whereas CX3CL1 cleaved by shedding enzymes, including a disintegrin and metalloproteinase 10 and 17 (ADAM10/17) and cathepsin S (CTSS), induces activation. We hypothesized that stress-induced depression is driven by alterations in microglial checkpoint signaling and CX3CL1-shedding enzymes, while Cx3cr1$^{-/-}$ mice remain protected from these molecular and behavioral consequences. Here, WT and Cx3cr1$^{-/-}$ mice (10-12 weeks old, n=7-20/group; only males were used due to paradigm-inherent territorial aggression) were subjected to chronic social defeat stress (CSDS). Behavioral outcomes, microglial phenotypes, and whole-hippocampal gene expression were assessed. Following 10-day CSDS, WT mice displayed anxiety-like behavior, anhedonia, increased microglial density, soma size and hyper-ramification, as well as elevated *Ctss* expression. In contrast, Cx3cr1$^{-/-}$ mice were behaviorally resilient, exhibiting a hypo-inflammatory transcriptional profile with reduced expression of tumor necrosis factor alpha (*Tnfa*), interleukin-1 beta (*Il1b*), checkpoint receptors (*lymphocyte-activation gene 3* and *Cd200r*), *Ctss* and *Adam10/17*. To capture the early dynamics driving this divergence, mice were exposed to a 6-day CSDS paradigm. WT mice exhibited a robust early neuroinflammatory transcriptional response, including increased *Tnfa*, *Il1b*, *Cd200r*, *Ctss*, *Adam10*, and *Cx3cl1* expression, whereas Cx3cr1$^{-/-}$ mice did not exhibit stress-induced upregulation of these transcripts. To further examine the role of CX3CL1 cleavage, we assessed the effects of selective ADAM10/17 inhibition via daily INCB7839 injections (50 mg/kg, i.p.) in WT mice exposed to 6-day CSDS. This treatment abolished the early inflammatory response and the upregulation of *Ctss*, closely phenocopying the Cx3cr1$^{-/-}$ transcriptomic signature. In conclusion, alterations in microglial checkpoint receptors may contribute to the distinct basal morphology and transcriptional profile of Cx3cr1$^{-/-}$ mice but are unlikely to account for their resilience to CSDS. Rather, converging evidence from CX3CR1$^{-/-}$ mice and pharmacological ADAM10/17 inhibition point to a key role for ADAM10/17-dependent fractalkine signaling in regulating the neuroinflammatory response to CSDS, which subsequently promotes microglial remodeling and the development of depression-like behavior in WT mice.

Disclosures: E. Dinur: None. **E. Robinson:** None. **L. Naggan:** None. **R. Yirmiya:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.06/BB29

Topic: G.03. Stress and the Brain

Title: Early life stress-induced alterations in extended amygdala glial morphology

Authors: *J. VILLARREAL, L. R. HALLADAY;
Dept. of Neurosci., Univ. of Arizona, Tucson, AZ

Abstract: Exposure to early life stress (ELS) is a major risk factor for neuropsychiatric and inflammatory disorders. Mounting evidence suggests that these effects may be driven by persistent disruption of glia, non-neuronal cells that modulate neural communication and neuroinflammation. Our lab uses a rodent model of ELS that reliably incites behavioral dysfunctions mirroring human clinical outcomes - maternal separation with early weaning (MSEW), during which pups are separated from the dam for 4h on postnatal days (P) 2-5, 8h on P6-16, and weaned 4 days early on P17. We previously identified a central locus for these effects - circuitry within the extended amygdala (EA). ELS has been linked with altered neuroinflammation, so we are exploring an unstudied question of whether MSEW incites behavioral dysregulation via alterations to EA-specific neuroimmune mechanisms. To this end, we assessed MSEW effects on microglial and astrocyte morphology and density, proxies for activational changes through which these glial cells may modulate MSEW outcomes. We harvested tissue from adult C57BL/6J MSEW mice and their non-stressed (NS) siblings, and immunolabeled Iba-1 and GFAP markers (microglia and astrocytes, respectively). We manually quantified Iba-1+ cellular morphology based on pre-defined types (i.e., ramified, intermediate, ameboid) and found MSEW to significantly increase active “ameboid” Iba-1+ cells specifically in the EA. There were no differences in Iba-1+ cellular density or immunoreactivity. GFAP+ cells were reconstructed in 3D using semi-automated tracing in the FIJI SNT Plugin for Sholl analysis and process arborization measurements. MSEW induced morphological atrophy in these cells, significantly decreasing both the Sholl area under the curve and total process length compared to NS mice. Overall, this evidence that MSEW leads to morphological changes in both astrocytes and microglia in the EA has potential implications for these cells’ functionality and interactions with neurons. Ongoing experiments will determine the impact of these changes on behavioral outcomes and adulthood stress-induced neuroimmune responses. These findings establish a foundation to examine mechanistic roles for microglia and astrocytes in ELS-associated neuropsychiatric and immunological health.

Disclosures: J. Villarreal: None. **L.R. Halladay:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.07/BB30

Topic: G.03. Stress and the Brain

Support: ISRAEL SCIENCE FOUNDATION grant No. 2330/23

Title: Long-Term Immune Tolerance Exacerbates Susceptibility to Stress-Induced Depression via Microglial Hypofunctioning

Authors: *E. ROBINSON, E. DINUR, L. NAGGAN, R. YIRMIYA;
The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: The innate immune system, including brain microglia, exhibits memory of prior immune challenges, fundamentally altering responses to subsequent stimuli. While immune tolerance (a state of diminished responsiveness following repeated inflammatory stimulation) is a well-established phenomenon, its long-term impact on vulnerability to psychological stress remains largely unknown. In this study, we firstly examined the effects of 6 daily injections of LPS on the behavioral and immunological responsiveness to a subsequent LPS administration, revealing a prolonged (> 3 weeks) state of tolerance, characterized by diminished peripheral and brain cytokine expression and attenuated sickness behavior. We then investigated whether long-term LPS tolerance alters behavioral and microglial responsiveness to a subsequent acute stressor. One week following the cessation of the 6 days tolerance induction, adult male mice (n = 8-10/group) were exposed to a 20 minutes forced swim stress (FSS). To assess long-term vulnerability, behavioral testing and microglial morphological analyses were conducted two weeks post-stress. Surprisingly, following FSS, LPS-tolerant mice exhibited exacerbated depressive-like symptoms, including anhedonia in the sucrose preference test and increased immobility in the forced swim test (FST). The divergent effects of repeated inflammatory stimulation on subsequent LPS vs. stress challenges suggested that diminished or dysregulated microglial responsiveness is detrimental for the stress response. To test this hypothesis, a low dose of LPS was administered to tolerant mice two hours before FSS exposure. This acute stimulation successfully rescued the exaggerated stress phenotype, and normalized the tolerance-associated microglial alterations. Conversely, administration of the microglial inhibitor minocycline to naive mice before FSS phenocopied the tolerant state, significantly increasing stress-induced depressive-like behavior. These results demonstrate that repeated inflammatory exposure induces long-term microglial immune tolerance and a dysregulated phenotype that, rather than conferring protection, renders individuals more susceptible to subsequent psychological stress. These findings reveal an important interaction between immune memory and stress susceptibility and highlight microglial modulation as a potential therapeutic target for neuroinflammatory and stress-related disorders.

Disclosures: E. Robinson: None. **E. Dinur:** None. **L. Naggan:** None. **R. Yirmiya:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.08/BB31

Topic: G.03. Stress and the Brain

Support: R21 AA031101
Health Science Transdisciplinary Award of Excellence awarded by SUNY Binghamton

Title: Cross-sensitization of Chronic Ethanol Drinking and Stress Modulates Mouse Anxiety-Like Behavior via IL-1β Signaling

Authors: *J. BACAR[1], M. V. SCROGER[1], D. M. LAM[2], A. E. MARTIN[2], T. D. DAVIS[2], F. P. VARODAYAN[1];
[1]Psychology, Binghamton Univ., Vestal, NY; [2]Pharmaceut. Sci., Binghamton Univ., Binghamton, NY

Abstract: Both alcohol (ethanol; EtOH) and stress independently activate the neuroimmune system and its master regulator interleukin-1β (IL-1β), suggesting a shared mechanism that may contribute to the stress-induced development of excessive alcohol drinking. IL-1β is a pro-inflammatory cytokine that canonically activates a MyD88-dependent pathway in response to acute challenges (i.e. alcohol and stress). However, the role of IL-1β at the intersection of alcohol and stress remains unclear. To bridge this gap, we first developed a mouse model of cross-sensitization between chronic ethanol drinking and stress and then administered a MyD88 antagonist drug to block the proinflammatory IL-1β response. The MyD88 antagonist transiently reduced ethanol intake in male and female mice with a history of chronic ethanol drinking. We then confirmed that chronic ethanol drinking followed by acute restraint stress increased anxiety-like behavior in both sexes, and this potentiation was sex-dependently modulated by the drug. Overall, this study indicates that ethanol intake and the cross-sensitization between ethanol and stress are both mediated by IL-1β response, though there are some key sex differences. Ongoing studies are investigating possible alcohol- and stress-induced changes in mPFC cell type-specific IL-1R1 receptor expression in both sexes. This study highlights targeting IL-1β signaling as a potential pharmacological treatment to reduce alcohol consumption and negative affective states in subpopulations of patients with AUD (e.g. comorbid stress disorder).

Disclosures: J. Bacar: None. **M.V. Scroger:** None. **D.M. Lam:** None. **A.E. Martin:** None. **T.D. Davis:** None. **F.P. Varodayan:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.09/BB32

Topic: G.03. Stress and the Brain

Support: R21MH134017
The Ronald J Taylor, MD ’73 Endowed Fellowship in Psychiatry Award 2023
Brain and Behavior Research Foundation Young Investigator Award 2022
1F31AA032134-01A1

Title: CD4+ T cells developmentally regulate bed nucleus of the stria terminalis physiology and associated behavior

Authors: *A. N. SICLAIR[1], J. ABRAMOVITZ[2], B. N. MATHUR[1], S. M. CLARK[2];
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Abstract: While neurodevelopmental disorders are clinically heterogeneous, common features include sex differences, altered stress responses, and immune dysregulation. Mounting evidence indicates that CD4+ T cells, key players in the adaptive immune system, may participate in developmental neuroimmune interactions that modulate stress-associated behaviors. How CD4+ T cells developmentally regulate neurophysiology in the brain regions encoding these behaviors, such as the bed nucleus of the stria terminalis (BNST), is unknown. Within the BNST, the oval nucleus (BNSTov) drives stress responsivity via a subpopulation of neurons expressing corticotropin releasing hormone (CRH). These CRH+ neurons exhibit sex differences and are immune-sensitive, positioning them as likely downstream targets of CD4+ T cell neuroimmune interactions. Therefore, we hypothesized that CD4+ T cells are required during development to establish sex differences in BNSTov CRH+ neurophysiology and related stress-associated behaviors. To test this, we treated neonatal mice with an α-CD4 antibody to transiently deplete CD4+ T cells, which coincides with the early postnatal period of neurodevelopment. Assessing BNSTov CRH+ neurophysiology in adulthood, we identified a basal sex difference in neuronal excitability: neurons from male mice were more excitable than those from females. We further found that α-CD4 treatment differentially altered BNSTov CRH+ neuronal excitability in males and females, eliminating the sex differences seen with control mice. At the synaptic level, we found that α-CD4 treatment differentially altered excitatory neurotransmission onto BNSTov CRH+ neurons in males and females, exhibiting an increase and decrease respectively. Behaviorally, we found that α-CD4 treatment decreased anxiety-like behavior in the light/dark box assay in females, eliminating existing sex differences. Altogether, these findings suggest that CD4+ T cells establish sex differences in BNSTov CRH+ neurophysiology and stress-associated behaviors, an effect that may contribute to stress-related emotional dysregulation and sex-specific phenotypes across neurodevelopmental disorders.

Disclosures: A.N. Siclair: None. **J. Abramovitz:** None. **B.N. Mathur:** None. **S.M. Clark:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.10/CC1

Topic: G.03. Stress and the Brain

Title: IL-6 rs1800795 gene variant psychoneuroendocrinoimmunology recovery to acute psychosocial stress in mexican university student

Authors: *F. G. SÁNCHEZ GARCÍA[1], Y. K. GUTIERREZ-MERCADO[2], F. JAUREGUI[3]; [1]CUCS, Univ. de Guadalajara, Guadalajara, Mexico; [2]Dept. of Clin., Univ. de Guadalajara - Ctr. Universitario Los Altos, Guadalajara, Mexico; [3]Univ. Nacional Autónoma de México, CDMX, Mexico

Abstract: The rs1800795 (−174G>C) SNP in the IL6 promoter modulates interleukin-6 (IL-6) expression, yet its consequences for integrated psychoneuroimmunological stress responses remain poorly characterized in Mexican populations. Most studies examine reactivity without assessing post-stress regulation, leaving unresolved whether genotypic differences reflect greater stress magnitude or impaired recovery. Mexican university students (N=30; G:G n=15, G:C n=15) underwent a modified Group Trier Social Stress Test (TSST-G) followed by four executive function paradigms (Go/NoGo, 2-Back, WCST, Stroop). Heart rate (HR) and respiratory rate (RR) were recorded at T0 (baseline), T1 (post-TSST), and T2 (post-cognitive battery). Blood samples at each timepoint allow serum IL-6 and cortisol quantification by ELISA (under processing). Genotyping used TaqMan SNP allelic discrimination. Wilcoxon and Mann-Whitney U tests were complemented with rank-biserial effect sizes (r) and Bayes factors (BF_{10}). The TSST-G induced sympathetic activation in 100% of participants ($W=0$, $p<.001$, $r\geq.86$, $BF_{10}>10^9$). Genotype differences emerged exclusively in recovery: G:G carriers retained greater residual HR (+16.5 bpm) and RR (+5.5 rpm) above baseline at T2 vs. G:C ($r\geq.78$, $BF_{10}\geq18$), despite equivalent reactivity at T1 ($p>.67$). Recovery indices showed rank-complete separation ($U=0$, $r=1.00$). Cognitive performance showed a speed-accuracy trade-off (latencies $z=+1.4$ to $+19.6$ SD above norms) without genotype differences, consistent with IL-6 mediation pending integration. Serum IL-6 and cortisol data are expected to confirm pro-inflammatory persistence and attenuated cortisol recovery in G:G carriers, enabling Genotype→IL-6→Autonomic Recovery mediation modeling. The rs1800795 G:G genotype marks differential autonomic regulatory efficiency, not stress magnitude, under acute psychosocial stress, consistent with IL-6 modulation of parasympathetic tone and HPA axis activity. These findings advance understanding of how inflammatory genetic variation shapes individual vulnerability to stress dysregulation.
Note: IL-6 and cortisol ELISA results are currently under laboratory processing and will be incorporated into the final version prior to submission. The autonomic findings presented here are complete and definitive.

Disclosures: F.G. Sánchez García: None. **Y.K. Gutierrez-Mercado:** None. **F. Jauregui:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.11/CC2

Topic: G.03. Stress and the Brain

Title: Sex Differences in the Effects of Oral Antibiotics on the Cellular and Behavioral Consequences of Sub-chronic Stress in Mice

Authors: *T. J. BORK[1], C. MCCALL[2], B. D. SACHS[1];
[1]Psychological and Brain Sci., [2]Villanova Univ., Villanova, PA

Abstract: Stress-related psychiatric disorders are increasingly common conditions that are notoriously difficult to treat. Identifying the factors that increase the risk of these conditions and defining the biological mechanisms through which they promote the development of these disorders could inform disease pathophysiology and reveal novel therapeutic strategies to improve mental health. Clinical findings suggest that oral antibiotics increase the risk of depression and anxiety, but preclinical studies have had mixed results. Administering antibiotics to rodents has been reported to induce depression- or anxiety-like behavior in some studies but to protect against stress-induced increases in depression- and anxiety-like behavior in others. The reasons for these discrepancies are unclear. The current study examined the effects of antibiotics on stress susceptibility in a model of sub-chronic stress in male and female c57BL/6 mice. Following exposure to oral antibiotics and/or stress, mice were tested in a panel of behavioral assays prior to their brains being examined for potential changes in hippocampal neurogenesis and microglial number. Overall, our results indicate that antibiotics increased susceptibility to stress in several assays, and some of these effects were more pronounced in females than males. Exposure to antibiotics also reduced the proliferation of progenitor cells in the hippocampus of unstressed, but not stressed, animals of both sexes but did not significantly impact the number of microglia or immature neurons in the hippocampus. Future work should examine additional potential mechanisms through which antibiotics impact stress susceptibility and behavior in males and females.

Disclosures: T.J. Bork: None. **C. McCall:** None. **B.D. Sachs:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.12/CC3

Topic: G.03. Stress and the Brain

Support: Canadian Institutes of Health Research Postdoctoral Fellowship 201811MFE-414896-231226
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National Institutes of Health grant R01MH127820

Title: Stress-activated brain-gut circuits disrupt intestinal barrier integrity and social behavior

Authors: *K. L. CHAN[1], L. LI[2], L. F. PARISE[7], F. CATHOMAS[8], K. B. LECLAIR[3], Y. SHIMO[4], H.-Y. LIN[9], R. DURAND-DE CUTTOLI[9], A. V. AUBRY[15], H. OH[10], J. ALVAREZ[16], T. DRESCHER[17], R. L. FISHER-FOYE[16], E. KUZYK[18], Z. XIE[11], A. OSMAN[19], C. YUAN[17], K. SONG[8], Z. WANG[8], G. PRICE[5], M. P. KASTER[20], B. KIM[12], J. WANG[13], H. HU[14], S. STANLEY[6], I. E. DE ARAUJO[21], S. J. RUSSO[22];
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[22]Neurosci., Icahn school of medicine at mount sinai, New York, NY

Abstract: BACKGROUND: Chronic psychosocial stress is a major risk factor for neuropsychiatric disorders such as major depressive disorder (MDD) and disorders of gut-brain interactions such as irritable bowel syndrome (IBS), two of the most prevalent disorders with high rates of co-morbidity. Potentially underlying this co-morbidity is the recent finding that chronic stress elicits low-grade inflammation, which is associated with the severity of both MDD and IBS symptoms. Increasing evidence suggests that the gut-brain axis, or connections between the central and enteric nervous systems, contributes to the etiology of these disorders. However, the mechanisms through which chronic stress influences gut pathophysiology including inflammation, and how this inflammation in turn impacts behavior is not fully known.
METHODS: Using the 10-day chronic social defeat stress (CSDS), a mouse model of chronic psychosocial stress that recapitulates biological and behavioral symptoms of MDD and IBS, we measured gut inflammation by flow cytometry, intestinal permeability by orally gavaging mice with FITC-Dextran, and depression-relevant behavior by social interaction testing. To identify neurocircuitry regulating stress-induced intestinal pathophysiology, we used retrograde tracing, whole-tissue staining and chemogenetic strategies to identify and manipulate brain-gut circuits.
RESULTS: Both male and female mice exposed to CSDS showed increased pro-inflammatory Th1 in the colon, greater intestinal permeability, and elevated circulating lipopolysaccharide (LPS) levels compared to unstressed control mice. We next identified that noradrenergic neurons in the celiac and superior mesenteric ganglia (CG-SMG) as well as enteric neurons in the colon become activated by stress, and ablating these cells protects against stress-induced gut pathophysiology. Retrograde tracing from the enteric neurons in the colon revealed that corticotropin-releasing hormone (CRH)-expressing neurons in the paraventricular nucleus of the hypothalamus (PVH) innervate the gut. Further, using chemogenetic activation or inhibition of PVH CRH^{+} neurons, we found that these neurons can regulate intestinal inflammation, barrier permeability, and social avoidance behavior induced by CSDS.
CONCLUSIONS: Collectively, our results illustrate a brain-gut circuit where stress signals are

conveyed from the brain to the gut to trigger intestinal inflammation and disrupt intestinal barrier function, potentially promoting depression-like behavior.

Disclosures: K.L. Chan: None. **L. Li:** None. **L.F. Parise:** None. **F. Cathomas:** None. **K.B. LeClair:** None. **Y. Shimo:** None. **H. Lin:** None. **R. Durand-De Cuttoli:** None. **A.V. Aubry:** None. **H. Oh:** None. **J. Alvarez:** None. **T. Drescher:** None. **R.L. Fisher-Foye:** None. **E. Kuzyk:** None. **Z. Xie:** None. **A. Osman:** None. **C. Yuan:** None. **K. Song:** None. **Z. Wang:** None. **G. Price:** None. **M.P. Kaster:** None. **B. Kim:** None. **J. Wang:** None. **H. Hu:** None. **S. Stanley:** None. **I.E. De Araujo:** None. **S.J. Russo:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.13/CC4

Topic: G.03. Stress and the Brain

Title: Stress-induced brain-reactive IgG links meningeal lymphatic activation to perivascular brain entry and behavioral susceptibility

Authors: *X. GUO[1], S. J. RUSSO[2];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Neurosci., Icahn school of medicine at mount sinai, New York, NY

Abstract: Major depressive disorder is associated with immune dysregulation, but whether humoral immunity is a causal mediator of stress susceptibility remains unclear. We tested whether chronic social defeat stress (CSDS) induces a meningeal lymphatic-antibody-brain pathway that allows circulating IgG to enter reward circuitry and promote behavioral deficits. In male and female mice, CSDS separated susceptible (SUS) and resilient (RES) animals by social interaction. SUS mice showed increased plasma IgG, enrichment of inflammatory IgG2a/IgG2b subclasses, and an inverse relationship between IgG abundance and social interaction. Intracisternal OVA/dextran tracing showed enhanced meningeal drainage to deep cervical lymph nodes in SUS mice, accompanied by expansion of IgG+ B cells and plasma cells. Confocal imaging of nucleus accumbens revealed IgG accumulation in a perivascular compartment bounded by CD31+ endothelial cells and AQP4+ astrocytic endfeet, consistent with entry through the neurovascular unit. Functionally, mice lacking mature IgG were protected from CSDS-induced social avoidance and anxiety-like behavior, whereas passive transfer of IgG purified from stress-susceptible donors into naive recipients was sufficient to induce social avoidance. Human data converged with this model: in MDD cohorts (n=138), inflammatory IgG subclasses, including IgG3, were elevated and correlated with perceived stress and brain-reactive IgG signals. Together, these data identify stress-induced IgG as a causal humoral mediator linking peripheral adaptive immunity to brain vascular entry and behavioral susceptibility. The findings support a model in which psychosocial stress enhances meningeal lymphatic antigen drainage and B cell activation, generating brain-reactive IgG that gains access to perivascular

reward-circuit niches, potentially through FcRn-dependent transcytosis, and promotes depression-related behavior. This antibody-brain axis provides a mechanistic bridge between stress, BBB biology, and mood disorders, and suggests that IgG subclass profiles and FcRn-directed interventions could define a targetable immune subtype of depression.

Disclosures: X. Guo: None. **S.J. Russo:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.14/CC5

Topic: G.03. Stress and the Brain

Title: Colitis Increases Susceptibility to a Subset of Stress-Induced Behavioral Alterations in C57BL/6 Mice

Authors: *A. VIRONE, B. D. SACHS, E. KHOO;
Psychological and Brain Sci., Villanova Univ., Villanova, PA

Abstract: Inflammatory Bowel Disease (IBD) is a debilitating condition that affects roughly 2.3 million people in the United States. Individuals with IBD have increased rates of mental illnesses, such as depression and anxiety, which can further impair functioning. However, the mechanisms underlying the link between IBD and psychiatric symptoms remain largely unknown. This study aimed to determine whether gut inflammation increases susceptibility to stress-induced behavioral changes in mice. We used the dextran-sulfate sodium (DSS) model of colitis and a three-day sub-chronic stress paradigm followed by behavioral testing and histological assessments of hippocampal tissue. In the light-dark emergence test (LDE), DSS significantly increased susceptibility to stress-induced anxiety-like behavior, as stress only significantly reduced the time spent and distance traveled in the light chamber in DSS-exposed animals, not in controls. A DSS-by-stress interaction was also observed in the open field test (OFT), in which stress only significantly reduced total distance traveled and distance and entries into the center in DSS-exposed animals, not controls. However, a significant three-way interaction was also observed in the OFT, in which the DSS-induced increase in stress susceptibility was only present in females. In the novelty-suppressed feeding test (NSF), stress significantly increased the latency to feed in the novel environment, but this effect was not impacted by sex or DSS history. In the sucrose preference test (SPT), no significant effects of stress or DSS were observed. In the Forced Swim Test (FST), stress reduced activity and latency to immobility, and a sex-by-DSS interaction was observed in which DSS reduced immobility latency in males but increased latency in DSS females. Following behavioral testing, brains were evaluated for cell proliferation via BrdU staining and microglial number (i.e., Iba1 immunoreactivity) in the hippocampus. Females had significantly more Iba1+ cells in the dentate gyrus and hilus compared to males. DSS significantly reduced the number of Iba1+ cells in the DG, but a similar effect in the hilus did not reach statistical significance ($p = 0.053$). Regarding

the BrdU analysis, females had more BrdU+ cells in the DG than males overall. However, a sex by DSS interaction was also observed, and this sex difference was only observed in DSS-exposed animals, suggesting that DSS increases cellular proliferation in females, but not males. Together, these findings show that colitis increases susceptibility to a subset of stress-induced behavioral changes while impacting both adult neurogenesis and microglia in the hippocampus.

Disclosures: A. Virone: None. **B.D. Sachs:** None. **E. Khoo:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.15/CC6

Topic: G.03. Stress and the Brain

Title: Exploring the Role of Ketamine in a Central Insulin Resistance Model of Depression

Authors: G. ZHANG[1], *S. TYE[2];
[1]Queensland Brian Institute,, [2]Queensland Brain Inst., The Univ. of Queensland, St Lucia, Australia

Abstract: We previously developed an animal model of depressive-like behaviour using central administration of alloxan, initially conceptualized as a model of central insulin resistance. New findings indicate it may instead reflect systemic inflammatory processes with central neurotoxicity. This study examined the behavioural and mechanistic effects of low-dose ketamine within this model.
Alloxan (0.5 mg/kg) or artificial cerebrospinal fluid (aCSF) was administered bilaterally via the intracerebroventricular route to male and female Wistar rats, with buprenorphine (0.03 mg/kg, s.c.) provided to a subset. Two weeks later, animals received either saline (0.9%) or ketamine (10 mg/kg, i.p.). Subsets underwent glucose tolerance testing, behavioural assays (Open Field, Novel Object Recognition, Forced Swim Test), cellular bioenergetic assays of peripheral blood mononuclear cells, and histological analyses of neuroinflammation.
Glucose tolerance was unchanged between groups. Histology revealed microglial activation, astrocytic aggregation, and disrupted ventricular morphology in alloxan-treated animals, alongside elevated CRP ($p<0.05$). In PBMCs, both ketamine- and alloxan-treated groups showed reduced glycolytic dependence ($p<0.05$), whereas combined treatment resembled controls, suggesting convergence of inflammatory and metabolic stressors on energy balance. Behaviourally, ketamine impaired short-term memory, an effect blocked by alloxan ($p<0.01$). Stress-coping behaviour did not differ significantly across groups, though buprenorphine independently increased immobility in the Forced Swim Test ($p<0.001$).
Alloxan induces neuroinflammatory and neurotoxic changes rather than peripheral insulin resistance, providing a CNS-focused model. Ketamine impaired cognition but not stress coping, with effects shaped by inflammatory-metabolic interactions. Buprenorphine confounded

behavioural outcomes, underscoring the importance of considering analgesic and metabolic contexts in translational ketamine research.

Disclosures: G. Zhang: None. **S. Tye:** None.

Poster

PSTR022: Stress: Neuroimmunology

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.16/CC7

Topic: G.03. Stress and the Brain

Support: Northeastern University

Title: Stress hormones trigger neutrophil extracellular trap release that contributes to behavioral changes

Authors: K. THANGAMANI[1], H. PRECE[1], J. CARTER[1], J. SURENDRAN[2], O. DOUGLAS[3], E. K. BRENGEL[4], C. F. FERRIS[5], ***E. OKEKE**[1];
[1]Northeastern Univ., Boston, MA; [2]Northeastern Univ., Jamaica Plains, MA; [3]Northeastern Univ., Ossining, MA; [4]Psychology, [5]Dept Psychology, Northeastern Univ., Boston, MA

Abstract: Introduction The interaction between neuroendocrine and immune systems contribute to homeostasis and the molecular mechanisms relevant in this cross-talk remain unclear. Psychological stress is known to drive systemic inflammation, raising the possibility that stress mediators such as glucocorticoids and catecholamines act directly on innate immune cells like neutrophils. The present study investigates the interplay between stress-associated hormones and neutrophil activity, and its potential contribution to alterations in behavior.**Methods:** We investigated neutrophil activation characterized by neutrophil extracellular trap (NET) formation after 28 days of chronic restraint stress in mice. Human neutrophils were treated with cortisol or epinephrine ex vivo to test whether these hormones trigger NET release. We also profiled receptor expression and asked whether neutrophils themselves produce these hormones. The behavioral consequences of administering NET-derived components to mice were assessed, and transcriptomic changes in NET-associated proteins following glucocorticoid receptor stimulation in humans were examined.**Results:** Chronic stress increased NET formation, with extracellular DNA increasing by roughly 60%. Cortisol alone was sufficient to drive NET release in human neutrophils. This was paired with higher adrenergic and glucocorticoid receptor expression and increased neutrophil-derived cortisol and epinephrine, pointing to an autocrine or paracrine amplification loop. Injecting NET-derived components into mice produced anxiety-like behavior, and glucocorticoid receptor activation in human cells upregulated the expression of genes encoding NET-related proteins.**Conclusion:** Our data reveal a reciprocal signaling axis between the neuroendocrine system and neutrophil-mediated immunity, whereby stress hormones promote neutrophil inflammatory activity and neutrophil-generated inflammatory mediators, in turn, contribute to stress-associated behavioral changes. Our results demonstrate

the importance of immune-driven inflammation as a mechanistic link between psychological stress and alterations in mood and behavior.

Disclosures: K. Thangamani: None. **H. Prece:** None. **J. Carter:** None. **J. Surendran:** None. **O. Douglas:** None. **E.K. Brengel:** None. **C.F. Ferris:** None. **E. Okeke:** None.

Poster

PSTR023: Gastrointestinal and Urinary Regulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.01/CC8

Topic: G.06. Autonomic Regulation

Support: NIH Grant DK133605

Title: Weight of Fluid in the Bladder Explains When Voiding Reflexes Activate

Authors: *Z. C. DANZIGER[1], P. SAXENA[2];
[1]Rehabil. Med. and Biomed. Engin., [2]Rehabil. Med., Emory Univ., Atlanta, GA

Abstract: The “micturition reflex,” which contracts the detrusor and relaxes the urethral sphincter, is the primary method by which the urinary bladder empties, yet we do not know how the nervous system determines when to trigger this reflex. It is often assumed that when some key physiological state (that is being sensed by bladder afferents) crosses a critical threshold that the micturition reflex engages, but to show this we must know what the sensed state actually is. Bladder pressure is a natural candidate because it changes dramatically at the transition between filling and voiding behavior, but the micturition reflex has been shown to trigger at different bladder pressures within the same experimental animal. Bladder tension is another candidate; but in our recent work, where we filled the bladder across a wide range of flow rates to create different tension profiles, we showed the micturition reflex triggered at consistent volumes rather than bladder wall tensions. This result begs the question of how bladder afferents that have local receptive fields could sense a global bladder property such as volume, which is challenging from an engineering perspective. Here we ask whether fluid weight (that can be sensed locally) rather than volume is the key physiological state the nervous system uses to trigger the micturition reflex. In urethane anesthetized Sprague Dawley rats, we filled the bladder with standard physiological saline as a baseline followed by a bioinert high-density or low-density fluid across multiple cystometric replicates. We found that a high-density fluid triggered the micturition reflex at a consistent and lower volume ($p= 0.0012$, 75% glycerol, N=6) and low-density fluids triggered the micturition reflex at consistent and higher volume ($p= 0.0019$, corn oil, N=8) compared to the saline baselines. These results suggest a simple method by which the nervous system could determine when to initiate the micturition reflex using bladder afferents that have spatially localized receptive fields: monitor how heavy the contents of the bladder are and void when a critical threshold is reached.

Disclosures: Z.C. Danziger: None. **P. Saxena:** None.

Poster

PSTR023: Gastrointestinal and Urinary Regulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.02/CC9

Topic: G.06. Autonomic Regulation

Support: R01 DK134431
R01 DK138907
R01 DK138907
U54 DK137329

Title: Functional characterization and classification of mechanosensitive bladder afferents

Authors: G. MANRIQUE-MALDONADO[1], X. SUN[2], ***M. D. CARATTINO**[3];
[1]Renal-Electrolyte Div., Univ. of Pittsburgh, Pittsburgh, PA; [2]Univ. of Pittsburgh, University of Pittsburgh, PA; [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Normal urinary bladder function relies on afferent fibers that detect and integrate mechanical and chemical cues related to bladder distension and convey this information to spinal neurons. Afferents not only transduce signals related to bladder distension but are also integral to pathological states, where they function as nociceptors encoding noxious stimuli. Despite decades of study, the molecular identities and functional roles of the various sensory neuron types innervating the urinary bladder have not been fully elucidated. Here, we developed a systematic approach to analyze and classify bladder afferents based on their response to both physiological and noxious filling. Action potentials evoked by bladder distension were recorded from an ex vivo bladder-pelvic nerve preparation. Spikes were isolated from multi-unit recordings and sorted offline using Spike2. Single units were classified based on their responses to physiological (15 µl/min) and noxious filling (30 s at intravesical pressures of 10, 20, 30, 40, 50, and 60 cmH_2O). Our study reveals the presence of three distinct types of mechanosensitive bladder afferents, two that respond to physiological distension (type I and II) and one that is activated by noxious stimulation (type III). Of the two populations that respond to physiological filling, one displays a linear increase in firing with bladder filling (type I), while the firing of the other plateaus as intravesical pressure increases (type II). Fast filling (130 µl/min) increases the discharge of all three afferent types, with the effect being most pronounced in those responding to noxious distension (type III). Corroborating the existence of three functionally distinct bladder afferent populations, Yoda1, a selective PIEZO1 channel activator, significantly increased the firing rate of types I and III during slow filling and of type III during noxious distension. In summary, we present a reliable and reproducible method for studying and classifying bladder afferents, while providing compelling evidence for the existence of three functionally distinct populations of mechanosensitive afferents, each activated and regulated by distinct mechanisms.

Disclosures: G. Manrique-Maldonado: None. **X. Sun:** None. **M.D. Carattino:** None.

Poster

PSTR023: Gastrointestinal and Urinary Regulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.03/CC10

Topic: G.06. Autonomic Regulation

Support: R01AG058814
K76AG054777

Title: Ageing Attenuates Extracellular ATP-Driven Transient Inward Currents in Male Detrusor Myocytes

Authors: *F. LEMTIRI-CHLIEH, G. A. KUCHEL, E. S. LEVINE;
Univ. of Connecticut Sch. of Med., Farmington, CT

Abstract: Age- and sex-related changes in detrusor smooth muscle excitability are thought to contribute to the pathogenesis of lower urinary tract dysfunction, yet the underlying cellular mechanisms remain incompletely understood. Adenosine triphosphate (ATP)-mediated purinergic signaling and voltage-gated calcium channels (VGCCs) are central regulators of detrusor myocyte depolarization and contractile activity. In this study, we used whole-cell patch-clamp electrophysiology in freshly isolated detrusor myocytes to define how ATP-evoked currents and VGCC activity are functionally integrated across the lifespan of male and female mice. Our data indicate that aging is associated with a selective impairment of ATP-evoked inward currents (I_{ATP}) in male, but not female, detrusor myocytes, while VGCC function is comparatively preserved. This deficit is consistent with, and may reflect, previously reported age-dependent reductions in $P2X_1$ receptor expression in male detrusor smooth muscle, providing a mechanistic explanation for diminished ATP-mediated depolarization with aging. In contrast, female detrusor myocytes exhibit relative preservation of purinergic signaling across age groups, indicating sex-specific regulation of detrusor excitability during aging. Given the critical role of ATP-dependent depolarization in triggering detrusor action potentials, these findings may have direct relevance for understanding age- and sex-dependent differences in bladder function. Together, our results suggest disrupted integration of purinergic signaling and membrane excitability as a potential cellular mechanism underlying detrusor dysfunction in aging males, with important implications for the development of targeted therapies for lower urinary tract symptoms.

Disclosures: F. Lemtiri-Chlieh: None. **G.A. Kuchel:** None. **E.S. Levine:** None.

Poster

PSTR023: Gastrointestinal and Urinary Regulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR023.04/CC11

Topic: G.06. Autonomic Regulation

Support: SECITHI (CF 1311312)
SECITHI (OVR 924549)
SECITHI (AFH 1157306)
SECITHI (SASM 1004334)

Title: Morphophysiological changes in the urinary bladder induced by lumbosacral ventral root avulsion in domestic rabbits

Authors: O. VARGAS RUIZ[1], M. MERCADO ROCHA[2], A. FLORES HERNANDEZ[1], S. SANCHEZ MENESES[1], Z. FLORES LOZADA[1], J. MORALES-MEDINA[3], F. CASTELÁN[4], M. MARTINEZ-GOMEZ[5], ***D. L. CORONA QUINTANILLA**[1];
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Abstract: Spinal cord and lumbosacral plexus injuries represent a significant health problem due to the motor, sensory, and autonomic sequelae they produce in affected individuals. One such injury is L6-S2 ventral root avulsion (VRA). L6-S2 VRA causes severe dysfunction of the lower urinary tract, leading to urinary retention, voiding abnormalities, and recurrent infections. However, the morphophysiological changes observed in the urinary bladder after VRA have not been fully studied. Therefore, the objective of this study was to determine the effect of L6-S2 VRA on the functional and morphological characteristics of the urinary bladder in domestic rabbits. Sixteen Chinchilla rabbits were divided into two experimental groups, Sham (n=8) and unilateral L6-S2 VRA (n=8). Fifteen days after surgery, bladder function was assessed using cystometrograms and urodynamic parameters, including threshold and maximum pressures, voided and residual volumes, and bladder efficiency. Histological analysis of the urinary bladder was also performed using hematoxylin and eosin-stained sections to evaluate structural changes. The results showed that the L6-S2 VRA caused significant alterations in bladder function. An increase in threshold and residual volume was observed, accompanied by a decrease in voided volume and bladder efficiency. Furthermore, the threshold and maximum pressures decreased significantly, indicating reduced contractile capacity of the urinary bladder. Morphological analysis revealed a significant increase in bladder weight and size in the rabbits with VRA compared to the Sham group, as well as disorganization of the bladder's histological layers. Specifically, an increase in the lamina propria, thinning of the smooth muscle layer, alterations in the urothelium, and a reduction in mucosal folds were observed. These findings could be related to tissue remodeling associated with L6-S2 spinal vascular atrophy. Our findings demonstrate that VRA induces significant functional and structural alterations in the bladder, compromising its storage and emptying capacity. Furthermore, these findings contribute to the understanding of the pathophysiology of lumbosacral injuries and provide important experimental evidence for the development of future therapeutic strategies for urinary function in patients with neurological lesions.

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Poster

PSTR023: Gastrointestinal and Urinary Regulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.05/CC12

Topic: G.06. Autonomic Regulation

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American Urological Association / Urology Care Foundation Research Scholar Award 1449517
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NIH-NIDDK RDK142807A

Title: A Neuromedin-S Spinal Circuit Coordinating Lower Urinary Tract Function

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Abstract: Lower urinary tract function (LUTF) requires precise coordination between autonomic pathways controlling bladder function and somatic pathways regulating external urethral sphincter (EUS) activity. Although the spinal cord is the principal neural hub integrating these functions, the specific neuronal populations coordinating LUTF remain poorly defined.To characterize spinal neuronal populations involved in LUTF, we generated a comprehensive single-nucleus transcriptomic atlas of the mouse lumbosacral spinal cord. To enrich for neurons engaged during LUTF, we used a cFos-based TRAP strategy to selectively label cells activated during repeated bladder filling and voiding in awake mice. Single-nucleus RNA sequencing identified 34 molecularly distinct neuronal populations, which were subsequently localized to anatomically defined regions using high-resolution spatial transcriptomics using the 10X Visium HD platform. Among these populations, we identified a previously unrecognized class of spinal excitatory interneurons expressing neuropeptide Neuromedin-S (Nms). Nms+ neurons are largely restricted to lumbosacral spinal segments and concentrated within the dorsal gray commissure. Anatomical tracing demonstrated that Nms+ neurons form extensive synaptic contacts with somatic motor neurons innervating the EUS, parasympathetic bladder preganglionic motor neurons, and sympathetic preganglionic motor neurons, while also projecting to supraspinal regions involved in micturition, including Barrington's nucleus, the parabrachial nucleus, and the periaqueductal gray. Silencing Nms+ neurons using tetanus toxin light chain produced profound urinary incontinence, characterized by loss of voluntary voiding and a marked increase in urinary events during micturition video thermography (MVT). Conversely, chemogenetic activation reduced urinary frequency and increased the latency to the first void during MVT. To investigate the underlying physiological mechanisms, we performed

urodynamics with EUS electromyography during optogenetic stimulation. Activation of Nms+ neurons elicited robust, frequency-dependent increases in EUS activity accompanied by slight increases in bladder pressure. Together, these findings identify Nms+ neurons as a novel spinal circuit essential for lower urinary tract control. By combining molecular profiling with anatomical and functional studies, this work reveals a spinal neuronal population that coordinates autonomic and somatic components of continence and provides a foundation for identifying analogous circuits in the human sacral spinal cord.

Disclosures: A.M. Sartori: None. **N. Klymko:** None. **R. Lee:** None. **A.M. Verstegen:** None.

Poster

PSTR023: Gastrointestinal and Urinary Regulation

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Program #/Poster #: PSTR023.06/CC13

Topic: G.06. Autonomic Regulation

Support: NIH-NIDDK DK125708
NIH-NIDDK RDK142807A

Title: Role of GABAergic Neurons in the Periaqueductal Gray for Maintaining Continence

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Abstract: Micturition is a complex process requiring precise coordination between the brain and lower urinary tract (LUT). Barrington's Nucleus (Bar) in the brainstem is the conductor that drives bladder contraction and sphincter relaxation. A primary input region to Bar is the ventrolateral periaqueductal gray (vlPAG), and it receives both forebrain inputs and sensory information from the LUT. Previous studies have shown that manipulation of excitatory Bar-projecting vlPAG neurons can bidirectionally control LUT activity. Through anatomical tracing, we discovered a population of inhibitory Bar-projecting vlPAG neurons ($PAG^{Vgat>Bar}$). It remains unknown to what extent this population exerts control over Bar activity. In this study using Vgat-Cre mice, we aim to characterize $PAG^{Vgat>Bar}$ and their role in maintaining continence. To first understand $PAG^{Vgat>Bar}$ activity, we used fiber photometry to record calcium dynamics (DIO-GCaMP6s) from $PAG^{Vgat>Bar}$ terminals during micturition events. A bladder catheter was implanted for cystometrogram (CMG) recordings to monitor intravesical pressure during continuous saline infusion. We observed time-locked calcium transients during full void contractions (VC) and smaller non-voiding contractions (NVC), confirming that this population is active during micturition events. To assess whether manipulating inhibitory vlPAG neurons could alter micturition, we inhibited PAG^{Vgat} by bilaterally expressing DIO-hM4D(Gi) in the vlPAG and quantified events in a 2-hour void spot assay. Chemogenetic inhibition of PAG^{Vgat}

resulted in many leaks, suggesting that PAG^{Vgat} are crucial for maintaining continence. Ongoing experiments specifically targeting the $PAG^{Vgat>Bar}$ projection will confirm if an intersectional approach will replicate our observed phenotype. Given that voiding requires temporal coordination between Bar and the LUT, we sought to bidirectionally perturb $PAG^{Vgat>Bar}$ during specific parts of the void cycle. To do so, we designed a closed-loop system to monitor CMG pressure and deliver acute optogenetic excitation or inhibition during both VCs and NVCs in mice expressing somBIPOLES bilaterally in $PAG^{Vgat>Bar}$. Preliminary findings reveal that optogenetic excitation can extend the inter-void interval without direct effect on bladder pressure. Ongoing experiments will test the effects of manipulations on bladder pressure and micturition behavior, and we anticipate that acute inhibition will allow for early subthreshold activation of Bar. Together, these results suggest that $PAG^{Vgat>Bar}$ neurons play a key role in voiding and maintaining continence alongside their excitatory counterparts.

Disclosures: R.Y. Lee: None. **N. Klymko:** None. **A.M. Sartori:** None. **A.M. Verstegen:** None.

Poster

PSTR023: Gastrointestinal and Urinary Regulation

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Program #/Poster #: PSTR023.07/CC14

Topic: G.06. Autonomic Regulation

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Takeda Science Foundation Fellowship Program

Title: Biased intraspinal synaptic connectivity from $Trpc4^{+}$ interneurons coordinates lower urinary tract output pathways

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Abstract: Interstitial cystitis/bladder pain syndrome (IC/BPS) severely impairs quality of life through chronic pelvic pain and lower urinary tract symptoms. We previously identified lumbosacral spinal $Trpc4^{+}$ neurons as a population that gates visceral pain and regulates bladder function in cyclophosphamide-induced cystitis. However, the intraspinal circuit mechanisms by which $Trpc4^{+}$ neurons coordinate lower urinary tract output remain unclear. To address this, we examined synaptic connectivity from $Trpc4^{+}$ dorsal gray commissure (DGC) neurons onto two major spinal output populations: lumbosacral preganglionic neurons (LS-PGNs), which regulate bladder contraction, and dorsolateral motor neurons (DL-MNs), which control external urethral

sphincter (EUS) muscle activity. Whole-cell patch-clamp recordings combined with optogenetic terminal stimulation revealed target-specific synaptic organization. LS-PGNs received inhibitory-biased synaptic input from Trpc4$^+$ DGC neurons, whereas DL-MNs received excitatory-biased input. These findings suggest that Trpc4$^+$ spinal interneurons coordinate lower urinary tract function by differentially regulating bladder contraction and EUS muscle activity. Target-specific synaptic bias onto LS-PGNs and DL-MNs may explain how Trpc4$^+$ neuron manipulation modulates cystitis-associated voiding dysfunction and visceral pain.

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Poster

PSTR023: Gastrointestinal and Urinary Regulation

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.08/CC15

Topic: G.06. Autonomic Regulation

Support: JSPSKAKENHI 25K02975
LOTTE Foundation grant 2025

Title: ATP contributes to the initiation of mechanically and chemically evoked swallowing in anesthetized rats

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Abstract: Introduction: It has been reported that purinergic P2X receptors expressed in a subset of vagal neurons are involved in laryngeal water- and acid-evoked swallowing. Here, we investigated whether ATP release is induced by multiple types of laryngeal stimuli that evoke swallowing reflexes in anesthetized animals. Methods: Experiments were performed using urethane-anesthetized male Sprague-Dawley rats. A swallowing reflex was identified by electromyographic bursts of the digastric and thyrohyoid muscles. First, we evaluated the effects of the non-selective P2X receptor antagonist 10 mM PPADS or 1 mM P2X3 antagonist AF353 on the initiation of swallowing evoked by laryngeal application of distilled water (DW), carbonated water (CW), 0.9 mM sodium chloride (NaCl), 1 μM capsaicin, mechanical stimulation with von Frey filament, and electrical stimulation of either the superior laryngeal nerve (SLN) and recurrent laryngeal nerve (RLN). Next, ATP release from an ex vivo laryngeal preparation was examined following chemical stimulation with DW, NaCl, and capsaicin and mechanical stimulation with a von Frey filament. ATP concentrations in the collected superfusates were quantified. Results: Laryngeal application of PPADS significantly reduced the

number of DW-, CW- and capsaicin-evoked swallows, but not NaCl-, SLN- and RLN-evoked swallows. PPADS slightly but significantly increased the swallowing threshold induced by von Frey filament stimulation. AF353 significantly reduced DW-, CW- and capsaicin-evoked swallows, but did not change the number of NaCl-evoked swallows and the swallowing threshold induced by von Frey filament stimulation. In the ex vivo preparation, DW, CW and capsaicin perfusion, as well as von Frey filament stimulation significantly increased ATP concentrations within 1 min compared with Krebs solution perfusion. In contrast, NaCl perfusion did not change ATP concentrations. Conclusion: These findings suggest that ATP contributes to the initiation of swallowing reflexes evoked by chemical and mechanical laryngeal stimulation.

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Poster

PSTR023: Gastrointestinal and Urinary Regulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.09/CC16

Topic: G.06. Autonomic Regulation

Title: A combined in vivo engraftment and ex vivo optogenetic approach reveals functional neuroeffector activity of transplanted human enteric ganglioids in host colon

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Abstract: Degeneration or dysfunction of the enteric nervous system (ENS) leads to various gastrointestinal (GI) motility disorders, including Hirschsprung disease, achalasia, gastroparesis, chronic intestinal pseudo-obstruction, and slow-transit constipation. hPSC-based cell therapy represents a promising approach to restore ENS function, but methods to assess functional integration of transplanted human neurons in host tissue remain lacking.Here, we performed subserosal transplantation of hSYN-ChR2-eYFP enteric ganglioids into distal colon of adult immunodeficient mice to enable optogenetic stimulation (opto n=7, vehicle n=4). Transplanted hPSC-derived enteric ganglioids survived long-term in NSG mice.At 16 weeks post-surgery, in vivo GI transit time (carmine red gavage) was significantly prolonged in mice injected with neurons vs. vehicle (p=0.041). The prolonged in vivo transit time suggests activity of the transplanted neurons induces localized neuromuscular regulation in the recipient colon.Following 16 weeks of in vivo engraftment, we demonstrate the functional engraftment of transplanted human enteric neurons by harvesting colonic explants and applying ex vivo optogenetic stimulation, showing light-evoked neuroeffector activity in host tissue. To test the

functional connectivity of transplanted neurons, we harvested colonic explants (muscularis-serosa layer with ganglioids) and performed ex vivo optogenetic stimulation (488 nm laser, 400 ms, 10 repetitions).Motility was quantified before vs. after stimulation using two independent methods (ImageJ): Standard Deviation (StDev) Z-projection and Particle Image Velocimetry (PIV).PIV delta displacement (post-pre) differed significantly between the cell and vehicle injection groups (Wilcoxon p=0.0242; permutation test p=0.0288, 10,000 shuffles; effect size r=0.857). Tissue from neuron transplanted group showed increased motility (mean delta 0.166±0.15 px, mean±SD; 6/7 animals increased). StDev STD confirmed increased spatial heterogeneity in optogenetic group (p=0.0424).These findings establish a platform for functional validation of transplanted human enteric neurons, with direct relevance to cell therapy development for ENS disorders.

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Poster

PSTR023: Gastrointestinal and Urinary Regulation

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.10/CC17

Topic: G.06. Autonomic Regulation

Title: Cortical Spreading Depolarization and Gastrointestinal Dysfunction in Migraine

Authors: *M. KAYA, A. HARRIOTT;
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Abstract: Gastrointestinal (GI) symptoms, including nausea, altered gut motility, and abdominal pain, are common non-headache manifestations of migraine and can impair oral medication efficacy. Spreading depolarization (SD), the electrophysiological correlate of migraine aura, activates trigeminovascular pathways, but whether SD disrupts brain–gut signaling to produce GI dysfunction remains unclear. We hypothesized that SD acutely impairs GI motility through descending modulation of gut motor circuits. Optogenetic SD was induced in channelrhodopsin-2 transgenic mice. Sham mice underwent the same preparation without SD induction. Both sexes were included and experimenters were blinded to group assignment. GI transit time (GITT) was assessed by oral gavage of 6% carmine in 0.5% methylcellulose after SD, with monitoring every 30 min for first red fecal pellet (n=10/group). Gastric emptying and small intestinal transit (GESITT) were assessed using Texas Red–dextran gavage 5 min after SD, followed by fluorometric analysis of the stomach and 10 intestinal segments (n=8/group). Fecal pellet count, fecal weight, and stool water content were measured for 60 min after SD, followed by glass bead expulsion testing (n=8/group). Colonic pressure activity was assessed by awake saline-infusion colonometry. Feeding and drinking were measured after SD (n=4/group). SD prolonged GITT compared with sham ($p<0.001$) and reduced fecal pellet output during the first 60 min ($p<0.001$). Texas Red–dextran distribution shifted proximally after SD ($p=0.008$), without differences in

distal intestinal fluorescence (p=0.267) or gastric emptying (p=0.561), consistent with slowed small intestinal transit rather than delayed gastric emptying. Fecal weight and stool water content were unchanged (p=0.125 and p=0.159), whereas bead expulsion latency was prolonged after SD (p=0.001), indicating impaired distal colonic propulsion. Colonometry showed reduced pellet-associated pressure activity before fecal pellet expulsion in SD mice. Feeding and drinking were unchanged, and no sex differences were detected across outcomes. These findings demonstrate that SD acutely disrupts upper and lower GI motility without altering consummatory behavior, identifying SD as a potential mechanistic link between migraine and GI dysfunction.

Disclosures: M. Kaya: None. **A. Harriott:** F. Consulting Fees (e.g., advisory boards); Served on advisory boards for Abbvie, Theranica and Axsome, and serves on board of directors for American Headache Society, American Migraine Foundation and Headache Cooperative of the Northeast.

Poster

PSTR024: Peripheral Signals and Nutrients on Glucose Regulation and Feeding

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.01/CC18

Topic: G.08. Food and Water Intake and Energy Balance

Support: University of Kentucky/Barnstable Brown Diabetes Center Pathway to Independence Grant

Title: Recurrent Hypoglycemia Selectively Blunts Distributed Brain Circuits Recruited by Acute Hypoglycemia

Authors: *I. PAPAZOGLOU, C. TAYLOR, A. RUMENSER, N. WHITE, S. FISHER; Univ. of Kentucky, Lexington, KY

Abstract: Hypoglycemia, a major threat to brain function and survival for individuals on insulin therapy, triggers centrally mediated responses to restore normal blood glucose levels. Recurrent hypoglycemia, common in insulin-treated diabetes, can blunt these responses and increase the risk for severe events. Here we mapped hypoglycemia-activated neurons across the mouse brain in healthy mice and mice exposed to recurrent antecedent hypoglycemia, a model of impaired hypoglycemia responsiveness. Using whole-brain 3D cFos mapping with automated atlas-based quantification, we identified a previously incompletely characterized, distributed, hypoglycemia-activated network with prominent activation noted in cortical, striatal, hypothalamic, thalamic, and hindbrain regions. However, In mice exposed to recurrent hypoglycemia preconditioning, responses were not uniformly reduced; instead, response blunting was concentrated primarily in limbic structures, while several other nodes, including key hypothalamic regions, remained comparatively intact. Together, these findings establish a brain-wide architecture of hypoglycemia-responsive circuits, highlighting newly identified hypoglycemia-recruited

neuronal populations, and provide novel insights on how recurrent hypoglycemia selectively and maladaptively remodels vulnerable neurocircuits.

Disclosures: I. Papazoglou: None. **C. Taylor:** None. **A. Rumenser:** None. **N. White:** None. **S. Fisher:** None.

Poster

PSTR024: Peripheral Signals and Nutrients on Glucose Regulation and Feeding

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.02/CC19

Topic: G.08. Food and Water Intake and Energy Balance

Title: Linking metabolic state to feeding events in freely behaving mice using continuous glucose monitoring

Authors: *L. SCHUSTER[1], A. SALAZAR[2], J. TERAN[1], A. EL HADY[2,3], E. J. DENNIS[4]; [1]HHMI Janelia Res. Campus, Ashburn, VA; [2]Univ. of Konstanz, Konstanz, Germany; [3]Max Planck Inst. of Animal Behavior, Konstanz, Germany; [4]Neurosci., Janelia Res. Campus, Ashburn, VA

Abstract: An animal's metabolic state drives decision-making in feeding and foraging. Neural circuits are embedded in a continuously fluctuating metabolic context where circulating nutrients, gut signaling and homeostatic feedback are all changing as behavior takes place. However, this state is typically assigned or inferred from food access rather than actively, physiologically measured. Continuous glucose monitoring (CGM) renders part of that invisible context observable.

We recorded from mice wearing CGMs in an open arena while retrieving grain or sucrose pellets from automated feeders (FED3) or live crickets from the arena floor. Sessions spanned fed and fasted conditions. Glucose readouts were integrated with videography, pose tracking, FED3 pellet logs, and behavioral annotations.

To predict pellet retrieval and consumption, we first validated FED3 pellet logs against manual annotations of eating onset and found that FED3 retrievals coincided within one to two seconds. Pellet retrieval episodes were structured into non-random bursty bouts that became larger if the animal had fasted but retained their overall organization without added travel.

We evaluated three different components of glucose activity: circadian rhythm, activity, and carbohydrate feeding events and are building models to better understand the contributions to and the predictive value of the glucose signal we measure.

Mice showed a strong ~24 hour glucose rhythm (amplitude: ~16 mg/dL) that aligned to the inverted light cycle of the vivarium, peaking during the active phase onset (cosinor) with variability (MAGE, CONGA, CV) that was stable with ad lib access to food and increased during fasting.

Aligning glucose to each feeding event showed that this signal is carbohydrate-specific: sucrose consumption raised glucose (+50 mg/dL at 15 min) more than a similarly caloric grain pellet

(+30 mg/dL), and live crickets did not raise it at all, suggesting that the readout might track carbohydrate quality rather than energetic intake within animal on a single session and across matched days (p=0.005). However, individual feeding events were not predictable from the glucose readout alone, suggesting that interstitial glucose might behave as a slow signal correlate of state rather than its cause.
Measuring glucose combined with pose-tracking and automated feeding offers a low-cost, accessible, and scalable framework to incorporate metabolic measurements as behavior unfolds both in the lab and outdoors.

Disclosures: L. Schuster: None. **A. Salazar:** None. **J. Teran:** None. **A. El Hady:** None. **E.J. Dennis:** None.

Poster

PSTR024: Peripheral Signals and Nutrients on Glucose Regulation and Feeding

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.03/CC20

Topic: G.08. Food and Water Intake and Energy Balance

Support: University of Kentucky CASH-KY Pilot Award
University of Kentucky/Barnstable Brown Diabetes Center Pathway to Independence Grant

Title: Lateral Hypothalamic Control of Hypoglycemic Arousal

Authors: *C. TAYLOR[1], A. RUMENSER[1], N. WHITE[1], H. BERINYU[1], S. SUNDERAM[2], S. FISHER[1], I. PAPAZOGLOU[1];
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Abstract: Hypoglycemia represents a critical barrier in diabetes management, with recurrent episodes causing attenuation of both counter-regulatory responses (CRR), and glycemia restorative behaviors. This attenuation is particularly problematic for diabetic individuals that experience nocturnal hypoglycemic episodes, during which arousal, a crucial step in activation of the CRR and glycemia restoring feeding, is often impaired. The connection of hypoglycemia and the central regulation of arousal is therefore an essential target in diabetes management. The lateral hypothalamus (LH) has been previously shown to regulate wake and feeding responses through neuropeptinergic systems. However, whether these neurons mediate the arousal and feeding responses to hypoglycemia remains unexplored. In this study we aim to characterize and functionally assess hypoglycemia-activated neurons in the lateral hypothalamus (LH^{HypoG+}). We used Targeted Recombination of Active Populations (TRAP2) alongside neurochemical profiling, and chemogenetics to identify and functionally assess LH^{HypoG+} neurons. Profiling of LH^{HypoG+} neurons revealed a heterogenous population with a partial overlap with neuropeptinergic neurons and a preference for orexin. To assess the functional impact of LH^{HypoG+} neurons on arousal, chemogenetic stimulation was combined with piezoelectric sleep

recordings. These recordings showed an increase in overall wakefulness, but did not show significant effects on concurrent feeding behavior or an acute effect on glycemia. These findings establish a molecularly diverse population of hypoglycemia-responsive LH neurons that couple hypoglycemia to arousal responses. This work advances our mechanistic understanding of how peripheral energy perturbations are transduced into integrated behavioral responses.

Disclosures: C. Taylor: None. **A. Rumenser:** None. **N. White:** None. **H. Berinyu:** None. **S. Sunderam:** None. **S. Fisher:** None. **I. Papazoglou:** None.

Poster

PSTR024: Peripheral Signals and Nutrients on Glucose Regulation and Feeding

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.04/Web Only

Topic: G.08. Food and Water Intake and Energy Balance

Title: Chronic exposure to a high fructose diet impairs effort and delayed-based decision making and alters metabolic parameters in male rats

Authors: *J. O. SUAREZ-ORTIZ[1], I. O. CONDE ROJAS[3], F. CORTÉS SALAZAR[2], J. MANCILLA-DIAZ[4], R. ESCARTIN-PEREZ[5];
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Abstract: Excessive consumption of fructose-containing diets is a contributor to metabolic diseases. Evidence suggests that high-fructose diets can alter neural systems involved in reward processing and cognitive control. The present study examined the effects of chronic exposure (118 days) to a high-fructose diet on effort- and delay-based decision making, and metabolic outcomes. Male Wistar rats of 17 postnatal days were assigned to three groups (n=14 / group): Control (no fructose), F20 (fructose 20%), and F35 (fructose 35%). Caloric intake from chow and fructose, and body weight were weekly monitored. A subset of subjects (n=8 / group) were assessed for breakpoints and decision making in an effort-based task through concurrent (linear vs exponential increments) schedules in third and fourth weeks. On day 32 the subjects were euthanized and serum determinations of LDL, HDL, total cholesterol and triglycerides were determined (n=4 / group); mesenteric and retroperitoneal adipose pads were dissected and weighted. The rest of the subjects (n=6 / group) continued the experimental protocol and underwent a intraperitoneal glucose tolerance test (IGTT; 2g of glucose ip / kg of body weight) on days 7, 21, 32 92 and 116 of the experiment; and from sixth to tenth week the decision making was evaluated through a delay-based task in which the subjects chose between a single non delayed pellet or five pellets delivered after a delay (1, 3, 7, 15, or 30 s) pellets. In weeks

12th and 13th subjects were evaluated in Elevated Plus Maze (EPM) and Open Field Test (OFT). In day 119 rats were euthanized, serum and adipose tissue evaluations were repeated; diastolic and systolic blood pressure (BP) and waist-to-height ratio (WHtR) were also measured. Fructose access reduced caloric intake from chow and increased total caloric intake during specific weeks of the study. Both F20 and F35 groups developed glucose intolerance by day 116 in IGTT, although no differences were detected in serum lipid measures. Body weight did not differ among groups; however, the F20 group accumulated more adipose tissue, and both fructose groups showed higher WHtR and blood pressure. Operant assessment revealed higher breakpoints in the F35 group, whereas effort- and delay-based tasks showed a greater preference for low-effort and immediate rewards, indicating increased impulsive choice. No differences were observed in EPM or OFT performance. These findings suggest that chronic fructose consumption increases motivation for palatable food, biases decision making toward impulsive choices in the absence of anxiety-like behavior, and promotes metabolic alterations associated with glucose intolerance.

Disclosures: J.O. Suarez-Ortiz: None. **I.O. Conde Rojas:** None. **F. Cortés Salazar:** None. **J. Mancilla-Diaz:** None. **R. Escartin-Perez:** None.

Poster

PSTR024: Peripheral Signals and Nutrients on Glucose Regulation and Feeding

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.05/CC21

Topic: G.08. Food and Water Intake and Energy Balance

Title: Changes in food choice during lactation

Authors: *E. KAYA, J. A. PEREIRA, C. KOSSE;
ETH Zurich, Zurich, Switzerland

Abstract: Lactation is arguably the most metabolically demanding stage of the female life cycle, requiring physiological adaptations that prioritize offspring needs. A fundamental aspect of these adaptations is milk production, which substantially increases energy and mineral demands. Previous studies have identified several physiological mechanisms that help meet these demands, including increased gastrointestinal capacity and alterations in hunger and satiety signaling. However, how the brain integrates these physiological signals and translates them into the behavioral adaptations required to support lactation remains poorly understood. To begin addressing this question, we examined how dietary mineral content influences brain-wide neuronal activity using whole-brain tissue clearing. We also investigated the effects of dietary mineral content on mineral-sensing mechanisms in the gastrointestinal tract using immunohistochemistry and Western blotting. Our findings will lay the groundwork for identifying the neural circuits through which mineral-related signals shape maternal physiology and behavior during lactation.

Disclosures: E. Kaya: None. **J.A. Pereira:** None. **C. Kosse:** None.

Poster

PSTR024: Peripheral Signals and Nutrients on Glucose Regulation and Feeding

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.06/CC22

Topic: G.08. Food and Water Intake and Energy Balance

Support: National Natural Science Foundation of China 32470888

Title: Mucosal enteric glial cells mediate intestinal adaptation to dietary lipids via lacteal remodeling

Authors: *M. YAO;
Sun Yat-sen Mem. Hospital, Sun Yat-sen Univ., Guangzhou, China

Abstract: Mucosal enteric glial cells mediate intestinal adaptation to dietary lipids via lacteal remodelingAuthors Tianrui Luo[1, 2], Zihao Liu[1, 2], Zhiming Ye[1, 2], Jiaoyan Ren[3]; **Maojin Yao**[1, 2*1]Medical Research Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou 510120, China; [2]Brain Research Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou 510120, China; [3]School of Food Science and Engineering, South China University of Technology, Guangzhou, 510641, China.
AbstractThe enteric nervous system (ENS) rapidly reconfigures the mucosal microenvironment in response to nutritional fluctuations. While enteric glial cells (EGCs) are recognized as sensors of intestinal homeostasis, how these expansive glial networks orchestrate structural adaptations to dietary changes remains unresolved. To dissect the specific glial subpopulations coordinating this rapid physical adaptation, we utilized an intermittent high-fat diet (IHFD) mouse model to simulate nutritional fluctuations. By integrating single-cell RNA sequencing (scRNA-seq) with spatial analyses, we found that mucosal EGCs (mEGCs) undergo a reactive transition IHFD challenge to coordinate mucosal adaptation. This reactive state is defined by concurrent $GFAP^{+}$ network expansion (76.1% ± 10.4 vs. 10.6% ± 2.8 in naive controls) and a specific shift toward a VEGF-C high-expressing subpopulation (78.5% ± 15.3 vs. 15.2% ± 3.4). To determine the functional requirement of mEGCs in mucosal adaptation, we ablated the mEGCs using $Gfap^{Cre}$;iDTR and $Sox10^{CreER}$;iDTR mices. Under IHFD stimulation, mEGC depletion prevented lacteal structural remodeling, restricting permeable button-like junction formation to 21.7% ± 10.9 (vs. 73.9% ± 11.8 in littermate controls). Crucially, targeted VEGF-C supplementation in ablated mice completely rescued this adaptation, restoring button junctions to 68.3% (± 11.7). Consistently, fluorocitrate-mediated mEGC inhibition suppressed VEGF-C expression and restricted button junction formation (51.6% ± 8.1 vs. 76.2% ± 9.4 in vehicle). Ultimately, this molecular and structural blockade impaired rapid chylomicron transport, limiting peak plasma triglycerides to 219.2 ± 32.1 mg/dL (vs. 386.4 ± 26.7 mg/dL in vehicle). In conclusion, these findings identify EGCs as dynamic sensors that translate nutritional fluctuations into structural mucosal adaptations via VEGF-C-mediated neuro-endothelial signaling. By defining this specific

glial-lymphatic regulatory mechanism, our study expands the functional repertoire of the EGCs, establishing its requisite role in gating intestinal lipid transport.

Disclosures: M. Yao: None.

Poster

PSTR024: Peripheral Signals and Nutrients on Glucose Regulation and Feeding

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.07/CC23

Topic: G.08. Food and Water Intake and Energy Balance

Title: EEG aperiodic exponent decreases after gastric distension to fullness by water loading

Authors: *S. LIU[1], N. DATTA[2], J. LOCK[2], T. P. COLEMAN[3];
[1]Electrical Engin., [2]Psychiatry and Behavioral Sci., [3]Bioengineering, Stanford Univ., Stanford, CA

Abstract: Gastric interoception influences daily eating and drinking habits not only in health but also in pathology. For example, patients with anorexia nervosa have been shown to develop altered gastric interoception that persists even after weight restoration (Kerr et al., 2016). Many prior studies have measured neural markers of gastric mechanosensation with vibratory pills (Mayeli et al., 2023) or balloons inflated in the stomach (Wang et al., 2018). While these provide controlled stimuli, they require specialized equipment, can lead to mild discomfort, and may not be possible to implement in child/adolescent samples. Prior studies have used water drinking, such as the two-stage water load task (WLT-II), as a more naturalistic and well-tolerated alternative (van Dyck et al., 2016). This paradigm relies on indirect measures of interoception assessed through the ingested water volumes instead of directly measuring the underlying physiology. In this work, we aim to study such underlying electrophysiologic markers of fullness that occur after WLT-II using electroencephalography (EEG). With the approval of the IRB at Stanford University, we recruited 33 participants (22 female, 17.8±4.2 years old, BMI 20.5±4.7) with no known gastrointestinal or psychiatric disorders. Participants fasted for 8 hours, and then we recorded 15-minute pre- and post-drink periods before and after they drank to fullness. Using FOOOF ("fitting oscillations & one over f"), we extracted alpha peak power (an oscillatory feature) and aperiodic exponent (an aperiodic feature) and compared if they changed. We used linear mixed effects models to account for developmental effects of participants who ranged from children to transitional aged youth. We found that the aperiodic exponent significantly decreased with increased age ($p < 0.001$) and after water loading ($p = 0.013$). Meanwhile, the alpha peak power did not significantly change across age ($p = 0.945$) or after water loading ($p = 0.114$). To localize which electrodes contributed to the change in the aperiodic exponent, we performed permutation cluster testing and identified one significant cluster that was widely distributed across the left hemisphere ($p = 0.030$), consistent with prior fMRI work that has demonstrated activation of regions in the left hemisphere after high gastric distension volumes (Wang et al., 2018). This demonstrates that broadband EEG changes may better capture

interoceptive processing compared to traditional spectral measures such as alpha power. More broadly, integrating electrophysiologic assessment with the WLT-II may provide objective, quantifiable readouts of gastric fullness using a well-tolerated task.

Disclosures: S. Liu: None. **N. Datta:** None. **J. Lock:** None. **T.P. Coleman:** None.

Poster

PSTR024: Peripheral Signals and Nutrients on Glucose Regulation and Feeding

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.08/CC24

Topic: G.08. Food and Water Intake and Energy Balance

Title: Gastrointestinal motility as an interoceptive signal for brain control of feeding

Authors: *C. YE, J. SONG, N. N. GUAN;
Tongji Univ., Shanghai, China

Abstract: Gastrointestinal motility varies with nutritional state, but whether state-dependent motility patterns are conveyed to the brain as interoceptive signals to shape feeding decisions remains unknown. Here we show in zebrafish that hunger and satiety are associated with two distinct patterns of gastrointestinal motility that are differentially represented in the nucleus of the solitary tract (NTS) of hindbrain. These motility states engage two feeding-related peptidergic populations: hunger-associated motility preferentially activates hypothalamic orexinergic neurons to promote feeding, whereas satiety-associated motility preferentially activates CART4-positive neurons in the caudal raphe to suppress feeding. Mechanistically, CART4 neurons directly inhibit orexinergic neurons through monosynaptic connections, linking satiety-related gut dynamics to suppression of feeding-promoting circuitry. Together, our findings identify two gut-to-brain neural pathways through which gastrointestinal motility patterns encode energy state and bidirectionally regulate feeding behavior.

Disclosures: C. Ye: None. **J. Song:** None. **N.N. Guan:** None.

Poster

PSTR024: Peripheral Signals and Nutrients on Glucose Regulation and Feeding

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.09/CC25

Topic: G.08. Food and Water Intake and Energy Balance

Title: Dietary ω-3 poly-unsaturated fatty acids attenuate seizure-related phenotypes in a Drosophila model of SCN1A epilepsy

Authors: *V. HAND[1], R. SCHUBACK[2], A. GRAY[2], T. KITAMOTO[4], A. IYENGAR[3]; [1]Dept. of Biol. Sci., The Univ. of Alabama, Double Springs, AL; [3]Biol. Sci., [2]The Univ. of Alabama, Tuscaloosa, AL; [4]Anesthesia, Univ. of Iowa Carver Col. of Med., Iowa City, IA

Abstract: Mutations in voltage-gated sodium-channel genes have been implicated in the pathology of heritable epilepsies. *Drosophila melanogaster* possesses only one sodium channel gene, *paralytic* (*para*), which is orthologous to nine sodium channel genes present in humans. The hyperexcitable, gain-of-function point mutant $para^{Shu}$ (M1350I) exhibits spontaneous seizures exacerbated by high temperature and a wing posture defect caused by muscular hypercontraction. The homologous variant of $para^{Shu}$ in *SCN1A* has been identified in a patient with epilepsy (Epi25K consortium). Previous studies found excitability phenotypes of $para^{Shu}$ are attenuated by dietary supplementation of milk lipids (Kasuya et al., 2019) and implicated the C18 ω-3 poly-unsaturated fatty acid (PUFA) α-linolenic acid (ALA) in the effect (Kasuya et al., 2023). We employed an automated video tracking system (IowaFLI Tracker) and behavior classification algorithm to quantify the effect of standard versus ALA-supplemented diets (0.005 to 0.05% w/v). We found significant dose-dependent improvement for $para^{Shu}$ in several categories, including average velocity, path linearity, total distance traveled, and frequency of immobilization and uncoordinated movement events. Wing posture defects also were reduced from 88.1% (n = 345) to 9.5% (n = 231). Supplementation of the ω-3 PUFAs eicosapentaenoic acid (C20) and docosahexaenoic acid (C22) yielded similar improvements, whereas the ω-6 PUFA linoleic acid (LA) exacerbated seizure phenotypes. Electrophysiological analysis of tethered flies indicated spontaneous seizures in $para^{Shu}$ were largely eliminated by ω-3 PUFA supplementation but not by LA. To investigate potential interactions between ω-3 and ω-6 PUFAs, flies were fed a fixed concentration of ALA (0.015% w/v) with increasing concentrations of LA and scored for seizure-related phenotypes. Flies fed both 0.015% ALA and LA exhibited 43% wing posture defect penetrance, while increasing LA concentration to 0.085% led to 100% penetrance. Collectively, these findings demonstrate that ω-3 PUFAs broadly suppress hyperexcitability-associated phenotypes in $para^{Shu}$, while ω-6 PUFA intake may mask these effects. Kasuya, J., Iyengar, A., Chen, H. L., Lansdon, P., Wu, C. F., & Kitamoto, T. (2019). Milk-whey diet substantially suppresses seizure-like phenotypes of paraShu, a Drosophila voltage-gated sodium channel mutant. *Journal of Neurogenetics*, *33*(3), 164-178. Kasuya, J., Johnson, W., Chen, H. L., & Kitamoto, T. (2023). Dietary supplementation with milk lipids leads to suppression of developmental and behavioral phenotypes of hyperexcitable Drosophila mutants. *Neuroscience*, *520*, 1-17.

Disclosures: V. Hand: None. **R. Schuback:** None. **A. Gray:** None. **T. Kitamoto:** None. **A. Iyengar:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.01/CC26

Topic: H.04. Emotion

Support: NIH Grant U01DA041022

Title: Longitudinal associations between early life stress, cortico-thalamic functional connectivity, and emotion regulation in adolescence

Authors: *R. HICKSON[1], A. PATEL[1], N. TOTAH[1], M. WEATHINGTON[2], E. SALARI[1], E. M. MULLER-OEHRING[3], T. SCHULTE[4];
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Abstract: Early life stress (ELS) is associated with disruptions in emotional development and increases adolescent psychopathology risk; yet, how it may impact large-scale brain network functional connectivity (FC) and the development of emotion regulation (ER) remains unclear. This study examined longitudinal associations among ELS, resting-state FC, and ER across adolescence.

We used data from 11,288 adolescents from the ABCD Study across the 2- through 6-year follow-up assessments (ages 10-18). Participants completed the Emotion Regulation Questionnaire, yielding measures of cognitive reappraisal and expressive suppression. ELS, derived across all years, was a latent construct based on stressful life events, family conflict, and family hardship. FC was derived from rs-fMRI data collected at the 2-, 4-, and 6-year follow-ups and included FC between the salience network (SN), frontoparietal network (FPN), and the default mode network (DMN) and the hippocampus, amygdala, and thalamus. Longitudinal structural path models examined autoregressive and cross-lagged associations among ER strategies, as well as effects of ELS and FC on later ER.

Models showed good fit to the data (CFIs > .94, TLIs > .91, RMSEAs < .05, SRMRs < .05). ER suppression showed stronger longitudinal autoregressive effects (i.e., greater temporal stability; βs = .38 to .52) relative to ER reappraisal (βs = .24 to .37). Higher ELS consistently predicted increased future suppression (βs = .03 to .13, ps < .01) and decreased future reappraisal (βs = -.02 to -.03, ps < .03). Greater SN-, DMN-, and FPN-thalamus FC were associated with increases in future suppression (βs = .02 to .05, ps < .05), whereas greater SN-hippocampus FC (β = -.03, p < .01) was associated with decreases in future reappraisal. ELS also moderated the association between FPN-hippocampus FC and ER suppression, with stronger FC predicting increased suppression at higher levels of ELS (βs = .05, p < .05).

Results indicate that ELS exposure is associated with longitudinal changes in ER strategies across adolescence. Greater cortical network-thalamic FC predicted increased suppression, suggesting that thalamocortical network organization may play an important role in shaping the maturation of emotion regulation during adolescence.

Disclosures: R. Hickson: None. **A. Patel:** None. **N. Totah:** None. **M. Weathington:** None. **E. Salari:** None. **E.M. Muller-Oehring:** None. **T. Schulte:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.02/CC27

Topic: H.04. Emotion

Support: KAKENHI JP21K07262
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Takeda Science Foundation

Title: Human resilience is encoded in functional connectivity and neural oscillations one hour after acute stress.

Authors: *N. WATANABE[1,2], S. YOSHIDA[2], R. KEERATIVITTAYAYUT[3,2], M. TAKEDA[2]; [1]Shizuoka Inst. of Sci. and Technol., Fukuroi, Shizuoka, Japan; [2]Res. Ctr. for Brain Communication, Kochi Univ. of Technol., Kami, Kochi, Japan; [3]Chulabhorn Royal Acad., Bangkok, Thailand

Abstract: Psychological resilience — the ability and process to adapt positively in the face of acute stress or adversity — varies substantially across individuals and is a key determinant of mental health outcomes. Human resilience is uniquely underpinned by higher-order cognitive processes such as self-confidence, tenacity, and positive reappraisal. Whether human resilience is represented in neurophysiological stress responses or has independent spatiotemporal representations remains unclear. We recorded multimodal neurophysiological responses from 102 healthy participants (M:F = 77:25; mean age 20.1 y.o.) across five resting-state sessions over 1.5 hours before and after acute stress via a cold pressor test. Individual resilience was assessed with the CD-RISC. Concurrent fMRI and EEG were recorded alongside pupil size, heart rate, respiration, salivary cortisol, and subjective stress ratings. Physiological stress responses showed no significant correlations with CD-RISC ($BF_{01} > 4.6$), indicating resilience is not simply reflected in known stress responses. Instead, resilience-related neural dynamics peaked at 60 min post-stress. fMRI functional connectivity identified two resilience-correlated networks at cluster-level $P_{FDR} < 0.05$: the salience network (SaN), negatively correlated, and the default mode network (DMN), positively correlated with CD-RISC. Resilient individuals showed progressive SaN reduction and DMN increase; susceptible individuals showed sustained SaN elevation. Spontaneous activity in the posterior hippocampus (fALFF) also positively correlated with resilience at 60 min post-stress ($P_{FDR} < 0.05$). EEG revealed that high-beta (26.5 Hz) and gamma (43.0 Hz) power negatively correlated with CD-RISC at 60 min post-stress ($P_{FDR} < 0.05$). Resilient individuals showed significant reductions; susceptible individuals showed sustained

elevation consistent with fMRI findings. Elastic-Net regression identified six predictors of resilience (*adjusted* $R^2 = 0.322$, $p = 1.07\times10^{-5}$): SaN, DMN, gamma power, posterior hippocampal activity, and high-beta — all at 60 min post-stress. In contrast, peripheral measures contributed negligibly. These findings demonstrate that human resilience emerges through time-lagged reorganization of cortical networks and oscillatory dynamics over one hour post-stress — a temporal window overlooked in prior research and a promising target for interventions against stress-related disorders such as PTSD.

Disclosures: N. Watanabe: None. **S. Yoshida:** None. **R. Keerativittayayut:** None. **M. Takeda:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.03/CC28

Topic: H.04. Emotion

Title: Beyond Temporal Segmentation: Quantifying Methodological Bias and Establishing Universal Feature Heirarchies in aBCI

Authors: *D. E. THOMPSON[1], T. SWEET[2];
[1]Ingram Sch. of Engin., Texas State Univ., San Marcos, TX; [2]Kansas State Univ., Manhattan, KS

Abstract: Affective Brain-Computer Interfaces (aBCI) frequently show high offline performance but fail in real time. We have shown this is largely driven by inflated offline performance estimates from data leakage caused by temporal segmentation. Here, we show that even without data leakage, temporal segmentation violates the independent and identically distributed (IID) assumption due to temporal autocorrelations in the EEG signal. This violation leads to machine learning algorithms learning localized, trial-specific characteristics rather than affective states. To isolate these vulnerabilities, we evaluated human EEG data from the SEED-IV dataset across three validation splits: a whole-trial baseline split, a segmented split without data leakage, and a segmented split with data leakage. Models were tested on two tasks: 4-class emotion identification and 72-class parent-trial identification. Differential entropy features were extracted across five frequency bands, and a Linear SVM model was evaluated via balanced accuracy. For emotions, the whole-trial split yielded 56% balanced accuracy, decreasing to 49% under the segmented split without data leakage. Thus, segmentation suppresses generalization. While the split with data leakage inflated emotion identification performance to 71%, the parent-trial identification task under that same split achieved 63% balanced accuracy, confirming that segmented models excel at tracking localized trial identities. To understand the driving mechanism, we evaluated what the models learned. Feature importance analysis revealed that all segmented configurations, regardless of the target task, caused a significant shift in classifier focus toward high-frequency beta and gamma bands compared to the whole-trial baseline. Temporal autocorrelation analysis revealed that segmentation causes adjacent segments to

remain highly autocorrelated, driving a fundamental violation of sample independence where the classifier executes template matching on trial-specific noise signatures rather than decoding genuine emotional states. This mechanistic failure directly accounts for leakage-driven accuracy inflation, modified feature importance, and the lack of model generalization. Ultimately, these findings suggest that temporal segmentation must be completely excluded from preprocessing pipelines to preserve methodological validity. Transitioning to a standardized, whole-trial framework provides a foundation to isolate genuine biological signatures and advance the field toward reliable, real-world applications.

Disclosures: D.E. Thompson: None. **T. Sweet:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.04/CC29

Topic: H.04. Emotion

Support: National Research Foundation of Korea (NRF) Grant RS-2023-00218987

Title: Interoceptive sensitivity shapes the temporal dynamics of emotional interference and enhances negative memory consolidation

Authors: *H. JUNG[1,2], Y. KIM[1], H. KIM[1];
[1]Psychology, Korea Univ., Seoul, Korea, Republic of; [2]Neurosci. and Cognitive Sci. Program, Univ. of Maryland, Col. Park, College Park, MD

Abstract: Interoception, the perception of internal bodily signals, is a fundamental component of emotional experience, with higher interoceptive sensitivity often linked to more intense emotional processing. Although individuals with greater interoceptive sensitivity exhibit stronger emotional interference—evidenced by delayed responses to negative versus neutral stimuli—the temporal dynamics of this phenomenon remain poorly understood. Because emotion is a dynamic process that unfolds over time, this study investigated how temporal trajectories of emotional interference vary with interoceptive sensitivity and how these temporal changes subsequently shape emotional memory. Fifty-one young Korean adults completed a Heartbeat Counting Task to assess interoceptive accuracy as an index of interoceptive sensitivity. They then performed a modified color-word emotional Stroop task, followed by an unexpected word memory test. The Stroop task presented emotional or neutral cue words followed by neutral filler words, allowing us to track the temporal carryover of emotional interference. Emotional interference (EI) scores were calculated by subtracting each participant's overall mean reaction time (RT) for neutral sequences from their RTs in emotional sequences. Repeated-measures ANOVA on EI scores showed that negative stimuli elicited a slow and transient interference effect, whereas positive stimuli produced a fast and sustained facilitation effect. Notably, correlation analyses showed that individuals with higher interoceptive sensitivity exhibited

stronger interference for negative stimuli during both early (r = .43, p = .007) and later phases (r = .33, p = .045). Furthermore, greater late-phase interference predicted enhanced memory recognition for negative stimuli (r = .40, p = .018). Finally, mediation analysis confirmed that interoceptive sensitivity indirectly influenced memory by amplifying this late interference (indirect effect = .13, p = .028). These findings suggest that interoceptive sensitivity shapes not only the initial impact of emotional stimuli but also their temporal unfolding and subsequent consolidation into memory. By examining the precise time course of emotional interference, this study advances our understanding of the dynamic role of interoception in emotional processing and highlights brain-body interactions underlying these temporal dynamics.

Disclosures: H. Jung: None. **Y. Kim:** None. **H. Kim:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.05/CC30

Topic: H.04. Emotion

Support: NIH Grant U01NS117838

Title: A Multimodal Platform for Investigating Human Emotional Autobiographical Memory Encoding and Recall using Wearable Eye Tracking

Authors: *M. DILBECK[1], W. JIANG[2], U. TOPALOVIC[3], N. HASULAK[5], S. HILLER[6], A. I. JANG[7], B. J. KNOWLTON[8], N. A. SUTHANA[4];
[1]Univ. of California Los Angeles, Los Angeles, CA; [2]Neurosurg., [4]Neurosurg. / Biomed. Engin., [3]Duke Univ., Durham, NC; [5]Phoenix Res. Consulting LLC, Gilbert, AZ; [7]Dept. of Psychiatry and Biobehavioral Sci., [8]Psychology, [6]UCLA, Los Angeles, CA

Abstract: Understanding how emotional autobiographical memories are encoded and retrieved in daily life remains challenging because most experimental paradigms rely on artificial laboratory stimuli. Here, we evaluated the feasibility of using wearable eye-tracking glasses to capture real-world autobiographical experiences and investigate emotional episodic memory as participants went about their normal daily lives. Adult participants wore eye-tracking glasses to record personal events of varying emotional valence once a day over seven consecutive days, capturing first-person video together with gaze and pupillometry in their natural environments. Approximately twenty-four hours after each recording, participants completed memory retrieval tasks at home while again wearing the eye-tracking glasses. These tasks included emotional valence ratings, verbal recall, and event segmentation of the previously recorded experience. At the conclusion of the study, participants completed a temporal order task spanning all recorded events. Data collection included emotional valence ratings, memory performance, pupillometry, and saccade measurements. Participants were additionally screened for trauma exposure and mood or anxiety disorders to explore individual differences in naturalistic emotional memory

processing. Wearable eye-tracking successfully enabled capture of emotionally diverse autobiographical experiences and repeated assessment of memory retrieval in participants' everyday environments outside the laboratory. Emotional valence was significantly associated with both recall performance and eye movement dynamics. Furthermore, preliminary results suggest participants with trauma exposure or mood disorders exhibit altered relationships between emotional valence, memory performance, and eye behavior. These findings support the feasibility of combining wearable eye-tracking with at-home memory assessments to study autobiographical emotional memory under naturalistic conditions. This approach may provide a valuable framework for understanding memory processing in neuropsychiatric disorders. A future direction of this research will integrate this platform in participants with chronic intracranial hippocampal and amygdala recording systems to elucidate the neural mechanisms underlying real-world emotional memory.

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Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.06/DD1

Topic: H.04. Emotion

Title: Intracranial responses to emotional face stimuli are age-dependent in limbic regions

Authors: *J. T. MILES[1], N. STAGGS[1], S. WEBB[1], J. OJEMANN[2];
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Abstract: Neural responses to affective stimuli change throughout childhood and into adolescence as our ability to recognize emotional facial expressions becomes more sensitive. Recent work using intracranial EEG suggests that the balance of sensorimotor and frontal involvement in processing affective stimuli shifts over the course of development. Here, we expand this work by examining age-dependent neural responses to emotional faces in limbic regions using intracranial EEG. Specifically, we tested whether similarity in event-related potentials (ERPs) driven by different emotional expressions became less similar with age. Data were collected from a cohort of 7-to-19-year-old participants during an emotional face processing paradigm who underwent stereo-EEG monitoring in the Seattle Children's Hospital epilepsy monitoring unit. All participants and/or their legal guardians gave informed consent prior to study participation. Posed images of actors making happy, neutral, angry, and fearful expressions were shown for 1 second, in random order, with 3 second delays between images. Image presentations with noise transients or interictal discharges were discarded, as were channels with fewer than 35 noise-free repeats of each expression type and channels with identifiable ictal activity. Altogether we analyzed data from 87 channels across 11 participants, each of which had at least 5 usable channels. We found that the pairwise correlations between

ERPs in limbic regions decreased significantly with age (n = 29, T =-3.03, R^2 = 0.23, p = 0.005), meaning that limbic region ERPs for different emotional expressions became less similar with age. Neither sensorimotor nor association regions had significant age-dependent correlations. These findings suggest that neural responses to different emotional expressions become more variable in the limbic system as it matures.

Disclosures: J.T. Miles: None. **N. Staggs:** None. **S. Webb:** None. **J. Ojemann:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.07/DD2

Topic: H.04. Emotion

Support: NIH Grant R00NS126492
Brain and Behavior Research Foundation

Title: Amygdala-targeted 10 Hz temporal interference stimulation attenuates anticipatory threat responses in humans

Authors: *Y. CHOO[1], A. ZHENG[2], H. LIN[1], J. MACMILLAN[1], J. SMITH[1], I. R. VIOLANTE[3], A. J. SHACKMAN[1], W. XIE[1];
[1]Psychology, [2]A. James Clark Sch. of Engin., Univ. of Maryland, Col. Park, College Park, MD; [3]Dept. of Med., Imperial Col. London, London, United Kingdom

Abstract: Amygdala-centered circuits play a key role in anticipatory arousal during threat anticipation, and their dysregulation is often implicated in anxiety disorders. Here, we tested whether noninvasive temporal interference (TI) stimulation can modulate these circuits while tracking anticipatory arousal in real time with pupillometry. Seventy-nine healthy adults completed a fMRI-validated threat-anticipation task across four experiments. Participants viewed digit streams of unpredictable duration, creating temporal uncertainty about when each trial would end. Each stream was superimposed on an upward or downward triangle. In baseline, triangles had no predictive meaning and participants judged whether the final digit was odd or even. In threat-anticipation phase, triangles perfectly predicted whether each trial would end with aversive (Threat) or benign (Safe) audiovisual outcomes. Exp. 1 (n = 20) confirmed that threat anticipation reliably increased pupil size, whereas cue-evoked pupil responses did not differ during the baseline phase, ruling out low-level sensory explanations. In Exp. 2-4, each TI condition used an active vs. sham crossover design during the threat-anticipation phase, with stimulation delivered through an electric-field-optimized montage targeting the right amygdala. Exp. 2 (n = 20) applied 10-Hz TI stimulation (2 mA, 2000 vs. 2010 Hz). Threat-induced pupil dilation was robust during sham blocks but significantly attenuated during active 10-Hz TI, reducing the Threat vs. Safe pupil difference to baseline levels. Participants could not distinguish active from sham, suggesting expectancy or peripheral sensation did not explain the effect. Exp.

3 (n = 20) tested whether high-frequency carrier current alone was sufficient to reduce threat responses. A 0-Hz envelope (2000-Hz carriers only) control condition did not attenuate threat-related pupil dilation, suggesting carrier current alone was insufficient. Exp. 4 (n = 19) tested whether any low-frequency TI envelope could reduce threat responses. A 40-Hz (2000 vs. 2040-Hz) active-control condition also did not attenuate threat-related pupil responses, providing preliminary support that the effect was specific to the 10-Hz envelope. These findings provide initial evidence that 10 Hz amygdala-targeted TI stimulation can dampen anticipatory threat-related arousal in humans. More broadly, they support TI stimulation as a noninvasive tool for probing frequency-dependent modulation of deep affective circuits, while motivating future work combining TI with neuroimaging to verify target engagement.

Disclosures: Y. Choo: None. **A. Zheng:** None. **H. Lin:** None. **J. MacMillan:** None. **J. Smith:** None. **I.R. Violante:** None. **A.J. Shackman:** None. **W. Xie:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.08/DD3

Topic: H.04. Emotion

Support: R37MH076136

Title: Neural representations of expected and experienced valence in the human prefrontal-limbic system

Authors: *B. GRAUL[1], A. STOLK[1], X. R. SUN[2,4], K. BUJARSKI[4], J. HONG[4], K. KHAN[5], C. CASTELBLANCO RIVEROS[3], T. D. WAGER[1];
[1]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [2]Neurosurg., [3]Dartmouth Col., Lebanon, NH; [4]Dartmouth Hitchcock Med. Ctr., Lebanon, NH; [5]UPenn MSTP, Philadelphia, PA

Abstract: How does the brain represent an affective experience we expect compared with one we actually have, particularly if the differences between expectation and experiences are small? We tested whether the neural representation of a felt affective experience is reactivated when that same experience is only anticipated from social information.Eleven patients undergoing intracranial monitoring viewed a cue, presented as the average rating of 10 prior viewers, that set an expectation about an upcoming image's pleasantness. This cue was systematically shifted away from the normative mean valence of the image. On each trial they rated their expectation, viewed the image, and rated their experience. The social cue reliably shifted both expected and reported valence (b=0.60 and 0.24; both p<0.001).Using each subject’s full electrode montage, we trained a within-subject classifier on high gamma power (70 to 150 Hz) to separate trials that each patient rated as positive (pleasant) or negative (unpleasant) after viewing. During image viewing this classifier separated valence reports well above chance in 10 of 11 patients, with population prevalence p<0.001, revealing a distributed high gamma signature of felt affect.We

then applied this classifier (trained during image viewing on valence report) to the earlier cue period, before any affective image appeared. We tested based on the subject's reported expectation (positive or negative), not on the eventual image report. In two adjacent windows the classifier's output tracked the trial's expectation after cluster correction (cluster p≈0.03), again in 10 of 11 patients. In other words, the same high gamma geometry that encoded felt experience also differentiated the socially induced expectation, seconds before the affective stimulus and from an entirely different visual display. Surprisingly, the anticipatory pattern ran opposite to experience: stronger positive expectations projected toward the unpleasant image pole, consistent with predictive or opponent coding of expected value rather than a simple preview of the expected experience.Together these results reveal a stable, distributed high gamma geometry shared between socially induced affective expectation and direct affective experience. Because the cue and image are different stimuli, this shared code cannot reflect simple sensory features. Whether the anticipatory signal causes the image experience to shift, and how regions such as vmPFC and amygdala communicate it, is the focus of ongoing analyses and an upcoming direct stimulation study.

Disclosures: B. Graul: None. **A. Stolk:** None. **X.R. Sun:** None. **K. Bujarski:** None. **J. Hong:** None. **K. Khan:** None. **C. Castelblanco Riveros:** None. **T.D. Wager:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.09/DD4

Topic: H.04. Emotion

Title: Entropy Optimization as a Candidate Organizing Principle Underlying Human Affective Phenomenon.

Authors: *J. J. CELENTANO;
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Abstract: The Human Affectome Project, (Shiller, 2024) presented a nested teleological framework aimed at generating an integrated understanding of human affective phenomenon. This poster proposes entropy optimization as a core principle unifying this nested model. Because life is a continuous struggle against the ever-increasing entropy of our universe, it is reasonable to speculate that the nervous system evolved to sense, predict and respond to changes in entropy. Here, entropy will be broadly treated as a reflection of waste (Clausius), disorder (Boltzmann), impurity (Nernst), uncertainty (Shannon) or freedom. At the heart of the proposal is the notion that, for many situations, positive valence (PV) is associated with moving towards an optimum entropy (OE) and negative valence (NV) with moving away from an OE. Many issues addressed in the 12 reviews cited in the Shiller paper can be viewed through the lens of OE. A fundamental example of **Physiological Feelings** is temperature. PV is associated with moving towards a comfortable temperature while NV is associated with excess heat (high

entropy, HE) or cold (low entropy, LE). Regarding water, NV results from HE dehydration due to vomiting, or diarrhea as well as LE associated with, fluid retention or constipation. **Sadness, Fear** and **Anger** can be triggered by HE situations including danger, frustration or uncertainty as well as LE in the form of physical confinement. Regarding **Hedonics**, the pleasure invoked by visual art, music or story telling involves some form of EO. LE forms can be monotonous or predictable while HE forms can be haphazard, dissonant or confused. Sporting events in which players do not follow the rules (HE) or the sides are highly mismatched making the outcome certain (LE) are less enjoyable. Unhealthy **Social** interactions can result from HE abandonment or neglect as well as LE domination or control. Undesirable political systems include HE anarchy and LE dictatorships. The poster will argue that **Happiness** and **Wellbeing** depend on OE involving many of the above issues. Regarding **Motivation**, the poster will stress the costs associated with accumulating LE and the importance of avoiding the unnecessary dissipation of reservoirs of LE. The universal nature of probability theory, under which increases in both thermodynamic and informational entropy naturally progresses (Cover, 2006), makes entropy optimization more than a simple metaphor in unifying our understanding of human affective phenomenon. This idea is presented within the growing trend of applying statistical physics to human activity and social dynamics, see Human Cooperation and the Entropy of Ideas (https://philarchive.org/rec/CELHCA).

Disclosures: J.J. Celentano: None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.10/DD5

Topic: H.03. Motivation

Support: Center on Compulsive Behaviors, Intramural Research Program, National Institutes of Health, Bethesda, Maryland

Title: A New Frustrative Nonreward Paradigm in Humans

Authors: *A. ERDAGI[1], L. LIUZZI[2], H. COATL-CUAYA[1], D. PANJA[1], Z. LI[1];
[1]Section on Synapse Develop. Plasticity, [2]Emotion and Develop. Br., NIH, Bethesda, MD

Abstract: Frustrative nonreward (FNR), the emotional and behavioral response to the omission, reduction, or delay of an expected reward, is present in both humans and animals and is characterized by increased motor activity and aggression across species. FNR is a central feature of irritability, a symptom common to DMDD, ADHD, autism spectrum disorder (ASD), depression, and other conditions, with notable clinical impact in childhood and adolescence. Because FNR is evolutionarily conserved, it has been used as a cross-species construct to study irritability and its brain mechanisms. Our laboratory previously developed the Alternate Poking Reward Omission (APRO) paradigm to induce FNR in mice. Here, we present a human

frustration task that mirrors APRO, providing a behavioral framework for inducing and measuring FNR in humans and aligning it with the mouse model. The task instantiates the FNR framework across three blocks. On each trial, participants press a force-sensitive bar to choose between two on-screen doors in pursuit of a monetary reward. Reward probability decreases across blocks, progressively increasing reward omission and opportunities for FNR. From the continuous force signal, we derive three behavioral measures for each trial: grip force (the magnitude of force exerted), hold duration (the duration for which the bar is held), and response time (the interval between door presentation and bar press). Subjective frustration is assessed using a 10-point Likert scale (0-9) administered before the task, between blocks, and after task completion. Baseline affective and irritability-related traits are assessed using the Affective Reactivity Index (ARI) and the Brief Irritability Test (BITe). Grip force, hold duration, response time, and self-reported frustration changed as reward became less predictable across blocks, confirming that the task induces frustration-related behavior. Together, these behavioral and affective readouts demonstrate that the paradigm elicits a measurable frustration response in humans.

Disclosures: A. Erdagi: None. **L. Liuzzi:** None. **H. Coatl-Cuaya:** None. **D. Panja:** None. **Z. Li:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.11/DD6

Topic: H.04. Emotion

Support: KBRI Basic Research Programs (26-BR-03-01, 26-BR-02-13)
National Center for Mental Health (MHER25C02)
Korean NRF grants (RS-2025-00517752, RS-2024-00397737) funded by the Ministry of Science and ICT

Title: Age-dependent coupling between cortical gradient organization and neutral-face representation in children

Authors: *Y. CHOI[1,2], Y. JEONG[1], M. JUNG[2];
[1]Dept. of Bio and Brain Engin., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [2]Cognitive Sci. Res. Group, Korea Brain Res. Inst., Daegu, Korea, Republic of

Abstract: A neutral face is not an absence of emotional information, but an affectively underspecified cue whose meaning depends on broader social-affective representations. This ambiguity matters in childhood, when emotion categories are still being refined. Weak facial cues are often assigned affective meaning along valence, and children tend to show a developmental negativity bias toward ambiguous faces. Interpreting such ambiguity requires mapping visual evidence onto higher-order representations. Functional gradients capture this

process as continuous axes of cortical hierarchy between unimodal visual and transmodal systems, beyond pairwise connections. We tested whether resting-state functional gradients, including sensory-association (SA), visual-somatosensory (VS), and modulation-representation (MR) axes, were associated with neutral-face position within emotion space and whether associations varied with age. Eighty-six typically developing Korean children aged 6-12 years (M_{age}=9.49; 40 female) completed the seven-expression Korean child-face task with emotion categorization, clarity/valence ratings, and rs-fMRI. Categorization responses were summarized as 7×7 confusion matrices, converted to Jensen-Shannon distances, and embedded with multidimensional scaling (MDS) to estimate each expression's position in emotion space. Neutral-face coordinates indexed how each child resolved neutral-face ambiguity within emotion space. Functional connectivity was embedded into cortical gradient spaces via diffusion embedding. We extracted gradient range, G1-G3 dispersion, and visual-anchored distances along the SA, VS, and MR axes. The 4D MDS fit well (stress=.094, R^2=.972), and theory-guided contrasts identified Dim1 as valence-like, consistent with valence ratings (r=.975, p<.001); lower Dim1 reflected more negative valence. Greater gradient expansion and visual-anchored separation were associated with lower neutral Dim1 across SA-, VS-, and MR-related distances, G1-G3 dispersion, and gradient range metrics (βs=−.289 to −.242, ps≤.030). Age moderated these associations. SA- and MR-related distances and G1-G3 dispersion showed significant age interactions (βint=.304-.350, ps≤.008), with stronger coupling in younger children. This pattern was consistent across parcellations and specific to neutral-face position on valence-like Dim1 rather than other MDS dimensions. These findings indicate that developing cortical hierarchies relate to how children place ambiguous facial cues within affective space, capturing individual differences in the representational geometry of social-affective uncertainty.

Disclosures: Y. Choi: None. **Y. Jeong:** None. **M. Jung:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.12/DD7

Topic: H.04. Emotion

Title: Mixed emotions in dementia: Evidence for preserved emotional complexity.

Authors: *A. ONZO[1], S. NOZAWA[2], T. TAKANO[3], C. KANAYA[4], K. ITO[5], N. ARISA[5], Y. HIROSE[5], K. MOGI[7], S. HOTTA[6];
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Abstract: As dementia progresses, people are often described as showing reduced verbal and emotional expression. However, such changes may not necessarily indicate a loss of emotional richness. Although dementia impairs cognitive functions such as memory and attention, some

aspects of emotional and social cognition may remain relatively preserved. Understanding the inner experiences of people with dementia, including those with moderate and severe impairment is an important research question.Between 2019 and 2020, the Designing for Dementia Hub in Japan conducted in-depth interviews with 88 people living with dementia (mean time since diagnosis = 4.9 years). Each interview lasted more than 60 minutes and covered a broad range of topics, including life history, experiences of dementia, sources of meaning and enjoyment, future aspirations, and everyday challenges.In our previous work, ratings based on Ekman's six basic emotions revealed that happiness was the most strongly expressed emotion, exceeding ratings of anger, disgust, fear, sadness, and surprise. Happiness appeared to be linked not merely to pleasant experiences but also to processes of adaptation, acceptance, and meaning-making, which motivated the present investigation of emotional complexity beyond basic emotion categories.In the present study, 13 independent raters read the interview transcripts, identified passages that appeared to reveal the participant's inner world, and assigned one- to several-word emotion labels to describe the emotions expressed in those passages. Emotional complexity was evaluated using several indices, including whether labels reflected a single emotion (e.g., gratitude) or multiple simultaneous emotions (e.g., gratitude and sadness), and whether they involved cognitively elaborated states related to personal values, life meaning, or social relationships.Analyses indicate that mixed emotions were identified significantly more often than single emotions. We investigated the content, targets, and complexity of these emotional experiences. These findings suggest that participants who had been living with a dementia diagnosis for an average of 4.9 years continued to express complex emotional and social evaluations of their circumstances despite cognitive decline.

Disclosures: A. Onzo: None. **T. Takano:** None. **K. Mogi:** None. **S. Hotta:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

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Program #/Poster #: PSTR025.13/DD8

Topic: H.04. Emotion

Support: Wellcome Trust Discovery award 226645/Z/22/Z

Title: Drift Diffusion Process of Emotion Judgment in Parkinson's Disease Patients.

Authors: *X. YANG[1], J. ZHANG[2], M. M. ZHU[3], S. LITTLE[2];
[1]Univ. of California, Berkeley, Menlo Park, CA; [2]Univ. of California, San Francisco, San Francisco, CA; [3]Neurol., UCSF, San Francisco, CA

Abstract: Affective symptoms are common in neurodegenerative diseases, including Parkinson's disease (PD). Affective rating paradigms in prior research have largely captured one-click endpoints, leaving the dynamics of emotion judgment processes underexplored. We address this gap by tracking the cursor trajectory during rating at millisecond resolution, enabling

examination of latent decision and execution processes using Bayesian Drift-Diffusion Modeling (DDM).
Across five baseline sessions, two PD patients viewed ~1,500 images sampled from two affective picture databases (i.e., NAPS and OASIS) while concurrent intracranial EEG recordings were obtained. They rated the emotional valence of the images on a sliding rating bar from -50 (very negative) to +50 (very positive), with cursor movement tracked.
Behavioral analyses reveal three key signatures of the emotion-judgment process in these patients: (1) an overall negativity bias relative to normative ratings (Patient 1: -7.12, Patient 2: -7.82; both $p < .001$), driven primarily by reduced positive ratings; (2) systematic cursor-trajectory differences across valence groups, significant in both patients: negative images drove the fastest cursor movement, and emotionally salient images (negative or positive) were initiated sooner than neutral ones; and (3) DDM parameter estimation providing a mechanistic account of these biases: rather than sharing a single mechanism, the patients showed distinct DDM characteristics during the rating process. P1 exhibited a starting-point bias toward positive responses ($z = 0.527$, Posterior Probability = 0.997) without detectable drift bias (v_intercept = -0.028, PP = 0.873), indicating an a priori response tendency without altered evidence accumulation; P2 showed a negative starting-point bias ($z = 0.456$, PP = 1.000) counteracted by a positive drift bias (v_intercept = +0.115, PP = 1.000).
These findings offer a fine-grained window into the temporal unfolding of affective decision-making in PD patients, showing that behaviorally similar negativity can arise from mechanistically distinct processes invisible to endpoint measures, with implications for understanding emotion dysregulation in PD and for linking behavioral signatures to concurrent neural dynamics.

Disclosures: X. Yang: None. **J. Zhang:** None. **M.M. Zhu:** None. **S. Little:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.14/DD9

Topic: H.04. Emotion

Support: Friends of BrainHealth Research Grant

Title: Decoupling of Emotion and Cognition in Mindfulness

Authors: *A. M. CAMPOS[1], G. BATCHALLI MARUTHY[1], S. RODRIGUEZ[1], J. GUERRERO[1], W. HOLCOMB[1], T. ELAIYARAJA[1], B. RYPMA[2];
[1]The Univ. of Texas at Dallas, Richardson, TX; [2]Behavioral & Brain Sci., The Univ. of Texas At Dallas, Richardson, TX

Abstract: Trait-mindfulness has been associated positively with attention (i.e., alerting, orienting, executive functioning as measured in Attention Network Task (ANT)) but the

mechanisms underlying these effects remain unknown. We posited that mindfulness-training might improve cognition (assessed in ANT and emotional Stroop (eStroop)) through emotion regulation (ER) processes that reduce stress (assessed via salivary cortisol, mood assessments, perceived stress). In such processes, attentional resources are focused on accepting emotional states thereby reducing the effect of negative physiological reactions on cognitive performance. This emotion-cognition decoupling hypothesis yields two predictions. First, we predicted that, following negative mood induction procedure (MIP), individuals with higher trait-mindfulness and those with mindfulness-training would exhibit slower reaction times (RTs) than lower trait-mindful individuals and those without mindfulness-training due to increased ER processes. Second, we predicted decoupling between cortisol indices of stress and executive function. 44 participants (19-81 YO; 7 M, 37 F) were assigned to either 8-weeks of mindfulness training or music listening. ANT and eStroop were completed before and after training, followed by negative MIP consisting of somber music and self-referential prompts. A subsample provided salivary cortisol during session 1, pre- and post-negative mood induction. Additional measures included mood, trait-mindfulness, and questionnaires assessing stress and ER. Depression ($p=0.017$), anxiety ($p=0.02$), stress ($p=0.05$), and worry ($p=0.008$) were reduced, and positive affect ($p=0.03$) was increased, in the mindfulness-trained group compared to the control group. In contrast, no differences were observed in reappraisal ($p=0.84$), suppression ($p=0.59$), and rumination ($p=0.60$). Mindfulness-trained participants demonstrated significantly slower executive control RTs on the ANT compared to the control group, which exhibited faster RTs ($p=0.04$). No differences in alerting or orienting RTs were observed. Trait-mindfulness moderated the relationship between cortisol reactivity and executive control function ($p=0.003$). However, no such effects were observed for alerting and orienting network functions. Mindfulness-trained participants also demonstrated significant slower RTs in the eStroop for negative high-valence ($p=0.045$) and positive high-valence ($p=0.039$) stimuli. No significant differences were observed in the control group. These results provide preliminary evidence for our emotion-cognition decoupling hypothesis.

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Poster

PSTR025: Emotional Processing in the Human Brain

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Program #/Poster #: PSTR025.15/DD10

Topic: H.04. Emotion

Support: R01AG075000/AG/NIA NIH
Virginia Tech Lay Nam Chang Dean’s Discovery Fund

Title: The Neuronal Roadmap to Emotion: Neural and Autonomic Coupling Underlying Emotion Dimensions in Resting-State fMRI

Authors: *C. KESSNER[1], X. CHAI[1], S. R. MCCLAFFERTY[1], B. KATZ[2], T.-H. LEE[3], B. SCARPA-FRIEDMAN[1];
[1]Virginia Tech., Blacksburg, VA; [2]Human Develop., Virginia Tech., Averill Park, NY; [3]Human Develop., Virginia Tech., Blacksburg, VA

Abstract: Peripheral autonomic activity provides a continuous physiological signal that may index emotion-relevant dimensions such as Valence, Motivation, and Arousal. However, it remains unclear whether physiology-derived estimates of these dimensions are associated with distinct patterns of intrinsic brain activity. To address this question, we recorded PPG simultaneously with resting-state fMRI in younger and older adults (N=91, age range =18-75 years) and applied a previously developed PPG-based model to generate physiology-derived regressors indexing Valence (parasympathetic nervous system), Motivation (α-sympathetic nervous system), and Arousal (β-SNS) (McClafferty & Friedman, 2026). These PPG-derived emotion-relevant physiological regressors were then used to model neural activity. Whole-brain analyses (TFCE 25,000 permutations, $p < 0.05$) reveal positive associations between the Motivation dimension with right middle temporal, angular, and middle frontal gyri. Valence showed negative associations across the right middle frontal, superior frontal, bilateral pre- and post-central gyri, and frontal pole. Arousal was negatively associated with activity in posterior midline regions. Targeted ROI analyses of subcortical nuclei identified associations (FDR corrected) with partially distinct neuromodulatory systems. Motivation was positively associated with midbrain dopaminergic engagement of the substantia nigra/VT, with additional involvement of opioid-associated reticular formation regions. Valence was negatively associated with the periaqueductal gray and reticular formation, consistent with serotonergic and mesocortical dopaminergic affective circuitry. Arousal was negatively associated with noradrenergic brainstem signaling involving the locus coeruleus and subcoeruleus, with limited dopaminergic involvement of the substantia nigra. The combination of PPG-derived physiological regressors and emotion dimensions gives rise to an integrated relationship of neural activation elucidating areas of uncertainty in the emotion experience. In future research, these regressors enable live tracking of viable factors related to neuromodulation and brain systems with practical associations to psychopathology.

Disclosures: C. Kessner: None. **X. Chai:** A. Employment/Salary (full or part-time):; Virginia Tech. **S.R. McClafferty:** A. Employment/Salary (full or part-time):; Virginia Tech. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); McClafferty Innovations, LLC. **B. Katz:** A. Employment/Salary (full or part-time):; Virginia Tech. **T. Lee:** A. Employment/Salary (full or part-time):; Virginia Tech. **B. Scarpa-Friedman:** A. Employment/Salary (full or part-time):; Virginia Tech.

Poster

PSTR025: Emotional Processing in the Human Brain

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Program #/Poster #: PSTR025.16/DD11

Topic: H.04. Emotion

Support: NIH Grant R34

Title: A multi-camera reconstruction pipeline for pose-invariant facial action-unit coding in naturalistic interaction

Authors: *K. SUN[1], K. S. FERSTER[2], K. DOKHOLYAN[3], A. E. FRIEDMAN[4], M. A. PARVAZ[5], J. GRINBAND[6];
[1]Columbia Unversity, New York, NY; [2]Icahn Sch. of Med. At Mount Sinai Grad. Training Program In Neurosci., New York, NY; [3]Icahn Sch. of Med. at Mount Sinai, Brooklyn, NY; [4]Icahn Sch. of Med. at Mount Sinai, Mamaroneck, NY; [5]Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]Columbia Univ., NEW YORK, NY

Abstract: Facial action units (AUs) provide a moment-to-moment measure of behavior and are widely used in affective neuroscience, social interaction research, and computational psychiatry. Most studies estimate AUs from a single frontal camera. However, natural conversation is characterized by continuous head motion that alters facial feature appearances, degrades AU measurements, and introduces pose-dependent error. We hypothesize it may substantially reduce the reliability of facial-behavior measurements in naturalistic settings.
To address this problem, we developed a synchronized multi-camera acquisition and reconstruction pipeline that generates a canonical frontal view of the face independent of head pose. Four cameras record at 50 Hz above and below eye-level (approximately ±15° elevation), with hardware triggering that maintains inter-camera synchronization (drift <1 ms). At each frame, facial landmarks detected across the four synchronized views are triangulated into a textured 3D facial reconstruction. Rigid-body registration aligns each reconstruction to a common frontal orientation, which is then re-rendered into a canonical 2D frontal view for AU estimation.
We quantified pose-dependent measurement degradation by comparing per scene AU intensity from rotated views against frontal-view estimates using Pearson correlation. Using public multi-view facial-expression data (FaceScape; 18 subjects, 20 expressions, rotations <±70°), we found that AU agreement from single cameras declined to 10% as head orientation deviated 60° from frontal pose. In contrast, AU estimates from our pipeline retained approximately 90% of near-frontal agreement across viewing angles, eightfold of single-camera estimates at large angles. Similar eightfold increases were observed for live dyadic sessions recorded and frontalized with our system (3 pairs of subjects x 4 sessions x 25 min) using two independent AU classifier frameworks (OpenFace and Libreface).
These results demonstrate that multi-camera 3D frontalization substantially reduces confirmed pose-dependent degradation of facial action-unit measurements during naturalistic behavior. In addition to improving facial-expression quantification in freely moving participants, the approach provides synchronized estimates of facial geometry and head motion, enabling future analyses of facial dynamics, social synchrony, and naturalistic social interaction in both healthy and clinical populations.

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Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.17/DD12

Topic: H.04. Emotion

Title: Executive Load and Inhibitory Demands Nullify Spontaneous Emotional Mimicry

Authors: *E. YENGISETTY, A. KHAN;
Indian Inst. of Technol. (IIT), Bombay, Mumbai, India

Abstract: Background: Spontaneous emotional mimicry is often conceptualised as an automatic, bottom-up reflex. However, emerging hierarchical models propose that affective motor responses are resource-dependent. While previous studies show mimicry survives inhibition, they often make emotional expressions explicitly task-relevant. We investigated whether spontaneous mimicry survives high executive demands and motor suppression when expressions are task-irrelevant, hypothesising that concurrent inhibitory control networks would gate downward affective motor commands. Methods: In a preregistered, within-subjects design (OSF preregistration: Y5PWA), healthy female adults (N = 44) completed an affectively passive visual Go/No-Go task with continuous facial EMG. Participants executed (Go) or withheld (No-Go) responses based on the colour of a frame surrounding a face (happy or neutral). Emotion was completely task-irrelevant. Baseline-corrected, Z-scored zygomaticus major (ZM) amplitude (300-1000 ms post-stimulus) was analysed via repeated-measures ANOVA (Emotion x Trial Type), cluster-based permutations, and Bayesian paired-samples tests. Results: Data revealed a complete absence of affective motor resonance. The baseline check (Happy-Go vs. Neutral-Go) and primary gating test (Happy-Go vs. Happy-No-Go) yielded null results. The ANOVA showed no main effects or interaction (all $F < 0.1$, $p > 0.8$). Cluster-based permutations confirmed temporally absolute suppression, with no transient micro-mimicry surviving multiple-comparisons correction. Bayesian analyses strongly favoured the null for both baseline mimicry under executive load (BF01 = 6.07) and the gating test (BF01 = 6.11), with model comparisons favouring the absence of an interaction (BF01 = 3.02). Conclusion: These preregistered findings challenge the assumption of mimicry as an obligatory reflex. Spontaneous affective resonance is preemptively abolished when executive networks are heavily taxed by parallel demands. When cognitive resources are monopolised, visual-to-motor affective translation is deprioritised before reaching the muscles. Multitasking and cognitive fatigue may therefore fundamentally impair the foundational motor mechanisms of empathy.

Disclosures: E. Yengisetty: None. **A. Khan:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.18/DD13

Topic: H.04. Emotion

Support: NIH Grant R01MH098348

Title: Childhoodemotionsocialization andstress-elicitedbrainactivity

Authors: *E. BAUER[1], C. EICKSTEAD[1], D. K. GREY[2], S. MRUG[1], D. C. KNIGHT[3]; [1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Psychology, The Univ. of Alabama at Birmingham, Birmingham, AL; [3]Psychology, UAB, Birmingham, AL

Abstract: Individual differences in neural reactivity to stress may be shaped by early emotion-related experiences, including supportive and unsupportive parental emotion socialization strategies. These parental behaviorssupport the development of children's emotion regulation abilities by shaping their understanding, expression, and management of emotions. However, the neural processes that underlie the relationship between emotion socialization and stress-reactivity are yet to be determined. Thus, the present study assessed the relationship between childhood emotion socialization and neural reactivity to stress in emerging adulthood. Participants included 301 individuals (males = 49.5%, females = 50.5%, Black = 66.8%, White = 33.2%, age range = 17-23 years, M = 20.03, SD = 1.51). Participants' reported on their parents' responses to negative emotions (i.e., sadness, anger, and fear) during childhood using the Emotions as a Child scale (Magai et al., 1997), which were used to derive broad scales of supportive (e.g., comforting child-focused) and unsupportive (e.g., disapproving, emotion-amplifying) parental emotion socialization strategies (Guo et al., 2017). Participants also completed the Montreal Imaging Stress Task during functional magnetic resonance imaging (Dedovic et al., 2005; Wheelock et al., 2016). Linear mixed-effects models predicted stress-elicited brain activity from supportive and unsupportive parental emotion socialization strategies. The results showed that stress-elicited dorsolateral prefrontal cortex (PFC) and amygdala activity varied with parental emotion socialization approaches. Specifically, higher supportive emotion socialization was related to lower amygdala reactivity to stress, whereas higher unsupportive emotion socialization was associated with lower dorsolateral PFC reactively to stress ($pFWE<0.05$). These findings are consistent with prior research suggesting that children raised in emotionally supportive environments learn to manage their emotions more effectively and perceive stress as less threatening (Whittle et al., 2014), which may have resulted in the lower amygdala reactivity to stress. Similarly, the dorsolateral PFC findings are consistent with prior research suggesting that children raised in emotionally unsupportive environments may not engage top-down cognitive control processes effectively or efficiently (Bounoua et al., 2025). These findings have important implications for understanding the relationship between childhood emotion socialization and neural stress reactivity.

Disclosures: E. Bauer: None. **C. Eickstead:** None. **D.K. Grey:** None. **S. Mrug:** None. **D.C. Knight:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.19/DD14

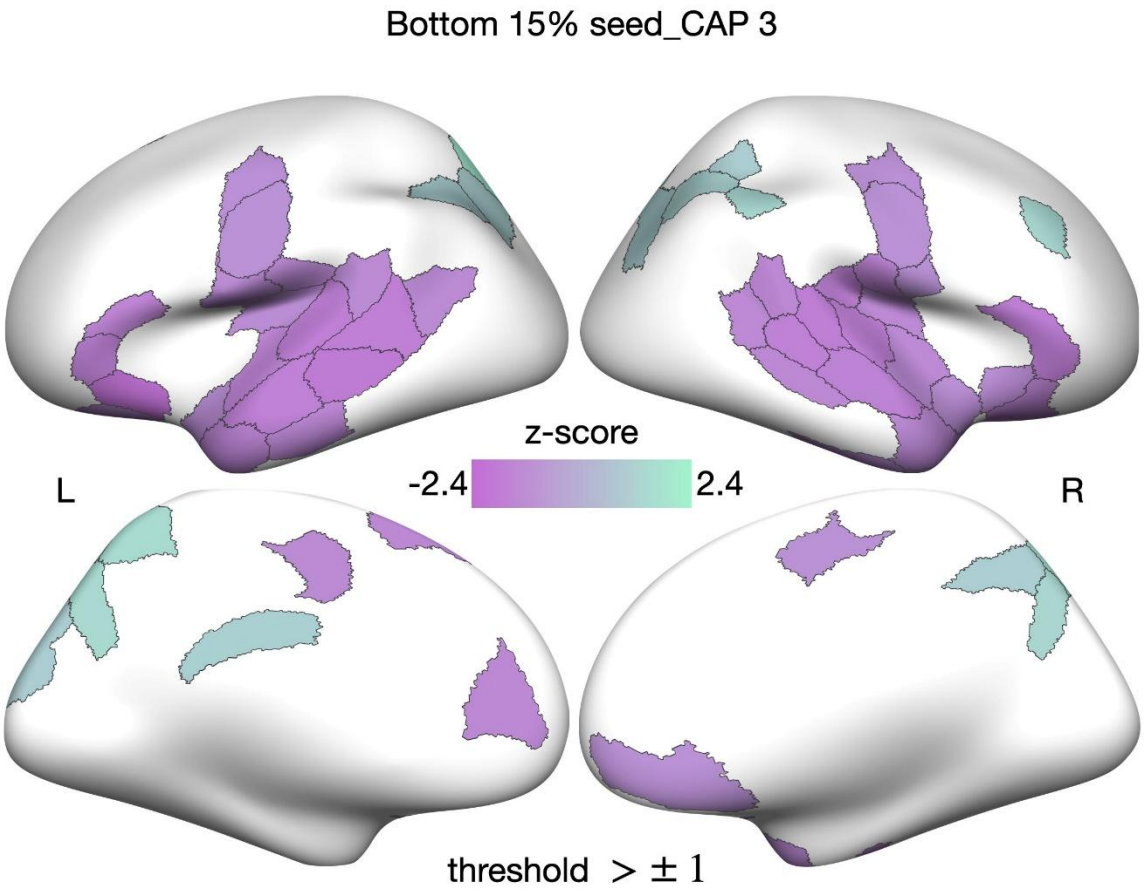
Topic: I.06. Social Cognition

Support: the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2026-25471465)

Title: Dynamics of the medial prefrontal cortex network and its relation to negative affect

Authors: T. LEE[1], N. KIM[1], *B. PARK[2];
[1]Dept. of Biomed. Informatics, [2]Ajou Univ. Sch. of Med., Suwon, Korea, Republic of

Abstract: The medial prefrontal cortex (mPFC) has been implicated in negative-affect-related processes, particularly regarding to emotion regulation and affective evaluation. Emotion-related processes are thought to emerge from dynamic configurations across diverse functional brain networks. In this study, we thus examined how co-activation pattern (CAP) cored at the mPFC are distributed as a sort of brain states and the dynamics are associated with negative-affect traits. For this study, we used rs-fMRI data from 1,080 participants, provided in the HCP S1200 release dataset (age = 28.78 ± 3.70 years; 495 males). Rs-fMRI data, canonically preprocessed using the statistical parametric mapping toolbox (SPM12), were temporally filtered with despiking, regressing out confounding factors, and band-pass filtering (0.01-0.1 Hz). Then, mPFC-seeded CAPs were defined with the strongest 15% signal frames and k-means clustering was applied to identify the CAP states within each frame set with the co-activation pattern analysis (TbCAPs). Multiple linear regression analyses were conducted with negative-affect traits as predictors and CAP-relevant variability metrics as outcomes, with demographic covariates. We found anger-physical aggression was significantly associated with a higher occurrence rate of CAP-driven third state derived from the bottom 15% of mPFC seed-signal frames. This state was characterized by DMN co-deactivation ($P < 0.005$, Bonferroni-corrected). Given prior evidence linking mPFC-DMN systems to emotion regulation and aggression to emotion-regulation difficulties, these findings may provide a network-level perspective for understanding aggression-related negative affect and its relevance to emotion regulation, which could inform future research on regulatory strategies.



Disclosures: T. Lee: None. **N. Kim:** None. **B. Park:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.20/Web Only

Topic: H.04. Emotion

Support: Intramural support from NBRC

Title: Brain networks activated when listening to Hindustani music ragas

Authors: *N. CHATTERJEE SINGH[1,2], R. SINGH[3], A. MATHUR[4], S. PADMALA[5]; [1]Psychology and Cognitive Sci., Ashoka Univerdity, Sonipat, India; [2]Psychology and Cognitive Sci., [3]Ashoka Univ., Sonipat, India; [4]Univ. of Nashville, Nashville, TN; [5]Ctr. for Neurosci., Indian Inst. of Science, Bangalore, India, BENGALURU, India

Abstract: Raga music from India has long been associated with emotions.The term ‘raga’ is defined as ‘the act of coloring or dyeing’ the mind. In this study, we investigated the neural correlates of emotions experienced while listening to ragas from North Indian Classical Music (NICM). A raga is a melodic framework constructed from five or more notes selected from a seven-note scale and is designed to evoke a distinctive emotional mood or rasa. The tonal structure of NICM is based on twelve octave divisions, with each interval defined by its frequency relationship to the tonic note. Specific combinations of tonal intervals generate varying consonance-dissonance relationships, which are thought to contribute to the subtle emotional distinctions elicited by different ragas. Although behavioural studies have demonstrated that ragas evoke differentiated emotional responses (Mathur et al., 2015), little is known about the neural mechanisms underlying these experiences. Using validated stimuli from Mathur et al.(2015) we conducted a functional neuroimaging experiment wherein participants listened to twelve ragas. A total of 31 participants were scanned in a 3T Philips Achieva scanner while they listened to ragas in the ‘gat’ mode presented in an alternating block design contrasting positive and plaintive conditions. Participants also provided ratings of the emotions experienced after listening. The experiment consisted of six runs, each containing four alternating 30-second blocks of raga compositions. Each run lasted 207.5 seconds. Functional imaging data were analyzed using the AFNI software package. Subject-level contrast images generated using the 3dDeconvolve function were entered into second-level group analyses using one-sample t-tests. Statistical thresholding at $p < 0.001$ (corrected) revealed significant activation in auditory and music-processing regions, including the auditory cortex, superior temporal gyrus, and temporal pole, as well as emotion-related regions such as the amygdala, nucleus accumbens, anterior cingulate cortex, and orbitofrontal cortex. Direct comparisons between the “happy” and “tensed” emotional conditions revealed differential activation in the medial orbitofrontal cortex, supporting its role in encoding affective valence during music perception.These findings provide neurobiological evidence that raga compositions reliably engage distributed neural networks involved in auditory processing, reward, and emotion, highlighting the capacity of traditional musical systems to evoke distinct emotional states through specific tonal structures.

Disclosures: N. Chatterjee Singh: None. **R. Singh:** None. **A. Mathur:** None. **S. Padmala:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.21/DD15

Topic: H.04. Emotion

Support: JSPS KAKENHI Grant Number JP25K13298

Title: Dissociation between subjective stress and multimodal psychophysiological responses in sensory processing sensitivity

Authors: *S. TANAKA[1], T. HAMA[2], H. KARIBE[1];
[1]Nippon Dent. Univ. Sch. of Life Dent. at Tokyo Dept. of Pediatric Dent., Tokyo, Japan; [2]Dept. of Med. Technol., Fac. of Hlth. Sciences, Ehime Prefectural Univ. of Hlth. Sci., Iyo-gun, Ehime, Japan

Abstract: Sensory processing sensitivity (SPS) is a temperamental trait characterized by heightened responsiveness to environmental and emotional stimuli and deeper information processing. Emotional responses in individuals with high SPS may not be fully captured by subjective stress ratings alone. This study examined SPS-related responses to negative emotional stimuli in virtual reality, focusing on dissociation between subjective stress and objective psychophysiological responses. Twenty healthy female university students were classified into High-SPS and Low-SPS groups based on the mean score of the Japanese 19-item Highly Sensitive Person Scale. Anger, disgust, and sadness stimuli were presented under visual-only and audiovisual conditions. During stimulus presentation, electrodermal activity (EDA), pulse rate (PR), prefrontal total hemoglobin responses measured by fNIRS, and eye movements were recorded. Area-of-interest analyses were conducted for the eyes, nose, and mouth. Subjective stress ratings showed no clear group differences in any condition, whereas objective measures revealed condition-dependent SPS-related differences. The clearest dissociation was observed for anger stimuli. Despite comparable subjective stress ratings, the High-SPS group showed larger EDA responses, indicating heightened sympathetic arousal. PR responses also showed condition-dependent group differences, but the dissociation was most consistent in EDA responses to anger. fNIRS showed larger left lateral prefrontal cortex (LPFC) total hemoglobin responses in the High-SPS group in the visual-only sadness condition. LPFC responses were also larger than medial prefrontal cortex responses within the High-SPS group in the visual-only anger and audiovisual sadness conditions, suggesting an LPFC-dominant pattern related to emotional processing or attentional control. Eye-movement analyses showed group differences in gaze allocation to the eye region in the visual-only anger condition. The Low-SPS group fixated on the eye region for longer and with a higher fixation proportion, whereas the High-SPS group showed delayed initial orienting to the eye region of angry faces. These findings suggest that SPS-related emotional responses may appear as a dissociation between subjective stress and objective responses. In particular, anger stimuli revealed a pattern in which individuals with high SPS did not necessarily report stronger stress, but showed heightened sympathetic arousal, altered eye-region orienting, and relative LPFC involvement. Multimodal assessment may help characterize latent emotional load associated with SPS.

Disclosures: S. Tanaka: None. **T. Hama:** None. **H. Karibe:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.22/Web Only

Topic: I.06. Social Cognition

Support: Kiwanis Neuroscience Research Foundation
Kinsey Neuropsychology Foundation

Title: Intelligence is more than the sum of its parts: A neuropsychological analysis of a common factor associated with cognitive and emotional intelligence.

Authors: *E. REEDY[1], K. RAMCHANDRAN[2], M. BOWREN, Jr.[3], S. COHEN-ZIMERMAN[4], J. GRAFMAN[5], D. TRANEL[6];
[2]Intrnl. Med., [3]Psychiatry, [1]Univ. of Iowa, Iowa City, IA; [4]Shirley Ryan Abilitylab, Chicago, IL; [5]Think and Speak Lab., Shirley Ryan Ability Lab., Chicago, IL; [6]Dept Neurol, The Univ. Of Iowa Neurosci. Grad. Program, Iowa City, IA

Abstract: Intelligence has long been defined as a multifaceted construct that encompasses skilled and adaptive behavior across many areas of life. Operationally, intelligence is often characterized as a latent factor (*g*) that is statistically extracted from measures of cognitive abilities. However, neuroscience and neuropsychology suggest that intelligence also encompasses social and emotional functions. The current research explores *g* as an overarching latent factor that describes not only cognitive, but also social and emotional intelligence. We pursued this objective in patients with focal brain lesions, due to their unique potential for exposing dissociations between discrete mental abilities. Our investigation used two independent populations of participants with brain lesions: 148 patients from the Iowa Neurological Patient Registry (INPR) and 166 from the Vietnam Head Injury Study (VHIS). We combined demographically adjusted scores from 13 cognitive intelligence tests (subtests from the Wechsler Adult Intelligence Scale III and 8 emotional intelligence tests (subtests from the Mayer Salovey Caruso Emotional Intelligence Test V2) in a bifactor (*g*+4) combined exploratory/confirmatory factor analysis (EFA/CFA). In Stage 1, an EFA was conducted on the more demographically heterogeneous INPR sample. In Stage 2, the INPR EFA was used to set up a VHIS CFA to evaluate generalizability of the structure to an independent brain lesion cohort comprised only of male combat veterans. When considered alongside the four domain-specific factors, g captured 60% (INPR)- 62% (VHIS) of variance across all 21 subtests. The domain-specific factors contributed an additional combined 27% (INPR)-31%(VHIS). The variance structure was stable across both samples in the EFA and CFA stages. The fit indices are in the acceptable range for the VHIS CFA (CFI=0.91; TLI=0.89, RMSEA =0.06, Confidence Interval [0.05,0.08]). These results indicate that the factor structure generalizes to the independent VHIS data despite its relative demographic homogeneity. This research indicates that *g* explains test variance beyond the domain of traditional cognitive tests. This challenges conventional notions of the measurement of *g*, suggesting that general intelligence may be a singular ability emergent from cognitive and affective brain systems.

Disclosures: E. Reedy: None. **K. ramchandran:** None. **M. Bowren:** None. **S. Cohen-Zimerman:** None. **J. Grafman:** None. **D. Tranel:** None.

Poster

PSTR025: Emotional Processing in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.23/DD16

Topic: H.04. Emotion

Support: NSF Grant 2239591

Title: Neural Correlates of Curiosity: A Multimodal Scoping Review

Authors: *S. WENE;
American Univ., Washington, DC

Abstract: Curiosity is important in directing motivation and attention and is influential in learning. While it has been hypothesized that curiosity activates reward processing brain areas by functioning as a reward, it is unknown what regions are implicated in curiosity, especially across methods and neuroimaging approaches as there is no systematic synthesis on the neural correlates of curiosity. We conducted a scoping review to examine how neuroimaging studies measure curiosity and what neural mechanisms are related to curiosity. The search generated 1358 abstracts, of which 37 articles (10 EEG, 7 MRI, 20 fMRI) met the criteria for inclusion in data extraction. Results from 16 task-based fMRI studies show that most studies focused on reward processing areas (e.g., VTA, striatum) within ROI analysis, but studies that have done whole brain analysis have found activation in other parts of the brain such as salience (e.g., cingulate, insula), and higher order thinking (e.g., PFC, cingulate) regions, suggesting that perception and attention may have a more prominent role in curiosity than previously thought. Within structural MRI studies, results indicate diverging findings on curiosity's correlation with gray matter volume. Additionally, when examining white matter integrity, curiosity was found in one study to be correlated with overall fractional anisotropy (FA), including portions of the fornix and superior longitudinal fasciculus, while another study found non-significant results for correlations between curiosity subscales and inferior longitudinal fasciculus FA and fornix mean diffusivity. Further, results examining network analyses show curiosity to be associated with reduced local efficiency, yet higher standardized clustering coefficient and small-worldness. Additional functional connectivity analyses also have varying results indicating that the frontoparietal and salience network may be implicated in curiosity. EEG studies have found meaningful connections between curiosity and a wide range of frequencies, most common theta and alpha, as well as ERPs such as the P300, LPC, RewP, and LPP. However, other studies found several of these frequencies and ERPs as non-significant, likely due to variance in study methodologies and underutilization of EEG in curiosity studies. The disparate findings within neural modalities suggest that curiosity is likely engaging many brain regions, predominately within the salience, reward, and frontoparietal networks. By using multimodal techniques, curiosity can be examined spatially and temporally giving rise to a higher understanding of what happens when the brain generates curiosity.

Disclosures: S. Wene: None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.01/DD17

Topic: H.05. Mood Disorders

Support: NIH Grant AG077002
NIH Grant NS041218
Neural Injury and Plasticity Travel Grant
Center for Neural Injury and Recovery Pilot Grant
MCGSO Professional Development Grant
MCGSO Student Research Grant Program

Title: Targeting Perineuronal Nets to Restore Plasticity in Depression-Like Behavior: Therapeutic Potential of 4-Methylumbelliferone

Authors: *P. WONNENBERG[1], K. CONANT[2], T. SULLIVAN[2], K. DIAL[3];
[1]Georgetown Univ. Med. Ctr. Interdisciplinary Program In Neurosci., Washington, DC;
[2]Neurosci., Georgetown Univ., Washington, DC; [3]Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Major depressive disorder (MDD) is associated with impaired neuronal plasticity and disruptions in excitatory/inhibitory (E/I) balance within key brain regions, including the hippocampus and amygdala. These deficits are thought to arise, in part, from chronic stress-induced neuroinflammation and alterations in the extracellular matrix (ECM), particularly within perineuronal nets (PNNs) that enwrap parvalbumin-positive (PV+) interneurons. Although PV+ interneurons are critical regulators of pyramidal cell activity, the impact of chronic stress on PV-pyramidal interactions and the therapeutic potential of targeting PNNs remain poorly understood. Emerging evidence suggests that PNN remodeling contributes to maladaptive circuit function by restricting synaptic plasticity and altering neuronal communication. Here, we use fiber photometry to monitor calcium dynamics in PV+ interneurons and pyramidal neurons in vivo during chronic corticosterone-induced depression-like states. Recordings from the hippocampus and amygdala are used to assess how stress alters E/I balance at the circuit level. In parallel, we employ immunohistochemistry to quantify PNN density and cellular localization, Western blotting to measure protein expression of ECM components and stress-related signaling markers, and behavioral assays to evaluate cognitive and affective outcomes. We further assess the effects of 4-methylumbelliferone (4-MU), an inhibitor of hyaluronan synthesis, as a strategy to modulate PNN integrity and restore plasticity. Together, these approaches allow us to link molecular, cellular, circuit, and behavioral consequences of chronic stress. Preliminary findings indicate that chronic stress enhances PV+ interneuron activity, contributing to reduced pyramidal neuron excitability and behavioral impairments. These changes are accompanied by increased PNN density and altered ECM-related protein expression. Treatment with 4-MU reduces PNN density, normalizes PV-pyramidal activity dynamics, restores protein expression profiles, and improves performance in cognitive and anxiety-related behavioral assays. Additionally, stress-induced alterations in PNN-associated proteins suggest widespread ECM remodeling that may contribute to persistent circuit dysfunction. Together, these findings identify ECM remodeling as a key mediator of stress-induced circuit dysfunction and support 4-MU as a promising therapeutic approach for restoring plasticity and alleviating symptoms of MDD.

Disclosures: P. Wonnenberg: None. **K. Conant:** None. **T. Sullivan:** None. **K. Dial:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.02/DD18

Topic: H.05. Mood Disorders

Support: NIH RO1AG077002
NIH AG071745
Georgetown University-MCGSO
ARCS Foundation
COSMOS Foundation
Dana Foundation
Source Research Foundation

Title: Title: 5-HT2A Receptor Deletion Reduces Parvalbumin and Perineuronal Component Expression and Drives Anxiety-Like Behavior

Authors: *K. DIAL[1], S. DEASY[3,1], P. WONNENBERG[4], T. SULLIVAN[1], J.-Y. WU[5], K. CONANT[2];
[2]Neurosci., [1]Georgetown Univ. Med. Ctr., Washington, DC; [3]Duke, Durham, NC; [4]Georgetown Univ. Med. Ctr. Interdisciplinary Program In Neurosci., Washington, DC; [5]Neurosci., Georgetown Univ., Washington, DC

Abstract: The serotonin 2A receptor (5-HT2AR) is broadly implicated in anxiety and emotional regulation, yet its contribution to hippocampal circuit integrity and anxiety-related behavior remains incompletely understood. Here we report that constitutive deletion of the 5-HT2AR in male and female BALB/c mice produces robust anxiety-like behavior across multiple paradigms, including the elevated zero maze, open field test, marble burying test, and sucrose splash test, without a concomitant effect on locomotor activity. Hippocampal protein analyses revealed reductions in parvalbumin as well as in perineuronal net components brevican and HAPLN4, consistent with reduced parvalbumin interneuron activity. Phosphoprotein analyses in male knockouts suggest possible alterations in GSK3β activity that may contribute to behavioral effects. Consistent with a functional role for 5-HT2AR in hippocampal network dynamics, acute application of the 5-HT2AR agonist DOI to wildtype hippocampal slices reduced sharp wave ripple abundance and increased inter-event interval, supporting the interpretation that parvalbumin levels are reduced in knockout animals. Preliminary calcium imaging data further suggest that 5-HT2AR activation drives rhythmic cortical network activity in regions adjacent to hippocampus, pointing to a broader circuit level influence of serotonergic signaling. These findings suggest that 5-HT2AR signaling maintains hippocampal inhibitory circuit integrity, with receptor loss producing convergent structural, biochemical, and circuit level changes that

manifest as anxiety-related behavior, with implications for the therapeutic targeting of 5-HT2AR in stress-related psychiatric disorders.

Disclosures: K. Dial: None. **S. Deasy:** None. **P. Wonnenberg:** None. **T. Sullivan:** None. **J. Wu:** None. **K. Conant:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.03/DD19

Topic: H.05. Mood Disorders

Support: PID2020-118582RB-I00 (MICIU/AEI/10.13039/501100011039 to MJG-F
PID2023-151640OB-I00 (MICIU/AEI/10.13039/501100011033) to MJG-F
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The National Institute on Drug Abuse (NIDA) U01DA043098 to HA
Hope for Depression Research Foundation to HA
Pritzker Neuropsychiatric Research Consortium to HA
"FPI_022_2022" predoctoral scholarship (CAIB) to JJ-P

Title: Sex-specífic antidepressant-like effects following adolescent ketamine in selectively bred low-responder rats: molecular correlates

Authors: *J. JORNET-PLAZA[1], E. K. HEBDA-BAUER[2], C. A. TURNER[3], H. AKIL[4], J. GARCIA-FUSTER[5];
[1]Univ. of the Balearic Islands and IdISBa, Palma, Spain; [2]Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI; [3]Michigan Neurosci. Inst., Univ. of Michigan, Willis, MI; [4]Univ. of Michigan, Ann Arbor, MI; [5]Med., IUNICS, Univ. Balearic Islands, Palma, Spain

Abstract: Previous studies from our group revealed sex- and dose-dependent antidepressant-like effects of ketamine in naïve adolescent rats. The present follow-up study aimed at validating the antidepressant-like effects of ketamine in an animal model of innate internalizing behavior (bred low responder, bLR, rats), while ascertaining molecular markers of treatment response. To do so, bLR rats of both sexes were selected after breeding at the University of Michigan facilities based on their locomotor response in a novel environment. Then, during mid-adolescence rats were treated i.p. with ketamine (5 or 10 mg/kg) or vehicle for 7 consecutive days. Antidepressant-like responses were assessed under the stress of the forced-swim test (FST) 30 min after a single dose, and 24 h after the 7-day treatment. For the molecular analysis, a separate cohort of bLR rats was treated with acute ketamine and euthanized 30 minutes post-administration, at which point brain tissue was collected from specific regions implicated in mood regulation. Statistical evaluations were done through two-way ANOVAs (independent variables: Sex and Treatment)

followed by *post-hoc* analysis when appropriate. The results showed that the highest dose tested of ketamine induced acute and repeated antidepressant-like responses by improving swimming behavior in the FST, although exclusively in male bLR rats (acute: vehicle=7±1 s vs. ketamine=15±2 s; p=0.023; repeated: vehicle=5±1 s vs. ketamine=10±2 s; p=0.027). The neurochemical results also showed sex- and region-specific effects, with increased hippocampal p-GSK3 by both ketamine doses exclusively in male bLR rats, while no significant comparisons were observed for females and/or the prefrontal cortex. Additionally, although two-way ANOVAs revealed several sex x treatment interactions for mTOR (both in hippocampus and prefrontal cortex), no *post-hoc* pair-wise comparison came out significant. Finally, acute ketamine did not modulate BDNF in either region studied. Ongoing experiments are evaluating the molecular correlates following the repeated treatment, with the aim of identifying potential neurochemical adaptations following multiple ketamine doses during adolescence. In conclusion, consistent with previous findings, the present results validated the antidepressant-like potential of ketamine in adolescence in a sex-specific manner, as now observed in an inborn model of internalizing behavior. Moreover, the observed antidepressant-like effects are associated with sex-specific alterations in neuroplasticity-related pathways. Future studies should better understand the mechanisms behind the observed sex differences.

Disclosures: J. Jornet-Plaza: None. **E.K. Hebda-Bauer:** None. **C.A. Turner:** None. **H. Akil:** None. **J. Garcia-Fuster:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.04/DD20

Topic: H.05. Mood Disorders

Support: NIH Grant R15S088776

Title: Interaction Between Early-Life Stress and Status Epilepticus in Shaping Depressive-Like Phenotypes

Authors: *T. BRADISH[1], C. LAU[2], S. PELL[2], K. BLANDIN[3], M. HEMMERSMEIER[2], J. J. THAYIL[2], C. KELLEY[2], K. LALLY[2], C. ENYERIBE[4], A. GARAPATI[2], T. GARCIA[2], J. N. LUGO, Jr.[5];
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Abstract: Early-life seizures and status epilepticus (SE) are associated with long-term neurological and psychiatric complications. Individuals with epilepsy commonly experience mood disorders, and evidence suggests a bidirectional relationship in which seizures can contribute to depression, while stress and depression may also increase seizure susceptibility. Early-life stress (ELS) is another major factor that disrupts emotional and neurological

development, leading to heightened stress reactivity, affective dysfunction, and lower seizure thresholds later in life. Because both ELS and early-life seizures alter emotional regulation, their combined effects may increase vulnerability to depressive-like behaviors in adulthood.This study examined the effects of ELS and a single episode of SE on depressive-like behaviors in C57BL/6J mice. ELS was induced using a limited bedding and nesting paradigm from postnatal day (PD) 2-9, and on PD10, mice received either kainic acid (KA) to induce SE or saline as a sham control. KA-treated mice were monitored for continuous seizures consistent with SE. In adulthood, mice underwent a series of behavioral tests to assess anxiety-like behavior, apathy, anhedonia, fatigue, and psychomotor activity using established paradigms. Our results found a significant interaction between stress group and gender, $F(1,96) = 4.41$, $p = .039$, in the amount of nestlet used in the nesting test. Significant main effects were found in total distance traveled between our SE mice and the control mice, $F(1,80) = 6.53$, $p = .012$, the amount of time spent in the open arms in ELS mice versus the controls, $F(1,80) = 5.27$, $p = .024$, and the duration spent in the closed arms in the ELS mice in comparison to the controls, $F(1,80) = 12.28$, $p < .001$. Open field had sex main effects for duration of time spent both in the center, $F(1,88) = 4.74$, $p = .032$, and the surround $F(1, 88) = 7.84$, $p = .006$. As well as the total distance traveled between sex, stress, and induction method, $F(1,88) = 5.66$, $p = .020$. Evaluation of the splash and sucrose preference tests revealed no significant main effects.These results indicate that ELS and a single episode of SE produce distinct and partially overlapping effects on long-term adult behavior. SE primarily altered locomotor activity in our animals, whereas ELS altered anxiety-related measures. The sex-dependent results found in the open field and nesting tests indicate that males and females react differently to early-life insults. These results indicate that early-life insults alter long-term behavioral outcomes, but are not necessarily associated with depressive-like behaviorisms.

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Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.05/DD21

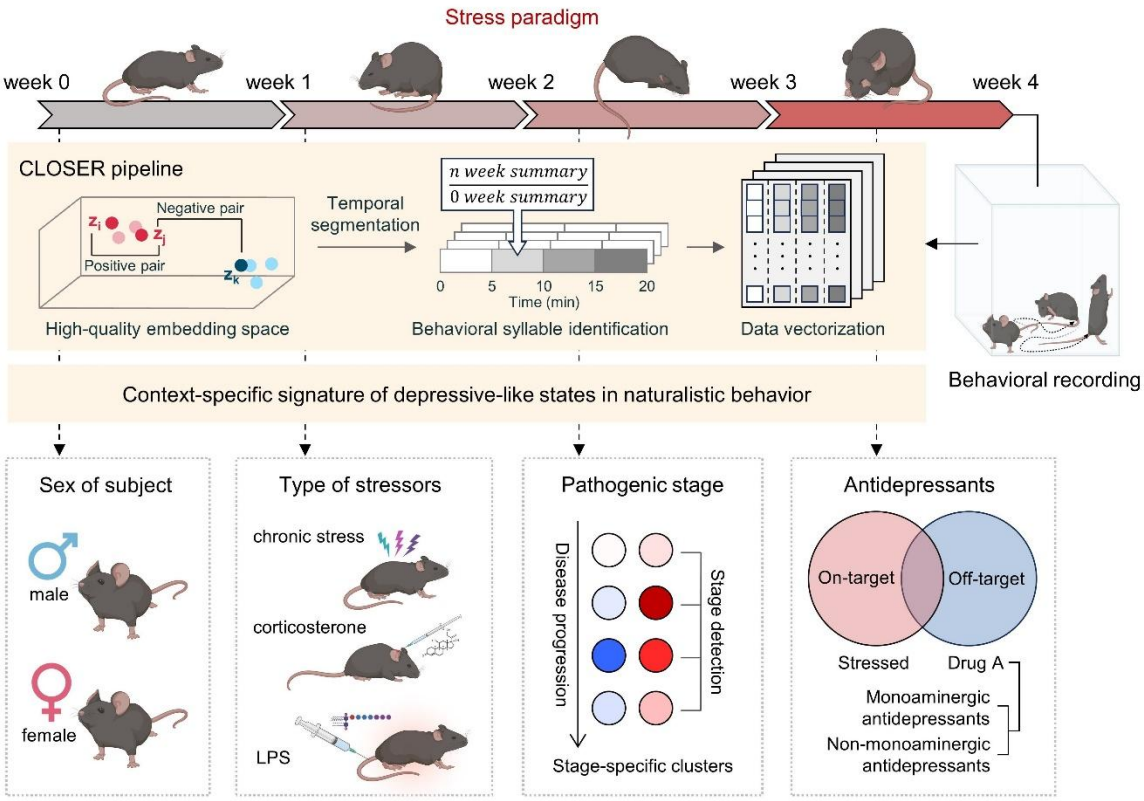
Topic: H.05. Mood Disorders

Support: National Research Foundation of Korea (NRF) grant 2020R1A2C301474213
National Research Foundation of Korea (NRF) grant RS-2024-00439379
Samsung Science and Technology Foundation project SSTF-BA1902-06
Korea Health Industry Development Institute RS-2024-00440398

Title: Naturalistic Behavior-based Platform for Precise Analysis of Depressive-like Symptoms

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Abstract: Major depressive disorder (MDD) is an etiologically diverse psychiatric disease with heterogeneous manifestations, making it difficult to diagnose with conventional assessment standards. In addition, the obvious incompatibility of the standard survey-based tests for human MDD and the behavioral assays for depressive-like phenotypes in mice makes clear the requirement for a non-invasive method for quantifying the expression of depressive-like state in naturalistic contexts. Here, we introduce a self-supervised machine learning platform, CLOSER (Contrastive Learning-based Observer-free analysis of Spontaneous behavior for Ethogram Representation), to monitor the spontaneous behavior in a depressive disease model with enhanced precision, reliability, and efficiency. This framework incorporates 3D pose skeleton data and kinematic features in a unique data augmentation strategy to characterize semantic behavioral syllables with a high-quality feature space. Using CLOSER, we uncovered distinct motion profiles in chronically stressed mice across both sexes and different disease stages. Furthermore, we quantified the drug-specific recovery of psychomotor symptoms, highlighting CLOSER's discriminative power for identifying drug efficacy. In offering an AI-driven decoding of exploratory behaviors, CLOSER proposes the standardization of depressive-like phenotype assessment in mouse models, thereby bridging preclinical and clinical diagnostics for psychiatric drug discovery.



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Poster

PSTR026: Depression and Anxiety

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Program #/Poster #: PSTR026.06/DD22

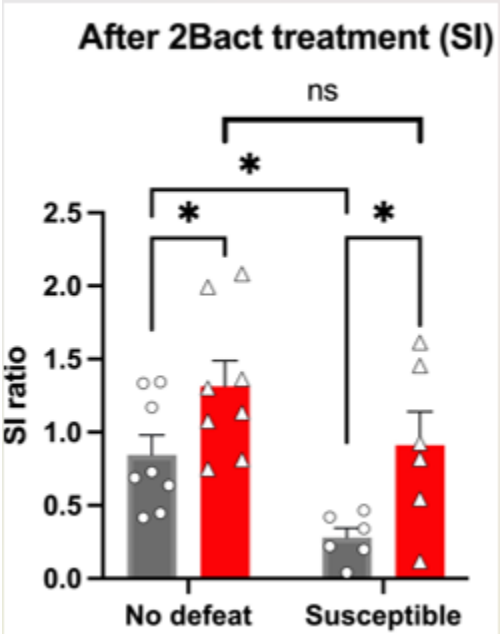
Topic: H.05. Mood Disorders

Title: The integrated stress response in depression

Authors: *D. HO-TIENG[1,2], N. SONENBERG[3], R. C. BAGOT[4], A. KHOUTORSKY[5]; [1]McGill Univ., Kirkland, QC, Canada; [2]Integrated Program in Neurosci., McGill Univ., Montreal, QC, Canada; [3]McGill Univ., Cote St-Luc, QC, Canada; [4]Dept. of Psychology, [5]Anesthesia, McGill Univ., Montreal, QC, Canada

Abstract: Recent studies have demonstrated that the reduction of depressive symptoms can be achieved through an increase in protein synthesis. A single dose of sub-anesthetic ketamine alleviates depression within 1-2 hours of administration for up to 21 days. However, due to ketamine's potential for abuse, narrow therapeutic window and delivery by injection, its clinical

use is limited. Since an increase in protein synthesis alleviates the symptoms of depression, we propose to target one of the central cellular mechanisms regulating protein synthesis, the Integrated Stress Response (ISR) pathway. Activation of the ISR pathway during cellular stress leads to the inhibition of protein synthesis. Conversely, inhibiting the ISR pathway increases protein synthesis. Recent studies have shown that a small molecule that inhibits the ISR pathway (known as 2BAct) results in ISR pathway suppression as shown by the prevention of neurological deficits in vanishing white matter disease. No toxicity or adverse effects have been observed for the prolonged administration of 2BAct and is currently in clinical development. Based on our promising preliminary data, we tested the hypothesis that depression phenotypes can be alleviated by 2BAct via activation of protein synthesis. In this project, we assessed the ability of 2BAct to prevent and reverse symptoms of depression in mice and study the underlying mechanism. We utilized the model of depression known as chronic social defeat stress in male mice and assessed their behavior using several well established behavioral tests for depression-like behavior. Our results have shown that reducing the ISR activity using 2BAct reduces some of the depression-like behavior (as shown in the graph below in the social interaction test (SI) after 2Bact administration of 30 days). All data analysis and quantification were done blinded with minimum N=5 per group. Mice that were not introduced to a CD1 aggressor were used as controls.



Disclosures: D. Ho-Tieng: None. **N. Sonenberg:** None. **R.C. Bagot:** None. **A. Khoutorsky:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.07/DD23

Topic: H.05. Mood Disorders

Title: Stress-vulnerability is associated with bacterial monoculture and pro-inflammatory gut bacteria whereas stress-resilience is associated with butyrate-producing probiotic bacteria in the chick social separation stress test

Authors: T. S. SMITH, G. M. WRIGHT, ***S. W. WHITE**;
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Abstract: Research using the Chick Social Separation Stress (CSSS) test has identified two unique genetic strains that differ in their onset to behavioral despair. The Black Australorp (BA) strain displays shorter latency while the Production Red (PR) strain displays longer latency to enter behavioral despair qualifying them as stress-vulnerable and stress-resilient, respectively. Additionally, the BA genetic line presents homologies with treatment-resistant depression (TRD). As gut biota has been shown to program stress-sensitivity early in life, this study sought to measure initial and progressive differences in gut bacterial population between the two strains. Male subjects from each strain were received one day post-hatch, housed in identical colony rooms, and provided the same diet for nine days. On day 9, both strains were exposed to a 90-minute isolation stressor to assess stress-sensitivity phenotypes. Fecal samples from both strains were collected on day 3 and day 8 post-hatch and bacterial DNA was extracted and sequenced, and community diversity and evenness determined. Analysis of onset to depression thresholds via MANOVA and Fisher's LSD post-hoc tests revealed BAs entered behavioral despair significantly faster than PRs at both the 25% and 95% onset thresholds, $p = .029$ and .019, respectively. On day-aged 3, BA chicks show enrichment in *Proteus mirabilis* and *Bacillus anthracis*, suggesting an early life pro-inflammatory microbial profile whereas PR chicks are enriched in probiotics like *Pediococcus acidilactici.* By day-aged 8, BA chicks become dominated by a monoculture of *Limosilactobacillus fermentum* whereas the PR strain is populated by butyrate-producing bacteria such as *Ruminococcus torques, Clostridium leptum, Flavonifractor plautii,* and *Oscillibacter sp.* Overall, more community stability was displayed in PR with less stability and diversity and pathobiont enrichment over time in BA. These findings suggest the stress-vulnerable and resilient phenotypes of the BA and PR genetic lines are associated with differences in gut bacteria populations and development. More specifically, the presence of pro-inflammatory bacteria and a bacterial monoculture profile in the BAs is consistent with gut dysbiosis and suggests a possible leaky gut. The two strains may serve as novel model organisms for studying the relationship between enterotypes and stress-sensitivity phenotypes. Future studies aim to measure baseline and stress-induced differences in corticosterone, inflammatory cytokines, lipopolysaccharides, kynurenine/serotonin ratios, and central BDNF levels between the two strains.

Disclosures: T.S. Smith: None. **G.M. Wright:** None. **S.W. White:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

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Program #/Poster #: PSTR026.08/DD24

Topic: H.05. Mood Disorders

Title: Impact of neonatal tryciclic antidepressant administration on adulthood behavior of CD1 male mice strain

Authors: D. LAGUNES-TRUJILLO[1], C. J. JUÁREZ-PORTILLA[2], R. C. ZEPEDA[3], R. VIVEROS CONTRERAS[2], V. HERNÁNDEZ ESLAVA[4], ***T. MOLINA-JIMENEZ**[5]; [1]Facultad de Medicina, [2]Ctr. de Investigaciones Biomédicas. Edificio T, [3]Univ. Veracruzana, Xalapa, Mexico; [4]Ctr. de Investigaciones Biomédicas. Edificio T, Univ. Veracruzana, Xalapa-Enríquez, Mexico; [5]Ctr. de Investigaciones Biomédicas, Univ. Veracruzana, Xalapa, Mexico

Abstract: Depression is a psychiatric disorder recognized as a global health concern, characterized by a lack of motivation and an inability to experience pleasure. Animal models are essential tools for elucidating the neurobiological mechanisms underlying depression and for developing novel pharmacological interventions. The neonatal administration of clomipramine (CMI), a tricyclic antidepressant, is a pharmacological model to develop depression-like behaviors in adult life. This model has been validated across different rat strains with some variation related to their natural baseline behavior. Then, translating the model to other species, such as mice, will require adaptation, given that mice differ in physiological and behavioral processes, but will ensure predictability and reproducibility. The objective was to investigate the effects of neonatal CMI administration in CD1 mice on motivational parameters. Mouse pups were allocated into two experimental groups: the control group, which received a solution of NaCl (0.9%), and the CMI group, which received 20 mg/kg of clomipramine hydrochloride (Sigma®). Treatments were administered daily subcutaneously (0.01 mL) once daily (at 12:00 p.m.) from postnatal day 8 to 21. Subsequently, at 7 weeks of age, the animals were evaluated using the Open Field Test, the Forced Swimming Test (FST), and the Sexual Incentive Motivation (SIM) test. Behavioral analysis revealed reduced locomotor activity and rearing behavior in the CMI group; however, no significant differences were observed in grooming behavior or in the measures obtained from the FST and SIM tests. These findings suggest that the applied dose is insufficient to induce behavioral alterations indicative of hopelessness in CD1 mice, but does result in subtle modifications in specific behaviors, such as exploratory activity.

Disclosures: D. Lagunes-Trujillo: None. **C.J. Juárez-Portilla:** None. **R.C. Zepeda:** None. **R. Viveros Contreras:** None. **V. Hernández Eslava:** None. **T. Molina-jimenez:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.09/DD25

Topic: H.05. Mood Disorders

Support: Fundación IMSS grant R-2019-1602-015

Title: Effects of cumulative stress on anxiety- and depressive-like behaviors in a multiple-hit stress model

Authors: *D. GUZMÁN RETANA[1,2], G. VARGAS RAMÍREZ[2], R. MERCADO[3], L. TORNER[4];
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Abstract: Early-life adversity and neonatal immune activation have been independently associated with long-term behavioral alterations; however, their combined and cumulative effects across multiple life stages remain unclear. Our aim was to determine whether multiple hits of different kinds exacerbate emotional disturbances or produce no additional impact beyond that induced by individual adverse experiences. Adult male and female Sprague-Dawley rats (n=8/group) were exposed to one or two early-life stressors according to group assignment A) Maternal separation (MS), where pups were isolated from mother and siblings 3h/day on postnatal days (PND) 1-14. B) ip. injection of Lipopolysaccharide (LPS, 0.5mg/kg) on PND14. Control and MS+LPS groups were included. All groups were evaluated before and after the onset of chronic unpredictable mild stress (CUMS, 3 weeks) in adulthood at PND60 (males) or PND75 (females). Anxiety- and depressive-like behaviors were assessed with open field, splash, fur state, and anhedonia tests. MS produced sex-dependent behavioral alterations across all tests. In the open field, three-way ANOVA revealed a significant effect of MS in males ($p=.0255$), while females showed significant MS x CUMS ($p=.0068$) and LPS x CUMS (B×C, $p=.0329$) interactions. Only CTRL animals showed significant changes after CUMS (males: $p=.0455$; females: $p=.0299$), suggesting that MS had already programmed a reduced stress response in adulthood. Fur state deteriorated significantly in all groups after CUMS in both sexes (Factor A, B and A×B: $p<.0001$), with LPS males and SM+LPS females showing the greatest decline. MS animals showed increased sucrose consumption in both sexes (males: $p=.0041$; females: $p<.0001$), pointing to compensatory hyperphagia rather than classical anhedonia. In the splash test, MS reduced total time grooming in both sexes (males: $p=.0148$; females: $p=.0154$), and MS females additionally showed the longest grooming latency (Factor A: $p=.0002$; A×B: $p=.0216$). These findings indicate that early adversity shapes long-term stress reactivity in a sex-dependent manner, inducing an anxiety-like phenotype that is no further exacerbated by subsequent stress exposure.

Disclosures: D. Guzmán Retana: None. **G. Vargas Ramírez:** None. **R. Mercado:** None. **L. Torner:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.10/DD26

Topic: H.05. Mood Disorders

Support: R01MH051399
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NIH T32-MH087004
The Hope for Depression Research Foundation
F31 MH133297-02
F99 NS143880-01

Title: A conserved nucleus accumbens transcriptional network defines stress resilience across sex.

Authors: *T. M. GYLES[1], L. HOLT[5], L. F. PARISE[7], R. L. FISHER-FOYE[9], A. GODINO[10], C. J. BROWNE[13], B. T. KIPP[11], A. M. MINIER-TORIBIO[10], T. MARKOVIC[14], T. DALY[12], L. LI[15], A. RAMAKRISHNAN[6], M. ESTILL[1], Y. YIM[10], A. M. CARDONA-ACOSTA[16], O. K. SIAL[17], C. A. NWAKAMA[2], C. A. BOLANOS-GUZMAN[17], L. SHEN[3], B. ZHANG[11], S. J. RUSSO[18], E. M. PARISE[8], E. J. NESTLER[4];
[2]Med. Scientist Training Program, [3]Nash Family Deptartment of Neurosci., [4]Neurosci., [1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [5]Neurosci. Dept., [6]Mount Sinai Sch. of Med., New York, NY; [7]Biomed. Sci., Florida Atlantic Univ., Boca raton, FL; [8]Biomed. Sci., Florida Atlantic Univ., Boca Raton, FL; [9]Neurosci., Icahn Sch. of Med. At Mount Sinai Grad. Training Program In Neurosci., New York, NY; [10]Nash Family Dept. of Neurosci., [11]Icahn Sch. of Med. at Mount Sinai, New York, NY; [12]Icahn Sch. of Med. at Mount Sinai, Atlantic Beach, NY; [13]Brain Hlth. Imaging Ctr., Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada; [14]Neurosci., Icahn Sch. of Med., New York, NY; [15]Inst. of Biophysics, Chinese Acad. of Sci., Shanghai City, China; [17]Psychological and Brain Sci., [16]Texas A&M Univ., College Station, TX; [18]Neurosci., Icahn school of medicine at mount sinai, New York, NY

Abstract: Chronic stress is a major risk factor for major depressive disorder (MDD), yet only a subset of individuals exposed to stress develop maladaptive behavioral outcomes. Human transcriptomic studies have revealed pronounced sex-specific molecular signatures in MDD, suggesting that the mechanisms underlying stress-related pathology differ between males and females. However, because resilience remains difficult to define and study in clinical populations, it is unknown whether adaptive responses to chronic stress are similarly sex specific or instead reflect conserved biological processes. While transcriptomic studies of chronic social defeat stress (CSDS) have identified molecular mechanisms associated with both susceptibility and resilience in male mice, whether these resilience- and susceptibility-associated transcriptional programs are conserved in female mice remains unclear. Here, we investigated the transcriptional architecture of stress resilience across sexes using CSDS, RNA sequencing, and co-expression network-based analyses.
We adapted the CSDS model for female mice and employed RNA sequencing to characterize susceptibility- and resilience-associated transcriptional programs across multiple brain regions. Female datasets were integrated with previously published male CSDS transcriptomic data using differential expression, rank-rank hypergeometric overlap (RRHO), expression pattern analysis, and co-expression network analysis. Although stress responses were largely sex specific, resilience-associated transcriptional signatures exhibited significant cross-sex concordance

within the nucleus accumbens (NAc) - but not other brain regions, whereas susceptibility-associated signatures showed minimal overlap across all regions. Expression pattern analysis similarly identified shared resilience-associated transcriptional trajectories uniquely in the NAc. Co-expression network analysis revealed partially conserved resilience-associated modules containing overlapping hub genes linked to glutamatergic signaling, synaptic plasticity, and neuronal maturation, including SLC17A7, NEUROD2, NEUROD6, and PAK1.
These findings identify the NAc as a key site of conserved resilience-associated transcriptional organization and suggest that resilience is supported by partially shared molecular networks across sexes despite broader sex-specific transcriptional responses to chronic stress.

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Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.11/DD27

Topic: H.05. Mood Disorders

Support: Arnold and Mabel Beckman Foundation
Emmanuel College

Title: Effects of voluntary exercise on glucocorticoid receptor expression levels and stress-related behaviors in mice heterozygous for the psychiatric risk gene Ankyrin 3 (Ank3)

Authors: *R. J. SULLIVAN[1], M. R. REILLY[2], R. JUSTINIANO SUAREZ[1], M. P. LEUSSIS[3]; [1]Psychology & Neurosci., Emmanuel Col., Boston, MA; [2]Psychology & Neurosci., Emmanuel Col., Peabody, MA; [3]Psychology & Neurosci., Fac. for Undergraduate Neurosci. (FUN), Boston, MA

Abstract: Ankyrin 3 (*Ank3*) codes for the ankyrin G protein, a scaffolding protein that helps organize and stabilize membrane proteins and the cytoskeleton, particularly those important for maintaining the axon initial segment. Human and animal studies of the *Ank3* gene have shown that decreased *Ank3* levels are associated with an increased risk for psychiatric disease and stress-susceptibility. To better understand the role of *Ank3* in stress susceptibility, we examined the impact of voluntary exercise on a psychiatric disease mouse model with reduced Ank3 levels. Specifically, after providing 6-week access to a running wheel or a stationary wheel, we measured the impact of voluntary exercise on behavior and physiology in heterozygous (HET) and wild-type (WT) Ank3 mice. Mood and stress-related behaviors were assessed using the

elevated plus maze (EPM), novelty suppressed feeding (NSF), and the forced swim test (FST). Following behavioral testing, we examined glucocorticoid receptor (GR) protein expression levels to assess whether voluntary exercise altered GR levels in Ank3 HETs compared to WT mice. We found that voluntary exercise decreased the latency to immobility in the FST ($p < .05$) but did not alter the total time immobile and there were no effects of genotype. In the EPM we found that voluntary exercise increased the number of rears ($p < .05$) but this was mainly driven by WT controls who showed a trend towards lower rears versus the other groups (genotype x exercise interaction $p = .078$). There were no differences in any other measure in the EPM. There were no effects of genotype or exercise in the NSF. When looking at voluntary exercise itself, there was no difference between HET and WT mice in total distance run during the exercise period. Preliminary analysis of GR levels in group-housed mice showed a 45% reduction in hippocampus and a 30% reduction in frontal cortex in HET compared to WT mice. After 6 weeks of isolation with or without voluntary exercise, we did not find a difference in GR levels between HET and WT mice. This suggests that social isolation may trigger changes in GR levels, which may also be related to lack of stress-related behavioral differences between WT and HET mice. Previous research has shown that chronic isolation impacts HET behavior more than WT behavior (Leussis et al., 2013). In our study, voluntary exercise impacted latency to immobility in the FST and rearing in the EPM, but no major behavioral differences were reported across genotypes, which may be due to the social isolation required for voluntary exercise measurements. Future studies could look at the impacts of voluntary exercise in group-housed mice to avoid the confounding stressor of social isolation.

Disclosures: R.J. Sullivan: None. **M.R. Reilly:** None. **R. Justiniano Suarez:** None. **M.P. Leussis:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.12/DD28

Topic: H.05. Mood Disorders

Support: INPRFM Grant NC123240.1.

Title: Influence of Chronic-Depression Models and SSRI Treatment on Vulnerability to Pentylenetetrazole-Induced Seizures in Rats

Authors: *S. M. SIMON[1], J. ROMERO-ELIZALDE[3], S. ALMAZAN-ALVARADO[4], A. VALDÉS-CRUZ[2];
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Abstract: Major depressive disorder and epilepsy are common neurological and psychiatric conditions that share a bidirectional relationship. These disorders involve overlapping mechanisms, including dysregulation of the hypothalamic-pituitary-adrenal axis, alterations in neurotransmitter systems, and limbic network changes. Chronic stress is a key factor contributing to both depressive symptomatology and increased seizure susceptibility. Therefore, understanding how chronic stress-induced depressive states interact with serotonergic interventions is essential for developing safer therapeutic strategies for depression-epilepsy comorbidity. The aim of this study was to compare the effects of depression models and antidepressants such as SSRIs treatment on epileptogenesis. Depressive-like behavior was induced using two models, Chronic Unpredictable Stress (CUS) and Social Isolation (SI), concomitant with treatment with fluoxetine (FLX) or citalopram (CIT) (10 mg/kg, s.c.) for 21 days. Sucrose water consumption (SWC) tests were conducted on days 7, 14, and 21 to assess anhedonia, followed by a 5-minute Forced Swim Test (FST). Subsequently, electrodes were implanted bilaterally in the hippocampus and prefrontal cortex. Ictogenesis was evaluated using the pentylenetetrazol (PTZ) model, with an initial dose followed by cumulative doses (20 or 10 mg/kg, i.p., every 10 min) were administered until status epilepticus (SE) was achieved. In SWC rats that receive CIT exhibited higher sucrose consumption across all three days of testing under all depression-conditions, while rats receiving CUS exhibited the lowest. In FST, both SSRIs reduced immobility time under all conditions. However, CUS exhibited more immobility compared to CONTROL rats, and swimming increased with CIT. EEG analysis indicated that stress-related effects were primarily confined to paroxysmal activity. Paroxysm latency decreased in SI and CUS compared to CONTROL. However, the number and cumulative duration decreased in CUS and SI compared to CONTROL. Moreover, CUS exhibited shorter cumulative durations than SI, both in cumulative measures and average cumulative duration. And FLX increased the latency to absence seizures. These findings suggest that stress-induced alterations modulate the thalamocortical circuitry involved in the generation of paroxysmal activity. Furthermore, SSRIs administered at doses effective in reducing depressive-like behaviors did not exacerbate epileptiform activity, supporting their safety and efficacy in young adults with acute epilepsy.

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Poster

PSTR026: Depression and Anxiety

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.13/DD29

Topic: H.05. Mood Disorders

Title: Sigma-1 receptor activation prolongs ketamine's antidepressant effects by consolidating NMDA receptor trafficking

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Abstract: Ketamine produces rapid antidepressant effects in treatment-resistant depression (TRD), yet these benefits are transient, necessitating repeated dosing and limiting clinical utility. The mechanisms that determine the durability of ketamine's efficacy remain unclear. Here, using the water immersion and restraint stress (WIRS) model of TRD, we identify the sigma-1 receptor (Sig-1R) as a critical regulator that consolidates ketamine-induced antidepressant effects. A single ketamine injection rapidly reverses stress-induced behavioral despair, restores intrinsic excitability of dentate gyrus granule cells, and normalizes synaptic NR2B-containing NMDA receptor signaling; however, these effects decay within days. Pharmacological activation of Sig-1R does not elicit antidepressant-like behavior on its own but selectively prolongs ketamine's behavioral and cellular efficacy for at least seven days, whereas Sig-1R antagonism abolishes ketamine-dependent synaptic and behavioral rescue. Mechanistically, Sig-1R activation stabilizes ketamine-induced redistribution of NR2B toward postsynaptic density compartments and sustains NR2B-mediated synaptic currents without altering basal glutamatergic transmission. These findings reveal Sig-1R-dependent consolidation of NMDA receptor trafficking as a key mechanism that transforms ketamine's rapid but transient actions into durable antidepressant outcomes, highlighting Sig-1R as a promising therapeutic target to extend ketamine efficacy in TRD.

Disclosures: Y. Lin: None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.14/DD30

Topic: H.05. Mood Disorders

Support: NSF Grant 1840279
NIH Grant R15MH139024

Title: Streptozotocin-induced hyperglycemia drives depressive-like behavior and hippocampal mitochondrial damage in both male and female mice irrespective of the APOE genotype

Authors: *L. E. KUSUMO, M. FOLH, J. DUHON, J. HENDRICKS, C. FOWLER, E. G. VICHAYA;
Psychology & Neurosci., Baylor Univ., Waco, TX

Abstract: The relationship between diabetes mellitus (DM), major depression (MD), and Alzheimer's disease (AD) is complex, such that one disorder increases risk for the others. Interestingly, the ε4 allele of the apolipoprotein (APOE) gene is associated with risk for each disorder. While known as the strongest risk factor for late-onset AD, APOE4 also increases risk for DM and late life MD. However, whether APOE4 increases risk for DM-induced depression

earlier in life is unclear. Therefore, the current study used a murine model of DM to explore this relationship. Further, as males are at increases risk for DM and females are at increased risk for AD and MD, we evaluated this relationship in male and female mice. Understanding how DM, APOE, and sex interact to modulate depression risk may provide insight for targeted treatments of depression. We used a 2 (+/- hyperglycemia) x 3 (wild-type [WT], knock-in [KI] APOE3, KI APOE4) factorial design in 8-week-old male and female C57BL/6J mice (N = 145). Hyperglycemia was pharmacologically induced using streptozotocin (STZ; 50 [males] or 70 [females] mg/kg/day i.p. for 5 days). STZ preferentially ablates pancreatic ß cells, decreasing insulin production, and inducing chronic hyperglycemia. Four weeks post-STZ, mice underwent behavioral testing, including open field, splash test (ST), marble burying (MB), forced swim test (FST), and contextual fear conditioning (FC). Following behavioral tests, hippocampal tissue was collected for evaluation of neuroinflammation and oxidative damage. STZ mice developed hyperglycemia (> 250 mg/dL blood glucose) and depressive like-behavior irrespective of genotype and sex. While STZ induced depressive-like behavior in FST and FC in both male and female mice, only male mice showed decreased grooming in the ST. Analyses of the hippocampus indicate that male STZ mice show increased *Tnf* expression, while female STZ mice show decreased *Bdnf* and *Gfap* expression. There were no significant effects of genotype. Spearman's correlational analyses show that *Bdnf* correlated with FCT and FST in female mice, but *Tnf* in males was not significantly correlated to behavior. Preliminary data from male mice indicate that STZ treatment was associated with mitochondrial swelling. Chronic hyperglycemia was associated with depressive-like behavior in both male and female mice irrespective of APOE genotype. However, the data also indicate the different mechanisms may be driving behavioral changes between male and female mice. Future studies are ongoing to further elucidate sex differences in hyperglycemia-induced neuroinflammation and mitochondrial dysfunction across multiple limbic structures in the brain.

Disclosures: L.E. Kusumo: None. **M. Folh:** None. **J. Duhon:** None. **J. Hendricks:** None. **C. Fowler:** None. **E.G. Vichaya:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.15/EE1

Topic: H.05. Mood Disorders

Support: Klarman Family Foundation Eating Disorders Grant
PSC-CUNY Awards
Doctoral Student Research Grant - CUNY Graduate Center

Title: Behavioral and Neural Correlates of Anxiety Predict Vulnerability to Activity-Based Anorexia

Authors: *J. ZHAO[1,3], E. LIKHTIK[4,1], N. BURGHARDT[3,2];
[1]Biol., [2]Psychology, CUNY Grad. Ctr., New York, NY; [3]Psychology, [4]Biol., Hunter College, CUNY, New York, NY

Abstract: Activity-based anorexia (ABA) is a widely used animal model of anorexia nervosa that combines restricted access to food with unlimited access to a running wheel. Previously, we demonstrated that this model yields vulnerable and resilient phenotypes, each characterized by distinct behavioral responses and changes in bodyweight. Here, we tested whether exposure to acute stress promotes expression of the vulnerable phenotype. Eight-week-old C57BL/6N female mice were either restrained in DecapiCones for 2 hours (stressed, n=15) or briefly handled (non-stressed, n=15) during the light cycle. They were then individually housed with a freely turning running wheel and tested in ABA conditions, during which they only had 2 hours of unlimited access to food at the onset of the dark cycle. Mice that lost 25% of their baseline weight were removed from the experiment and characterized as 'vulnerable,' while those that remained in the experiment for all 10 days were characterized as 'resilient.' Overall, stressed mice ate less and lost more weight than non-stressed controls, resulting in a higher proportion of stressed mice exhibiting the vulnerable phenotype (control 47% vs. stressed 80%, p= 0.058). Given the association between stress and anxiety, we hypothesized that animals with higher levels of anxiety at baseline are at higher risk of being vulnerable to ABA. To test this, we evaluated baseline levels of anxiety in the open field test prior to ABA exposure. Consistent with our hypothesis, the number of entrances into the center of the open field at baseline was lower in mice that subsequently exhibited ABA vulnerability than those that exhibited ABA resilience (p= 0.006). In addition, center entries correlated positively with day of removal from the ABA paradigm (n=42, r= 0.405, p= 0.008). Finally, we investigated whether activity of the bed nucleus of the stria terminalis (BNST) during exploration of the open field predicts vulnerability to ABA. We recorded local field potentials from the anterodorsal BNST of female mice (n=6) and found that BNST theta (4-10 Hz) power was lower when mice were in the center than in the periphery of the open field (p=0.049). Notably, the magnitude of this change positively correlated with day of removal from the ABA paradigm (r= -0.94, p= 0.005), indicating that greater suppression of BNST theta upon entry into an anxiogenic environment is associated with increased resilience to ABA. This work indicates that behavioral and neurophysiological responses to anxiogenic environments predict risk and resilience to ABA. Our findings may inform the development of biomarkers for early diagnosis of anorexia nervosa.

Disclosures: J. Zhao: None. **E. Likhtik:** None. **N. Burghardt:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.16/EE2

Topic: H.05. Mood Disorders

Support: PAPIME PE305125
PAPIIT IN225925

Title: Differential outcomes after different kinds of stress in male and female Wistar rats.

Authors: *Y. B. VIDAL-DE LA O[1], P. TORRES-CARRILLO[2], D. B. PAZ-TREJO[3], H. SANCHEZ-CASTILLO[4];
[1]Univ. Nacional Autónoma De México, Ciudad DE Mexico, Mexico; [2]Lab. de Neuropsicofarmacología, Univ. Nacional Autónoma de México, Mexico City, Mexico; [3]Psychology Sch., [4]Psychobiology and Neurosciences, Univ. Nacional Autonoma de Mexico, Mexico City, Mexico

Abstract: Stress is a major predisposing factor for the development of stress-related disorders, including anxiety and depression. The behavioral consequences of stress are influenced by several factors, such as age, sex, and stressor type. Although different stress paradigms are known to produce distinct behavioral outcomes, relatively few studies have directly compared multiple stressors in both male and female subjects.
The aim of the present study was to characterize the behavioral effects of different stress models in male and female Wistar rats. Animals were exposed to the chronic unpredictable stress battery (CUSB), post-weaning social isolation (PWSI), or predator scent stress (PSS). Hedonic processing was evaluated using the saccharin preference test (SPT) and a free-choice test (FCT), anxiety-like behavior was assessed using the elevated zero maze (EZM), and coping strategies were evaluated using the forced swim test (FST). Behavioral data were subsequently analyzed using k-means clustering to identify stress-response profiles.
CUSB and PSS induced anhedonia in females, evidenced by reduced saccharin consumption. In contrast, stress-induced reductions in caloric reward consumption were observed primarily in males. Females did not show significant alterations in milk consumption following stress exposure. Anxiety-like behavior was increased following chronic stress exposure in both sexes, whereas social isolation induced anxiety-like behavior only in females, as reflected by reduced time spent in the open arms of the EZM. No significant differences were observed in FST measures, including swimming, immobility, or rearing behaviors.
Cluster analysis identified three distinct behavioral profiles, which we termed eustress, distress-1, and distress-2. Importantly, these clusters were not determined solely by stress exposure but by the interaction among stressor type, sex, and behavioral outcomes. These findings suggest that stressor type and biological sex differentially shape behavioral adaptations to adversity. suggesting that stress adaptation may be better understood as a multidimensional process rather than a single continuum of vulnerability. Together, these results highlight the importance of incorporating both sexes and multiple stress paradigms in preclinical research and support a phenotype-based framework for understanding individual differences in stress responsiveness.

Disclosures: Y.B. Vidal-De La O: None. **P. Torres-Carrillo:** None. **D.B. Paz-Trejo:** None. **H. Sanchez-Castillo:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

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Program #/Poster #: PSTR026.17/EE3

Topic: H.05. Mood Disorders

Support: NIH Grant R01DK140347
NIH Grant R21AT011203

Title: Prolonged treatment with tryptophan-producing bacteria modulates serotonin signaling in the brain and reduces anxiety-like behavior in mice

Authors: *L. SAVAGE-HUNT[1,2,3], M. HUGHES[2], B. M. GIRARD[2], M. WARGO[4], S. E. HAMMACK[3], B. LAVOIE[2];
[2]Dept. of Neurolog. Sci., [3]Dept. of Psychological Sci., [4]Dept. of Microbiology and Mol. Genet., [1]Univ. of Vermont, Burlington, VT

Abstract: The gut microbiome is rapidly emerging as a strong candidate for targeted treatment of various psychological disorders. Altering populations of specific bacteria in the gut has been demonstrated to significantly impact multiple systems relating to anxiety and depressive disorders, and elevating serotonin signaling is a common treatment for these disorders. The precursor to serotonin, tryptophan, can cross the blood-brain barrier through competitive transport, and increases in circulating tryptophan may lead to increases in brain serotonin. In the present study we explored the effects of prolonged treatment of mice with a specific strain of tryptophan producing bacteria, *Bacillus (B.) subtilis 1A2*, on anxiety behavior and corresponding molecular changes in the brain. Mice were orally gavaged daily for 6 weeks with either PBS, the tryptophan synthase null mutant *B. subtilis 1A1*, or the tryptophan synthase positive strain *B. subtilis 1A2*, starting at 8 weeks of age. Behavioral testing occurred at 0, 2, 4, and 6 weeks of treatment using the acoustic startle response paradigm, a known measure of anxiety behavior. After 6 weeks of treatment, blood, serum, distal colon, raphe nucleus, hippocampus, and amygdala samples were collected. Serotonin and tryptophan levels were measured through high performance liquid chromatography and gene expression of key enzymes and receptors related to serotonin synthesis and signaling were assessed with quantitative polymerase chain reaction. We found that startle response to acoustic stimuli was suppressed after 6 weeks of treatment with the *B. subtilis 1A2* bacteria, but not in mice treated with *B. subtilis 1A1* or PBS. However, this effect was not observed at shorter treatment time points. Additionally, elevations of serotonin levels were observed in serum and raphe nucleus samples from mice treated with the *B. subtilis 1A2* bacteria compared to PBS treated mice at the prolonged, 6-week timepoint. Upregulation of genes encoding for key serotonin receptors were also detected at this later time point in the hippocampus and amygdala of mice treated with *B. subtilis 1A2* compared to those treated with *B. subtilis 1A1*. These results suggest that leveraging tryptophan producing bacteria as a long-term treatment can have beneficial effects on behaviors associated with psychiatric disorders such as anxiety and provide clear targets for future studies to more thoroughly elucidate the mechanisms of this treatment.

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Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.18/EE4

Topic: H.05. Mood Disorders

Support: NIH Grant: 5T34GM136481

Title: Sex differences in depressive-like behaviors and Nicotine-induced reward in mice exposed to exercise.

Authors: *J. SORAPURU[1], K. A. MARQUEZ[2], Y. SHERAFAT[3];
[1]California State Univ. San Marcos, Big Bear City, CA; [2]Psychology, California State Univ. San Marcos, San Marcos, CA; [3]California State University, San Marcos, San Marcos, CA

Abstract: Nicotine is a highly addictive psychoactive drug. In both humans and rodents, females exhibit greater withdrawal symptoms and more depressive-like behaviors. Specific nicotinic acetylcholine receptor subunits have been linked to antidepressant-like effects, although their role in female mice remains poorly understood. Exercise reduces nicotine-seeking and depressive-like behaviors in rodent models, while NACHO knockout reduces nicotinic acetylcholine receptor expression. This study examined sex differences in nicotine reward and depressive-like behavior in NACHO knockout and wildtype mice. Adolescent mice were assigned to exercise or non-exercise groups. Depressive-like behavior was assessed using the Forced Swim Test, and nicotine reward using Conditioned Place Preference. Conditioned Place Preference results showed no significant differences in nicotine preference between exercising male and female NACHO knockout mice or between exercising female NACHO knockout and wildtype mice. However, exercising wildtype females displayed significantly greater nicotine preference than exercising wildtype males. Non-exercising female NACHO knockout mice also showed significantly lower nicotine preference than exercising wildtype females. Forced Swim Test results showed no significant differences between exercising wildtype and NACHO knockout males or females. Because exercise appeared to have a stronger influence on depressive-like behavior than sex or genotype, non-exercising mice were examined separately. Wildtype non-exercising males spent significantly less time mobile than wildtype non-exercising females. Exercising wildtype females spent significantly more time mobile than non-exercising wildtype males and both non-exercising NACHO knockout groups. When genotype, sex, and exercise were considered together, non-exercising female NACHO knockout mice appeared to be the most vulnerable group. Exercising wildtype males and females spent significantly more time mobile than non-exercising female NACHO knockout mice. This may reflect estrogen-mediated modulation of nicotinic receptor subunits involved in reward, motivation, and stress regulation. Reduced receptor signaling in the NACHO knockout model, combined with lack of exercise, may further increase depressive-like behaviors. Recent immunofluorescence studies indicate that aged wildtype female mice exhibit reduced NACHO expression in the hypothalamus and hippocampus compared to males. Assessing NACHO expression in adolescence may help clarify sex differences in NACHO function and associated behaviors.

Disclosures: J. Sorapuru: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH Funding. **K.A. Marquez:** None. **Y. Sherafat:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.19/EE5

Topic: H.05. Mood Disorders

Title: Hekabe Platform: Behavioural and Synaptic Signatures of Chronic Social Defeat Stress Support its Utility for Rapid-Acting Antidepressant Discovery

Authors: *C. J. MALTBY[1], J. PINTO[2], A. KELLERSOHN[2], E. PASCHEN[2], P. STOLYAR[3], S. C. LEISER[3], M. BIANCHI[2];
[1]Ulysses Neurosci. Ltd, Dublin, Ireland; [2]Ulysses Neurosci. Ltd., Dublin, Ireland; [3]AbbVie, Cambridge, MA

Abstract: Background: Major depressive disorder is associated with stress-induced behavioural and synaptic dysfunction, yet translationally relevant preclinical models for antidepressant screening remain limited. Chronic social defeat (CSD) is a psychosocial stress paradigm with strong face, construct, and predictive validity for depression-related phenotypes. Here, we evaluated the CSD model using ketamine as a benchmark rapid-acting antidepressant and assessed synaptic alterations using the Hekabe platform in hippocampus (HPC) and prefrontal cortex (PFC) synaptosome preparations from stress-susceptible and resilient mice. **Methods**: Male C57BL/6J mice underwent a 10-day CSD protocol with repeated exposure to aggressive CD-1 resident mice. Social preference (SP) testing classified animals as susceptible (SP<100) or resilient (SP>100). Susceptible animals received vehicle or ketamine (10 mg/kg, s.c.), and SP was repeated 24 h later. PFC and HPC tissue were collected post-behaviour. Synaptosomes were isolated and SV2A, synaptophysin, PSD-95, and spinophilin quantified by multiplexed infrared Western blotting. **Results**: CSD produced clear behavioural segregation into susceptible (42%) and resilient (58%) phenotypes. Susceptible mice exhibited social avoidance versus controls; resilient mice showed normal social interaction. Ketamine significantly reversed social avoidance 24 h post-dose ($p<0.0001$). CSD-susceptible mice showed significant reductions in pre- and post-synaptic markers across PFC and HPC, including SV2A ($p<0.0001$; $p=0.0360$), synaptophysin ($p=0.0006$; $p=0.0249$), PSD-95 ($p<0.0001$; $p=0.0367$), and spinophilin ($p=0.0002$; $p=0.0003$). Ketamine robustly normalised these deficits across both regions. Resilient animals displayed synaptic profiles closely resembling ketamine-treated mice, suggesting synaptic integrity preservation underlies stress resilience. **Conclusions**: The CSD paradigm produces reproducible behavioural and synaptic deficits pharmacologically responsive to ketamine. The Hekabe platform demonstrates convergence of behavioural outcomes with quantifiable synaptic biomarker changes, supporting translational relevance for rapid-acting antidepressant screening.

Resilient animals further highlight the utility of this paradigm for investigating stress susceptibility, resilience, and synaptic restoration.

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Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.20/EE6

Topic: H.05. Mood Disorders

Support: Research Training Program (RTP) scholarship from the Australian Government
Graeme Clark Institute Top-up scholarship
ARC DECRA Fellowship (DE220100302)
Graeme Clark Institute Cross-faculty collaboration grant

Title: Criticality analysis reveals altered hippocampal network dynamics in a chronic CORT model of depression-like behaviour

Authors: *H. WANG[1], Y. JUNG[1], S. REISINGER[2], C. GUBERT[3], A. J. HANNAN[2], M. R. IBBOTSON[1], S. PRAWER[1], W. TONG[1];
[1]Univ. of Melbourne, Melbourne, Australia; [2]Florey Inst. of Neurosci. and Mental Health, Univ. of Melbourne, Melbourne, Australia; [3]La Trobe Univ., Melbourne, Australia

Abstract: Strong evidence exists that neural systems operate near a critical regime, a dynamic state characterised by balanced propagation of activity across networks[1]. Disrupted critical dynamics may reflect altered brain function and have been associated with neuropsychiatric disorders[2]. Chronic corticosterone (CORT)-treated mice are a commonly used model of depression-like behaviour[3]. Here, we tested whether altered hippocampal criticality is associated with depression-like behaviour in this model. Male C57BL/6 mice received CORT or β-CD vehicle (Control). Depression-like behaviour was assessed by the novelty-suppressed feeding test (NSFT), and spontaneous hippocampal activity was recorded under anaesthesia using multichannel probes. Firing-based and criticality measures were extracted from electrophysiological activity. CORT-treated mice showed increased NSFT latency and reduced food consumption, confirming a depression-like phenotype. Criticality metrics also exhibited altered hippocampal network dynamics: CORT-treated mice showed a reduced branching ratio, a shorter avalanche duration, and an increased deviation-from-criticality coefficient (DCC) in both spiking activity and local field potentials (LFP). By contrast, firing measures, such as firing rate and inter-spike-interval, didn't differ between groups.We further used machine learning to determine whether criticality-derived features could distinguish CORT and control. Using branching ratio, avalanche duration, and DCC, a support vector machine achieved 85% cross-validated accuracy. Additionally, we assessed sex-dependent effects by comparing these findings

with results from female cohort. Together, these findings show that chronic CORT shifts hippocampal activity away from criticality and that features can detect and classify network alterations that are difficult to capture with firing metrics. Hippocampal criticality may provide a useful framework for investigating circuit dysfunction with depression-like behaviour.

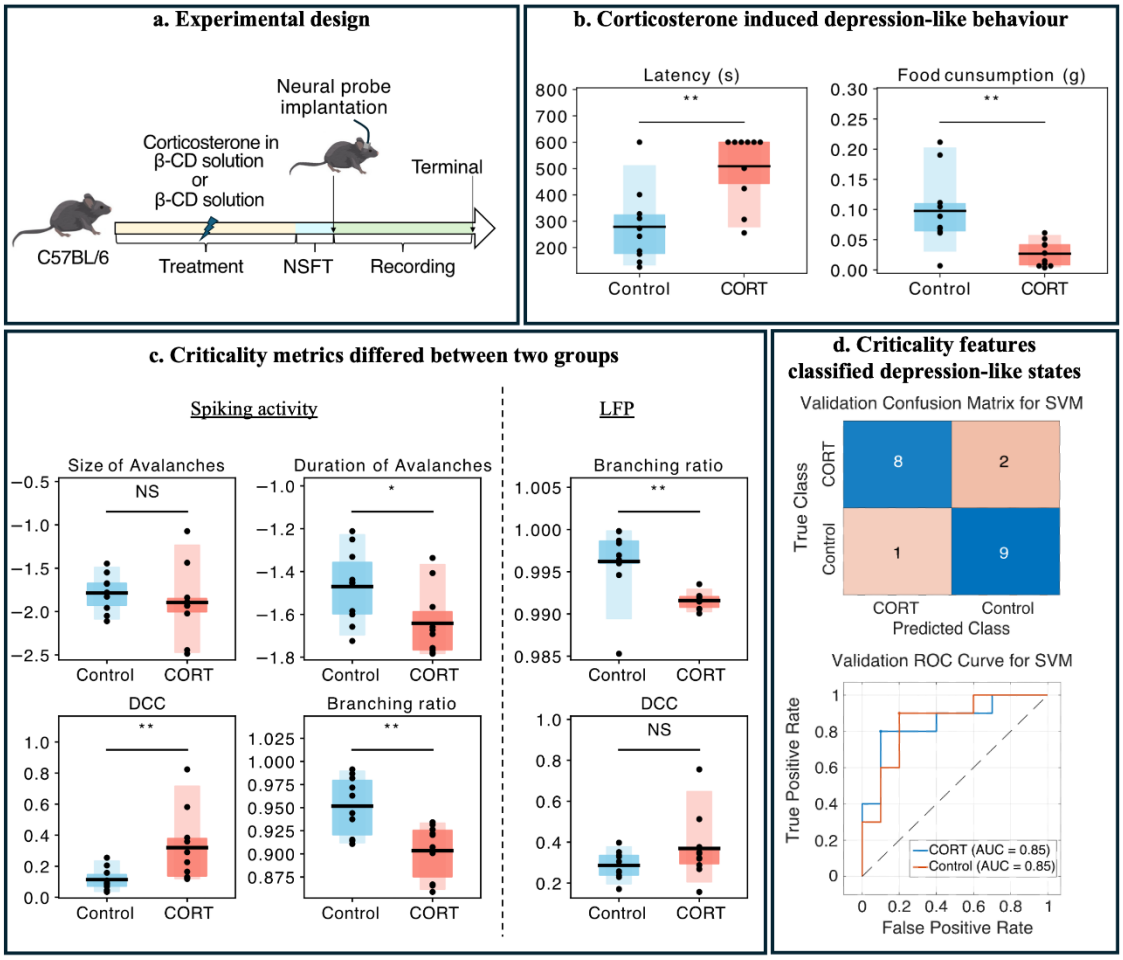


Figure. Criticality. analysis reveals altered hippocampal network dynamics in a chronic CORT model of depression-like behaviour. a. Experimental timeline for chronic CORT exposure, washout, behavioural testing, and electrophysiological recording. b. CORT-treated mice showed depression-like behaviour in the novelty-suppressed feeding test, with increased feeding latency and reduced food consumption. c. Criticality measures showed group-dependent changes, including altered avalanche duration, branching ratio, and deviation-from-criticality coefficient (DCC). d. Criticality features supported machine-learning classification of CORT-treated and control mice, shown by the confusion matrix and receiver operating characteristic curves. Data are shown as box plots with individual animals. Statistical comparisons were performed using Mann–Whitney U tests; *p < 0.05, **p < 0.01, NS, not significant.

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3. Zimmern, V. (2020). Why Brain Criticality Is Clinically Relevant: A Scoping Review. Frontiers in Neural Circuits, 14, 54. https://doi.org/10.3389/fncir.2020.00054

Disclosures: H. Wang: None. **Y. Jung:** None. **S. Reisinger:** None. **C. Gubert:** None. **A.J. Hannan:** None. **M.R. Ibbotson:** None. **S. prawer:** None. **W. Tong:** None.

Poster

PSTR026: Depression and Anxiety

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.21/EE7

Topic: H.05. Mood Disorders

Support: NIH R01MH129643
New York Stem Cell Foundation
CIHR Postdoctoral Fellowship

Title: Blood-brain barrier gene regulatory alterations due to early life stress

Authors: *K. SULLIVAN, M. DEBERARDINE, R. LIN, F. D. ROGERS, A. MINERVA, S. BENNETT, C. J. PENA;
Princeton Univ., Princeton, NJ

Abstract: Early life stress (ELS) is a major risk factor for neuropsychiatric disorders, yet the molecular mechanisms by which it confers long-term vulnerability remain poorly understood. While prior work has largely focused on neuron-intrinsic adaptations, emerging evidence suggests that non-neuronal populations, including vascular and glial cell types, may play critical roles in shaping adult stress susceptibility. Here, we investigate how ELS alters cell type-specific developmental gene regulatory programs across neuronal and non-neuronal populations in the dopaminergic midbrain.

To address this, we performed single-nucleus multiomic sequencing to jointly profile gene expression and chromatin accessibility in the ventral tegmental area, a region implicated in stress-related behaviors and neuropsychiatric disease. We generated a developmental time series spanning postnatal days P1, P7, P14, P21, and P60 under standard rearing and ELS conditions, with four sex-matched animals per timepoint. ELS was induced from P10-P17 using a combined maternal separation and limited nesting paradigm.

We identified 29 major cell types, including 21 neuronal and 8 non-neuronal populations. ELS produced cell type- and stage-specific disruptions in developmental regulatory trajectories. Notably, astrocytes and endothelial cells exhibited both transient and persistent regulatory changes, including programs associated with barrier integrity, molecular transport, and inflammatory signaling. These findings nominate candidate transcription factors and regulatory elements that may mediate long-lasting effects of early adversity on neurovascular function.

Together, this work demonstrates that ELS reshapes developmental gene regulatory programs in the VTA in a highly cell type-specific manner and identifies the blood-brain barrier as a previously underappreciated target of early adversity. Ongoing behavioral experiments will test whether candidate neurovascular regulatory factors are sufficient to alter stress-related phenotypes, providing a functional framework for linking ELS-induced regulatory changes to adult psychiatric vulnerability.

Disclosures: K. Sullivan: None. **M. DeBerardine:** None. **R. Lin:** None. **F.D. Rogers:** None. **A. Minerva:** None. **S. Bennett:** None. **C.J. Pena:** 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.; Autobahn Therapeutics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Autobahn Therapeutics. F. Consulting Fees (e.g., advisory boards); Autobahn Therapeutics.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.01/EE8

Topic: H.08. Drugs of Abuse and Addiction

Title: Artificial Reactivation of a Cocaine-Associated Engram in the Dorsal Dentate Gyrus Attenuates Cocaine Prime-Induced Reinstatement of Drug-Seeking

Authors: *M. CUTLER[1], L. H. EDWARDS[2], L. PAPANIKOLAOU[3], M. WILSON[2], M. BRODY[2], W. WADE[2], S. ARORA[4], A. STRATMANN[3], S. CAÑUELAS DEL VALLE[3], S. L. GRELLA[2];
[1]Loyola Univ. Chicago, CHICAGO, IL; [2]Loyola Univ. Chicago, Chicago, IL; [3]Loyola Univ., Chicago, IL; [4]Rosalind Franklin Univ., North Chicago, IL

Abstract: Relapse-prevention strategies aimed at reducing relapse following abstinence primarily focus on reducing cravings that lead to drug-seeking triggered by stress, drug-related cues, or re-exposure to the drug. Because addictive drugs form persistent associative contextual memories, we investigated how reactivation of cocaine-related hippocampal memories influences subsequent drug-seeking. Here, we tagged dorsal dentate gyrus (dDG) memory ensembles involved in encoding either a first or fourth cocaine exposure (15mg/kg, i.p) in male and female c57BL/6 mice using a TetTag approach. Mice underwent cocaine conditioned place preference (CPP), extinction, and reinstatement. We assessed whether optical reactivation of tagged cocaine-related ensembles could substitute for a cocaine priming injection to reinstate CPP, whether reactivation altered cocaine-induced reinstatement, and if these effects differed depending on stage of drug exposure. We also compared these effects to reactivation of saline-associated ensembles. Cocaine produced robust locomotor activation during conditioning and sensitization developed across repeated drug exposures. Reactivation of a cocaine-related engram alone did not reinstate CPP. However, reactivation of the first cocaine exposure engram attenuated cocaine-induced reinstatement. In contrast, reactivation of the fourth exposure engram did not confer this protective effect. Interestingly, reactivation of saline-associated ensembles also reduced cocaine-induced reinstatement specifically in females, suggesting dDG ensemble reactivation may modulate relapse-related behavior through interference or neuromodulatory disruption of cocaine-associated representations, consistent with our prior work. These findings raise the possibility that early contextual experiences form competing or destabilizing

representations that interfere with later cocaine-seeking when reactivated. Females also displayed greater sensitivity to locomotor-inducing effects of cocaine memory reactivation, although this was dissociated from CPP. Together, these findings show that cocaine memories are distinct across drug experience and selective reactivation of dDG engrams can differentially influence drug-seeking.

Disclosures: M. Cutler: None. **L.H. Edwards:** None. **L. Papanikolaou:** None. **M. Wilson:** None. **M. Brody:** None. **W. Wade:** None. **S. Arora:** None. **A. Stratmann:** None. **S. Cañuelas del Valle:** None. **S.L. Grella:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.02/EE9

Topic: H.08. Drugs of Abuse and Addiction

Support: Dean's 1% Fund

Title: Solitary But Not Social Exercise Blunts Methamphetamine Sensitization in Mice

Authors: *A. S. RAUHUT[1], S. AHMAD[1], Z. BOCHICCHIO[2], L. BURCHELL[1], A. HALCHENKO[1], A. SCHMID[1], A. GNAGEY[1];
[1]Neurosci., [2]Psychology, Dickinson Col., Carlisle, PA

Abstract: Pre-clinical animal studies have corroborated the use of physical exercise as a non-pharmacological intervention for Methamphetamine Use Disorder. However, the exact environmental factors that contribute to the efficacy of physical exercise are unknown. The present experiment, using an animal model of addiction (i.e., behavioral sensitization), examined the interaction of physical exercise (i.e., home-cage wheel running; HCWR) and housing density (single vs. pair) on methamphetamine sensitization in mice. We predicted that methamphetamine would cross sensitize with exercise in pair housed mice such that these mice would show an augmented response to the acute and chronic locomotor-activating effects of methamphetamine and display enhanced conditioned hyperactivity compared to singly house exercise mice. A 2 (Single vs Pair) x 2 (Saline vs. Methamphetamine) design was employed. Female, Swiss Webster mice (N = 30) were housed singly or in pairs for 6-weeks with home-cage running wheels. Then, mice were subjected to a two-injection methamphetamine sensitization protocol and underwent three phases: Conditioning, CR Test and Methamphetamine Challenge. During the conditioning phase, Pair-Housed (n = 8/group) and Single-Housed mice (n = 7/group) received injections of either saline or methamphetamine (2.0 mg/kg) prior to a 30-minute locomotor activity session. The CR Test and Methamphetamine Challenge sessions occurred 7 days later. During the CR Test and Methamphetamine Challenge sessions, mice received either saline or methamphetamine (1.0 mg/kg) prior to a 15- and 60-minute locomotor activity session, respectively. Singly housed exercise mice were responsive to the acute, locomotor-activating effects of methamphetamine

but failed to show sensitization. Paired housed exercise mice were more responsive to the acute, locomotor-activating effects of methamphetamine than singly housed exercise mice and showed methamphetamine sensitization. Both singly housed exercise and paired housed exercise mice showed robust conditioned hyperactivity and did not differ. Collectively, these results suggest single housing combined with exercise blunted methamphetamine sensitization whereas pair housing combined with exercise failed to alter methamphetamine sensitization. The latter outcome may stem from either stress-induced "resource guarding" between co-habiting female exercise mice or cross-sensitization between social exercise and methamphetamine. The interaction of housing density and exercise on methamphetamine sensitization is complex, with solitary exercise producing strong anti-addiction effects.

Disclosures: A.S. Rauhut: None. **S. Ahmad:** None. **Z. Bochicchio:** None. **L. Burchell:** None. **A. Halchenko:** None. **A. Schmid:** None. **A. Gnagey:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.03/EE10

Topic: H.08. Drugs of Abuse and Addiction

Support: National Natural Science Foundation of China (no.82301681)
National Natural Science Foundation of China (no.82288101)
Brain Science and Brain-like Intelligence Technology-National Science and Technology Major Project (no. 2021ZD0200800)

Title: Prolonged abstinence sustains a recurrent drug craving state by reorganizing ACC engrams

Authors: *X. LIU[1], L. LU[2];
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Abstract: Even after prolonged abstinence, drug-related cues trigger intense craving, traditionally quantified as the overall level of drug-seeking behavior. However, craving is not a monolithic state—it likely encompasses richer, more complex behavioral dynamics that remain largely unexplored. Using a rat cocaine self-administration model, we found that cue-induced seeking was enhanced after prolonged abstinence, but crucially, behavioral microstructure analysis revealed that this enhancement reflects a reorganization of seeking dynamics rather than a mere elevation of response counts. Late-abstinent animals exhibited: 1) faster anticipatory engagement (shorter latency to first response and higher early-session responding); 2) sustained maintenance (accelerated onset and persistent responding across the session); and 3) increased persistent/repetitive responding (more timeout responses, prolonged post-cue responding, and longer response bouts). These findings demonstrate that prolonged abstinence transforms the

structure of craving behavior—shifting it toward faster initiation, sustained engagement, and especially cue-triggered perseverative, repetitive responding. To explore the neural basis, we focused on anterior cingulate cortex (ACC) engrams. ACC engram cells showed higher reactivation after abstinence, and bidirectional chemogenetic manipulation of these engrams bidirectionally regulated the craving state, establishing a causal link. Together, our study uncovers a multidimensional behavioral architecture of craving states that is obscured by traditional unidimensional measures, and identifies ACC engrams as a key substrate for the recurrent craving state after prolonged abstinence.

Disclosures: X. Liu: None. **L. Lu:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

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Topic: H.08. Drugs of Abuse and Addiction

Support: Philippines Department of Science and Technology Grant 2024-1365

Title: Social exposure during conditioning in rats reduces conditioned place preference for morphine, but not for methamphetamine

Authors: G. JANAIRO[1], J. C. MUNAR[1], *C. GREGORIO[2], G. J. QUIRK[1], **R. CENA-NAVARRO**[1];
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Abstract: There is increasing interest in the effects of social exposure on substance use disorder (SUD). Social exposure during abstinence reduces addictive behavior in animal models (Venniro et al., 2022). However, it is not known whether social exposure during conditioning can reduce the acquisition of addictive behavior. We addressed this question for two commonly abused drugs: the opioid morphine (MO) and the stimulant methamphetamine (MA), using conditioned place preference (CPP). Male and female Sprague-Dawley rats received i.p. injections of either MO (7.5 mg/kg) or MA (1 mg/kg) for 5 days in a CPP chamber either alone (drug-alone group) or with a sex-matched cagemate (drug-social group). A saline-alone and a saline-social group served as controls. After 8 days of abstinence, the level of CPP (rat tested alone) was significantly higher in both drug-alone groups compared to saline-alone controls (MO $p<0.001$; MA $p<0.001$). CPP in the MO-social group was significantly lower than MO-alone group ($p=0.010$) and did not differ from saline-alone controls ($p= 0.105$). When separated by sex, this reduction in MO-social CPP was only significant for females, although MO-social males showed lower levels of drug-primed reinstatement following extinction compared to MO-alone males ($p=0.035$). Social exposure also had an anxiolytic effect in females, but not in males, in an open field test ($p=0.011$). For MA, there was no significant effect of social exposure on CPP,

reinstatement, or anxiety-like behavior. Our findings suggest that social exposure reduces the addictive effect of repeated morphine administration, resulting in a “social buffering” of conditioning. The selectivity of this effect for MO (vs MA) is consistent with the involvement of the endogenous opioid system in social exposure, which may reduce its susceptibility to morphine-induced changes (Van den Berg et al., 1999). Our findings suggest (at least for opioids) that the likelihood of developing SUD may be determined by the social context in which drug exposure occurs.

Disclosures: G. Janairo: None. **J.C. Munar:** None. **C. Gregorio:** None. **G.J. Quirk:** None. **R. Cena-Navarro:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

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Program #/Poster #: PSTR027.05/EE12

Topic: H.08. Drugs of Abuse and Addiction

Support: Research from Dr Marta Miquel’ lab received research funding for the R&D&I project PID2021- 128852NB-I00 "ERDF A way to do Europe” from MCIN/AEI El contrato de Elena Martín-González es parte de la ayuda JDC2023-051708-I, financiado por MCIU/AEI/10.13039/501100011033 y por el FSE+ SUBV25/00031 Subvenciones para el desarrollo de actividades de investigación relacionadas con la prevención de los trastornos del juego, con los efectos derivados de dichos trastornos o los riesgos asociados a esta actividad, Ministerio de Derechos S

Title: Control from the rearguard: Role of cerebellar lobule VIII and Purkinje-DCN projections in cocaine self-administration and drug-seeking behavior

Authors: *E. MARÍN SAMPIETRO, J. GUARQUE-CHABRERA, E. MARTÍN-GONZÁLEZ, M. MIQUEL;
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Abstract: In line with two findings from our laboratory showing that (1) modulation of the cerebellar posterior vermis (lobule VIII, LVIII) alters preference for cocaine-associated stimuli, and (2) synaptic stabilization markers, namely perineuronal nets (PNNs), are upregulated in this region following prolonged abstinence in a voluntary cocaine consumption model. The present study investigated the role of LVIII in cocaine self-administration using chemogenetic tools (designer receptors exclusively activated by designer drugs, DREADDs) and assessed cocaine associated plasticity markers. Two experiments were conducted. First, we examined the contribution of the dorsal vermis (LVIII) to cocaine intake and drug seeking behavior. Second, we established a causal model of cortical regulation of the deep cerebellar nuclei (DCN) through Purkinje cell activity. Male Sprague-Dawley rats underwent yugular catheterization for

intravenous cocaine self-administration and stereotaxic surgery for DREADD infusion. In Experiment 1, AAV-hSyn-hM4D(Gi)-mCherry/AAV-hSyn-hM3D(Gq)-mCherry/AAV-hSyn-EGFP were infused into LVIII. In Experiment 2, the inhibitory LVIII manipulation (hM4D) was combined with a retrograde Cre strategy targeting Purkinje neurons projecting to the dorsolateral interposed and lateral nuclei. As an agonist Clozapine-N-oxide (CNO) or saline were administered intraperitoneally 20 min before each session. Following recovery, animals underwent 15 daily 1-h cocaine self-administration sessions under a fixed-ratio 1 (FR1) schedule. Cerebellar manipulations were performed during the last five sessions, and drug seeking behavior was assessed 24 h after the last cocaine session and CNO-free. Viral expression was verified histologically, and neuronal activity and plasticity were evaluated using c-Fos immunoreactivity and Wisteria floribunda agglutinin (WFA) labeling of PNNs. Behaviorally, Experiment 1 showed that inhibiting inhibitory interneurons of LVIII (Golgi, basket, and stellate cells), thereby increasing Purkinje-mediated inhibition of the DCN, reduced cocaine intake during the final self-administration sessions and prevented subsequent drug seeking. In Experiment 2, direct manipulation of the Purkinje cell-DCN pathway using a Cre-loxP strategy appeared to normalize the increased Purkinje output induced by LVIII inhibition, resulting in behavioral responses comparable to controls. Collectively, these findings identify the cerebellum as a critical component of drug consumption and drug-seeking behavior and support its potential as a therapeutic target for addiction treatment.

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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.06/EE13

Topic: H.08. Drugs of Abuse and Addiction

Title: Nucleus accumbens and basolateral amygdala ensembles differentially mediate cocaine seeking after abstinence

Authors: *A. LABANCA[1], V. KONDEV[2], T. MARKOVIC[5], R. FUTAMURA[3], Y. YIM[4], L. HOLT[7], A. M. MINIER-TORIBIO[4], E. KAHN[6], D. J. CAI[8], M. SALERY[9], E. J. NESTLER[10]; [1]Icahn Sch. of Med. At Mount Sinai Grad. Training Program In Neurosci., New York, NY; [3]Neurosci., [4]Nash Family Dept. of Neurosci., [2]Icahn Sch. of Med. at Mount Sinai, New York, NY; [5]Neurosci., [6]Icahn Sch. of Med., New York, NY; [7]Neurosci. Dept., Mount Sinai Sch. of Med., New York, NY; [9]Nash Family Dept. of Neurosci. & Friedman Brain Inst., [8]Mount Sinai, New York, NY; [10]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Despite the prevalence of drug relapse and overdose-related deaths in the human population, existing clinical interventions are lacking, making it essential to characterize the neurobiological mechanisms underlying cue-induced craving that drives drug seeking. Growing

evidence suggests that sparse populations of cells, referred to as neuronal ensembles, play a critical role in encoding learned associations between drugs of abuse and drug-related cues. Here we explore the synergistic contribution of neuronal ensembles in the nucleus accumbens (NAc) and basolateral amygdala (BLA), key regions in mediating positive valence and reward, in encoding of cocaine-related memories. We assess the impact of memory perturbations such as extinction learning on the recruitment of NAc and BLA ensembles and characterize the ensemble cells' molecular properties with the ultimate goal of elucidating neuronal substrates that mediate drug responses, and how this is disrupted after extinction. We utilize *Arc*-CreER^{T2} mice and cocaine intravenous self-administration to tag *Arc*-ensemble neurons recruited throughout various phases of the addiction cycle. Mice undergo drug-context re-exposure after extinction learning or forced abstinence to uncover the role of these experiences on drug memory recall and updating. We demonstrate that extinction learning drives drug-associative memory updating through decreased reactivation of *Arc*-ensembles in both the NAc and BLA, which was not observed in homecage abstinent controls. These results uncover a mechanism by which extinction of drug-context associative memories attenuates drug responses via the modulation of ensemble reactivation. Furthermore, we posit that our findings contribute to understanding how extinction destabilizes drug-cue associations to improve drug-seeking outcomes after forced abstinence. RNA-sequencing is underway to examine the molecular profile of the ensemble cells that encode cocaine-seeking and uncover how extinction changes their molecular properties to impact reactivation.

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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

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Topic: H.08. Drugs of Abuse and Addiction

Support: Lundbeck Foundation R359-2020-2301
Lundbeck Foundation R266-2017-4331
Lundbeck Foundation R276-2018-792

Title: Striatal dopamine circuitry differentially encodes reward-seeking behavior on a sub-regional scale

Authors: *S. OVROM[1], S. H. JØRGENSEN[1], L. P. POSSELT[1], J. COLL MARQUÈS[1], M. E.-S. HERVIG[1], F. HERBORG[1], D. BANG[2], U. GETHER[1];
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Abstract: Many drugs of abuse activate the dopaminergic system. Dopamine (DA) has long been understood to play a critical role in learning and motivation, and repeated activation of this system facilitates addictive behavior. The densest dopaminergic projections to the ventral striatum (VS) and dorsal striatum (DS) make the striatum the major dopaminergic input center of the brain. In this study we combine a learned behavioral task with multi-region dLight1.3b fiber photometry to investigate DA dynamics across the striatum. We trained mice in an operant task, and with probes in the VS and the lateral and medial DS (DLS and DMS, respectively), we identify unique characteristics of dopamine release across striatal subregions during reward-seeking behavior. Then, by manipulating the stimulus, action and reward in subsequent behavioral sessions, we show that striatal DA circuitry is modulated in a subregionally-specific manner in response to novel reward-seeking obligations. We then employed a cre-dependent PKA sensor, ExRai-AKAR-II, alongside dLight1.3b in the VS and DLS of D1-cre mice to explore the downstream, intracellular effects of differential dopamine dynamics in the striatum. Our data links differential release across dopaminergic circuitry to the functional consequences of D1 receptor activation during discrete reward-seeking behavior. Finally, we explore heterogenous dopamine circuit activation during maladaptive reward-seeking by applying an optogenetic paradigm to our existing operant behavioral task. By varying the timing of the onset of stimulation, we explore the positive relationship between onset of dopaminergic activity and addictive behavior. These results will be discussed in the context of drugs of abuse.

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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA053743
NIH Grant DA054714

Title: Multi-Omic Profiling Reveals Cell-Type-Specific Gene Regulatory Networks in The Rat Nucleus Accumbens

Authors: *G. M. TWA[1], C. E. NEWMAN[1], R. A. PHILLIPS, III[2], J. J. TUSCHER[3], J. J. DAY[1]; [1]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; [2]LIBD, Lieber Inst. for Brain Develop., Baltimore, MD; [3]Neurobio., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Genomic enhancers, through their dynamic accessibility, mediate gene regulatory network (GRN) interactions between transcription factors (TFs) and their downstream gene targets. The precise control of these mechanisms is essential for the transcriptional programs that support a diversity of cell types and their homeostatic functions within the brain. Transcriptional

dysregulation within the nucleus accumbens (NAc), a key brain region for reward-related learning and motivated behavior, has been previously associated with substance use disorders (SUDs). However, the specific GRN mechanisms and the enhancers mediating their activity remain unresolved at the cell-type level, hindering the development of novel targeted therapeutics. To address this knowledge gap, we collected multi-omic sequencing data from ~50,000 nuclei (paired snATAC-seq and snRNA-seq) from 21 rats (Male + Female). Within our data, we identify 10 transcriptionally defined cell-type clusters, recovering previously described populations of medium spiny neurons (MSNs), interneurons, and glia. Multi-omic analysis with SCENIC+ identified 191 GRN modules comprising expressed TFs, the putative enhancers they bind, and downstream genes whose expression is associated with both enhancer accessibility and TF expression. GRN modules with high cell-type-specific activities include known developmental regulators, such as *Dlx1*, *Fli1*, and *Sox9*. We sought to further characterize the regulatory mechanisms that define the Grm8-MSN population, which, despite representing a limited portion of cells in the NAc, expresses the highest proportion of the mu opioid receptor *Oprm1*. We find that many of the upstream regulators of Grm8-MSN marker genes belong to homeodomain TF families, including *Cux2*, *Pbx1*, and *Pbx3*. The enriched expression of these TFs and their motifs across an array of candidate enhancers associated with multiple marker genes suggests a central role in defining this cellular identity. Furthermore, sequence-to-function modeling with ChromBPNet concordantly identifies homeodomain family motifs as important predictive features of chromatin accessibility in putative marker gene enhancers, specifically within Grm8-MSNs. Ongoing experiments will validate the cell-type-specific activity of these putative enhancers, packaged in reporter AAV constructs and injected into the NAc, using *in situ* RNA-scope. Characterizing these enhancers will generate mechanistic hypotheses about GRN dysregulation in SUD and enable us to develop new transgenic tools to test these hypotheses via cell-type-specific manipulations.

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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

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K01DA054449 (HN),
R01AA014351 (FW),
R37DA054370 (TCJ),
T32GM145408 (LS, SK),
TL1TR002380 (AJW, FTBE)

Title: Brain-wide profiling of 'punishment-reactive' afferent neuronal projections to the rostromedial tegmental nucleus (RMTg) in mice

Authors: *S. VETTLESON-TRUTZA[1], R. OWUSU MENSAH[2], A. O'BRIEN[5], T. KERR[5], J. TRAN-VU[3], A. ANWAR[1], H. NEDELESCU[6], F. WEISS[7], E. KOYA[8], B. T. HOPE[9], J. GLASER[10], T. C. JHOU[11], N. SUTO[4];
[2]Mol. Pharmacol. and Exptl. Therapeut., [1]Mayo Clin., Rochester, MN; [3]Mayo Clin., Anaheim, CA; [4]Dept. of Mol. Pharmacol. & Exptl. Therapeut., Mayo Clin., Rochester, MN; [5]Dept. of Mol. Pharmacol. and Exptl. Therapeutics, Mayo Clinic, Rochester, Rochester, MN; [6]Neurosci., Scripps Res. Inst., San Diego, CA; [7]Dept. of Neurosci., Scripps Res. Inst., La Jolla, CA; [8]Univ. of Sussex, Brighton, United Kingdom; [9]Behav Neurosci, NIDA IRP, NIH, Baltimore, MD; [10]MBF Biosci., Williston, VT; [11]Neurosci., Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD

Abstract: Brain-wide profiling of 'punishment-reactive' afferent neuronal projections to the rostromedial tegmental nucleus (RMTg) in mice

[1]Sara Vettleson-Trutza, [1]Richard Nana Abankwah Owusu Mensah, [1]Abbey O'Brien, [1]Tony Kerr, [1]Jonathan Tran-Vu, [1]Alex Anwar, [2]Hermina Nedelescu, [2]Friedbert Weiss, [3]Eisuke Koya, [4]Bruce T. Hope, [5]Nate O'Connor, [6]Jack Glaser, [7]Thomas C. Jhou, [1]Nobuyoshi Suto[1]Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN [2]Department of Neuroscience, The Scripps Research Institute, San Diego, CA [3]School of Psychology, University of Sussex, Falmer, Brighton, UK [4]Behavioral Neuroscience Research Branch, NIDA/IRP/NIH, Baltimore, MD [5]Arnas Technologies, Essex Junction, VT [6]MBF Bioscience, Williston, VT [7]Department of Neurobiology, University of Maryland Baltimore, Baltimore, MD

Abstract

The rostromedial tegmental nucleus (RMTg) projects inhibitory GABAergic neurons to the dopaminergic neurons in the ventral tegmental area of the mesolimbic dopamine "reward" pathway. Punishment suppresses appetitive behavior in part by recruiting neurons in the RMTg and thus these punishment-reactive neurons appear to provide 'brake' on motivated behavior. Such behavioral suppression is presumably mediated by similarly punishment-reactive afferent neuronal projections to the RMTg. We have thus conducted brain-wide profiling - from the prefrontal cortex to the cerebellum - of punishment-reactive afferent projections to the RMTg in male and female C56BL/6 mice. Animals first received the retrograde tracer cholera toxin B (CTB) conjugated with a fluorescent dye (Alexa Fluor 488) in the RMTg and were then operant trained to self-administer saccharine (FR1, 1 hour daily) and recognize aversive foot-shock as punishment. Mice finally received foot-shock or no shock (control), sacrificed and perfused, and their brains were serially sectioned at 50 microns, immunolabeled for the activation marker Fos, imaged using slide scanning microscope (Zeiss Axioscan Z.1) and analyzed using brain-wide image analysis software, NeuroInfo (MBF Bioscience).

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Disclosures: S. Vettleson-Trutza: None. **R. Owusu Mensah:** None. **A. O'Brien:** None. **T. Kerr:** None. **J. Tran-Vu:** None. **A. Anwar:** None. **H. Nedelescu:** None. **F. Weiss:** None. **E. Koya:** None. **B.T. Hope:** None. **J. Glaser:** None. **T.C. Jhou:** None. **N. Suto:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

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K01DA054449(HN)
R37DA054370(TCJ)
T32GM145408(LS, SK)
R01AA014351(FW)
TL1TR002380 (AJW, FTBE)

Title: Linking compulsive behavior across obesity, eating disorders and drug addiction via punishment-reactive 'brake' neurons

Authors: *R. N. A. OWUSU MENSAH[1], A. O'BRIEN[1], S. VETTLESON-TRUTZA[1], T. KERR[1], C. WAKAYAMA[2], H. NEDELESCU[3], F. WEISS[4], E. KOYA[5], B. T. HOPE[6], N. J. O'CONNOR[7], T. C. JHOU[8], N. SUTO[1];
[1]Mayo Clin., Rochester, MN; [2]Harvard Med. Sch., Boston, MA; [3]Neurosci., Scripps Res. Inst., San Diego, CA; [4]Dept. of Neurosci., Scripps Res. Inst., La Jolla, CA; [5]Univ. of Sussex, Brighton, United Kingdom; [6]Behav Neurosci, NIDA IRP, NIH, Baltimore, MD; [7]MBF Biosci., Williston, VT; [8]Neurosci., Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD

Abstract: Along with obesity, binge eating disorder (BED) and bulimia nervosa (BN) - as examples of "food addiction" - share similar behavior and brain profiles with substance use disorders (SUD) suggesting a common cause. Like drug craving and use in patients with SUD, food craving and eating in patients with BED/BN as well as some obese individuals can persist despite adverse consequences (punishments). We previously reported, as with extensive exposure to obesogenic diet high in fat and sugar, extensive exposure to cocaine or alcohol - known to cause addiction-like brain changes and punishment-resistant "compulsive" drug intake in rats - can cause similarly punishment-resistant "compulsive" food intake in rats (Laque et al., 2022, *British Journal of Pharmacology*, 179:2589-2609). Thus, similarly common - rather than drug or diet-specific - changes in the brain likely underlie compulsive behavior across obesity, eating disorders and drug addiction. Since punishment suppresses appetitive behavior in part by activating neurons in the brain, including those in the rostromedial tegmental nucleus and the lateral habenula, diminished neural punishment-reactivity in these brain sites and beyond could manifest as punishment-resistant food intake. Here, we identify whole-brain neural punishment-reactivity changes from the prefrontal cortex to the cerebellum at the single cell resolution in rats that have undergone extensive (~10 weeks) cocaine, alcohol or obesogenic diet exposures by

combining serial sectioning/staining (at 50 microns), slide scanning microscope (Zeiss Axioscan Z.1) and automated brain-wide image analysis software (MBF NeuroInfo).

Disclosures: R.N.A. Owusu Mensah: None. **A. O'Brien:** None. **S. Vettleson-Trutza:** None. **T. Kerr:** None. **C. Wakayama:** None. **H. Nedelescu:** None. **F. Weiss:** None. **E. Koya:** None. **B.T. Hope:** None. **N.J. O'Connor:** None. **T.C. Jhou:** None. **N. Suto:** None.

Poster

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K01DA054449 (HN)
R01AA014351 (FW)
T32GM145408 (LS, SK)
TL1TR002380 (AJW, FTBE)

Title: Brain-wide profiling of cocaine-reactive afferent neuronal projections to three subnuclei of the deep cerebellar nucleus: fastigial (medial), interposed, and dentate (lateral) nuclei

Authors: *R. HEIDER[1], R. OWUSU MENSAH[1], A. O'BRIEN[1], S. VETTLESON-TRUTZA[1], T. KERR[1], J. TRAN-VU[1], H. NEDELESCU[3], F. WEISS[4], E. KOYA[5], N. J. O'CONNOR[6], J. GLASER[7], N. SUTO[2];
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Abstract: Brain-wide profiling of cocaine-reactive afferent neuronal projections to three subnuclei of the deep cerebellar nucleus: fastigial (medial), interposed, and dentate (lateral) nuclei

[1]Robin Heider, [1]Richard Nana Abankwah Owusu Mensah, [1]Abbey O'Brien, [1]Sara Vettleson-Trutza, [1]Tony Kerr, [1]Johnathan Tran-Vu, [1]Alex Anwar, [2]Hermina Nedelescu, [2]Friedbert Weiss, [3]Eisuke Koya, [4]Nate O'Connor, [5]Jack Glaser, [1]Nobuyoshi Suto [1]Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN [2]Department of Neuroscience, The Scripps Research Institute, San Diego, CA [3]School of Psychology, University of Sussex, Falmer, UK [4]Arnas Technologies, Essex Junction, VT[5]MBF Bioscience, Williston, VT

AbstractThe deep cerebellar nuclei (DCN), the primary output channel of the cerebellum

previously recognized primarily for its role in motor modulation, is more recently implicated in cocaine reward and motivated behavior through its excitatory monosynaptic projections to the ventral tegmental area (Carta et al., 2019, Science, 363, eaav0581). These cerebellum to midbrain projections presumably receive neuroanatomical signals from cocaine-reactive neuronal projections to DCN, although afferent neuronal projections to this brain site have not been fully characterized. We have thus conducted brain-wide profiling - from the prefrontal cortex to the cerebellum - of cocaine-reactive afferent neuronal projections to three subnuclei of DCN - fastigial (medial), interposed, and dentate (lateral) nuclei - in male and female C56BL/6 mice. Animals first received the retrograde tracer cholera toxin B (CTB) conjugated with a fluorescent dye (Alexa Fluor 488) into one of the three DCN subregions and were habituated to receive IP injections of saline in an open field chamber where their locomotor activity was monitored. Finally, animals received the test IP injection of cocaine or saline (control) in the open field chamber, sacrificed and perfused. Their brains were removed, serially sectioned at 50 microns, immunostained for the activation marker Fos, photographed using a slide scanning microscope (Zeiss Axioscan Z.1) and analyzed using brain-wide image analysis software NeuroInfo (MBF Bioscience) for Fos and CTB expression at the single cell resolution. We will present findings related to the brain-wide profiling of cocaine-reactive (Fos+) afferent projections to DCN subnuclei and thereby revealing the upstream circuitry through which cocaine signals may reach the cerebellum.
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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.12/EE19

Topic: H.08. Drugs of Abuse and Addiction

Support: DA054449
U01DA055017
UG3DA055167
R21AA030184
R01AA014351
T32GM145408
TL1TR002380

Title: NeuroInfo for brain-wide profiling of afferent and efferent neuronal projection in rats with single cell and axonal terminal level resolution

Authors: *H. NEDELESCU[1], R. OWUSU MENSAH[3], A. C. O'BRIEN[4], S. VETTLESON-TRUTZA[5], J. TRAN-VU[4], R. HEIDER[5], A. ANWAR[4], T. KERR[4], E. KOYA[7], F. WEISS[2], N. J. O'CONNOR[8], J. GLASER[9], N. SUTO[6];
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Abstract: Comprehensive brain-wide profiling methods combining whole-brain clearing using delipidation process and opaque protein solvent, whole-mount immunolabeling and volume image capturing using light-sheet microscopes are widely used to study intact mouse brain circuitry and cellular morphology. However, both whole-brain clearing and labeling intact rat brains - which are larger than mouse brains (roughly ~3 times larger in volume) - remain challenging, and light-sheet microscopes may not provide the resolution necessary to visualize deep brain structures and quantify axonal terminals. We have thus developed an automated rat brain-wide profiling method for rats by combining serial brain sectioning, conventional tissue immunolabeling, slide scanning microscopy and image analysis software - NeuroInfo (MBF Biosciences) - capable of automated “2D brain section to 3D whole-brain reconstruction”, and brain-wide image analysis of rat brains at the single cell and terminal level resolution. Briefly, [1] rats received an retro/anterograde tracer for afferent/efferent profiling and was sacrificed/perfused, [2] whole rat brains are serially sectioned at 50 microns, immunolabeled (if necessary) and mounted on slides, [2] labeled serial sections are captured at 10x for cell bodies and 20x for axonal terminals using a slide scanner (Zeiss Axioscan Z.1), [3] 2D images of each brain section are aligned to the Waxholm 3D reference rat brain atlas, [4] brain regions are annotated according to the atlas and [5] region-specific anatomy and cellular morphology are analyzed at single cell/terminal level resolution guided by AI-driven machine learning. Using this method, we demonstrate brain-wide profiling of afferent neuronal projection to the three major regions of the mesolimbic dopamine “reward” pathway (ventral tegmental area, nucleus accumbens core, dorsal medial prefrontal [prelimbic] cortex) in adult rats. We also demonstrate rat brain-wide profiling of efferent neuronal projection from the dentate/lateral nucleus of the (deep) cerebellar nuclei - the primary output channel of the cerebellum.

Disclosures: H. Nedelescu: None. **R. Owusu Mensah:** None. **T. Kerr:** None. **E. Koya:** None. **F. Weiss:** None. **N.J. O'Connor:** None. **J. Glaser:** None. **N. Suto:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.13/EE20

Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA-DA000467
ZIA-DA000434

Title: Distinct prelimbic cortex ensembles encode response execution and inhibition

Authors: *R. MADANGOPAL[1], Y. ZHAO[2], C. HEINS[3], J. ZHOU[4], B. LIANG[5], G. BARBERA[6], K. LAM[2], L. E. KOMER[7], S. J. WEBER[8], D. THOMPSON[9], Y. GERA[10], D. PHAM[12], K. E. SAVELL[1], B. L. WARREN[13], D. CAPRIOLI[14], M. VENNIRO[15], J. M. BOSSERT[16], L. A. RAMSEY[9], H. P. JEDEMA[17], G. SCHOENBAUM[11], D.-T. LIN[9], Y. SHAHAM[18], F. PEREIRA[19], B. T. HOPE[20];
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Abstract: Learning when to initiate or withhold actions is essential for survival, requiring the integration of past experiences with new information to adapt to changing environments. The prelimbic cortex (PL) plays a central role in this process, with a stable PL neuronal population (*ensemble*) recruited during operant reward learning to encode response execution. However, it is unknown how this established reward-learning ensemble adapts to changing reward contingencies, such as reward omission during extinction. Specifically, does the same ensemble adjust its activity to support behavior suppression, or is a distinct ensemble recruited for this new learning? Our data show that operant extinction learning recruits a distinct PL Extinction ensemble to support response inhibition, and concerted engagement of both ensembles encodes both ongoing and subsequent context-specific behavior. Using single-cell calcium imaging, we longitudinally tracked PL neurons in rats as they pressed a lever for food rewards (Training), learned to suppress responding upon reward omission (Extinction), and reinstated responding following exposure to a non-contingent "priming" pellet (Reinstatement). We trained decoders on individual rats' PL activity patterns to predict trial-wise responses and used a novel *in silico* deletion approach to identify separate PL Training and Extinction ensembles associated with response execution and inhibition, respectively. Critically, both ensembles were re-engaged and maintained their distinct roles during Reinstatement. These findings highlight ensemble-based encoding of multiple, even opposing, learned associations within the same region, demonstrating how selective ensemble recruitment enables behavioral flexibility under changing contingencies.

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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.14/EE21

Topic: H.08. Drugs of Abuse and Addiction

Support: K99DA059608
NIDA IRP
NIH SIP
NIH CCB

Title: Development of MultipleXed Population Selection and Enrichment single nucleus RNA-sequencing (XPoSE-seq) to study transcriptional programs of target populations

Authors: *P. ARRIAGA, R. MADANGOPAL, P. SARAVANAN, R. PALAGANAS, A. R. HOLMES, D. THOMPSON, K. WOODS, O. R. DRAKE, M. BRENNER, D. PHAM, E. VAN LEER, J. H. CHOI, B. T. HOPE, K. E. SAVELL;
NIH, NIDA IRP, Baltimore, MD

Abstract: Background: Understanding how complex behaviors arise from heterogeneous brain cell populations at the molecular level requires transcriptomic techniques that preserve both cell type resolution and subject-level identity. However, current high-throughput snRNA-seq platforms are not optimized for isolating specific neuronal populations or for retaining controlled representation of biological replicates. To address this gap, we developed XPoSE-seq (Multiple**X**ed **Po**pulation **S**election and **E**nrichment snRNA-seq), a flexible and scalable approach that combines antibody-based multiplexing with flow-cytometry-based enrichment of nuclei prior to large-volume, microwell-based snRNA-seq. **Methods:** We generated XPoSE-tags targeting the nuclear pore protein Nup62, coupled to both a far-red fluorophore for sorting and oligo barcodes for demultiplexing. We validated XPoSE-seq in rat ventromedial prefrontal cortex (vmPFC) by isolating neuronal nuclei from four homecage rats across two captures. We then applied the workflow to Fos-mRFP transgenic rats exposed to a novel context, sorting behaviorally active mRFP-positive and non-active mRFP-negative neuronal nuclei from the same biological samples. Sequenced nuclei were demultiplexed, clustered, annotated, and analyzed using pseudobulk differential expression approaches. **Results:** We verified successful nuclei tagging and multiplexing with XPoSE-tags, and combining XPoSE-seq and an activity-dependent transgenic rat, we enriched for neurons active during novel context exploration. This isolated active population included multiple cell types, and differential gene expression (DEG) analysis was more sensitive when analyzing the isolated active nuclei compared to the unenriched capture. Overall, XPoSE-seq enhances targeted snRNA-seq sensitivity, enabling

discovery of cell-type-specific changes in normal and disease states within the central nervous system.

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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.15/EE22

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Intramural Research Program (IRP)

Title: Protein changes in synaptoneurosomes and dendritic spines of rats after food seeking using flow cytometry and expansion microscopy

Authors: *E. UKPONG[1], A. EDWARDS[2], F. RUBIO[3], C. DUNN[4], S. ZHANG[5], B. T. HOPE[6]; [1]NIH, NIDA IRP, Baltimore, MD; [2]NIDA IRP/Neuronal Ensembles in Drug Addiction Section, Bel Air, MD, ; [3]Behavioral Neurosci. Res., NIDA IRP, Baltimore, MD; [4]NIH, NIA IRP, Baltimore, MD; [5]Natl. Inst. of Health, Natl. Inst. on Drug Abuse, IRP, Baltimore, MD; [6]Behav Neurosci, NIH/NIDA, Baltimore, MD

Abstract: The medial prefrontal cortex (mPFC) to nucleus accumbens (NAc) circuit is important for learning in animal models of addiction. Neuroadaptations within the pre-synaptic mPFC glutamatergic terminals onto the post-synaptic dendritic spines on medium spiny neurons (MSNs) in NAc are to be an important mechanism for this learning. We used flow cytometry of synaptoneurosomes (FCS) procedure for assessing molecular alterations in selectively activated synapses after food seeking behavior. First, AAV expressing YFP was injected into the mPFC and the expressed YFP protein was transported over 6-8 weeks to mPFC-specific presynaptic endings in the NAc core subregion. We then trained rats to lever press for food pellets paired with a light cue followed by 3-4 weeks abstinence in their home cages. Rats were tested by returning them to the food-paired light cue (relapse test group) to activate relapse-specific synapses. We dissected the NAc core 0, 30 and 60 min after cue-induced relapse and prepared synaptoneurosomes that contain both intact pre- and post-synaptic compartments. We used our FCS protocol to quantify different proteins induced exclusively in the mPFC-NAc synaptoneurosomes labeled with YFP, including the ribosomal protein S6 that we identified previously as a potential marker of synaptic activity. We found increased S6 at 30 and 60 min after food seeking. Expansion microscopy analysis confirmed increased S6 locally at the dendritic spines. Future studies will test the hypothesis that the number of S6-positive (activated) spines is greater in Fos-positive neurons vs. Fos-negative neurons after food seeking. In future

studies, we will use S6 to identify other synaptic protein alterations induced selectively in synaptic ensembles mediating learning in drug addiction models

Disclosures: E. Ukpong: None. **F. Rubio:** None. **C. Dunn:** None. **S. Zhang:** None. **B.T. Hope:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.16/EE23

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA/NIH IRP (Hope)
NIH CCB (Savell)
NIDA U01DA055017 (PI, Suto)
UG3DA055167 (PI, Suto)

Title: A Fos-based targeted recombination of active populations (Fos-TRAP) transgenic rat for genetic access to behaviorally activated ensembles and engrams.

Authors: *B. T. HOPE[1], K. E. SAVELL[2], A. R. HOLMES[4], A. SOBUKUNOLA[5], J. LEE[5], C. T. RICHIE[7], S. JACKSON[1], F. RUBIO[6], L. A. RAMSEY[5], N. SUTO[8], R. MADANGOPAL[3]; [1]NIDA IRP, NIH, Baltimore, MD; [3]Neuronal Ensembles in Addiction Section, [2]NIH, NIDA IRP, Baltimore, MD; [4]Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD; [6]Behavioral Neurosci. Res., [5]NIDA IRP, Baltimore, MD; [7]Genet. Engin. and Viral Vector Core, Natl. Inst. on Drug Abuse, BALTIMORE, MD; [8]Dept. of Mol. Pharmacol. & Exptl. Therapeut., Mayo Clin., Rochester, MN

Abstract: Background: Learned associations are encoded by long lasting molecular and cellular alterations (*engrams)* within sparse patterns of strongly activated neurons, called neuronal ensembles, typically identified using activity-dependent genes (e.g. *Fos)*. Fos-TRAP2 transgenic mice have advanced the study of ensembles and engrams by enabling permanent Cre-dependent labeling and manipulation of recently active Fos-expressing neurons following 4-hydroxytamoxifen (4-OHT) administration. However, rats are the species most often used for the study of drug-associated learning, relapse, and complex motivated behaviors, and their larger brains provide more tissue for molecular and cellular analyses. **Methods:** We generated a Sprague-Dawley Fos-TRAP2 knock-in rat by inserting the Fos-P2A-iCreERT2 construct from the Fos-TRAP2 knockin mouse (DeNardo et al, 2019 Nat Neurosci) between the coding sequence of exon 4 and the 3' UTR of the rat Fos gene, and generated a knockin transgenic rat using Biocytogen's Extreme Genome Editing System. Transgene sequence and insertion sites were confirmed by PCR, Southern blotting and sequencing and positive founders were used to generate four F1 heterozygous breeding pairs. We are now optimizing conditions for their use in behavioral experiments. We used 15 min novel context exposure (versus home cage controls) to activate the transgene and injected different doses of 4OHT intraperitoneally (IP) or

intravenously (IV) at different times relative to the start of novel context exposure and assessed expression of a Cre-dependent fluorescent reporter in mPFC. We also used mass spectrometry to determine time courses for 4OHT levels in blood plasma and brain to help determine optimal time window for 4OHT-dependent tagging of behaviorally activated neurons. **Results:** Fluorescent reporter expression in mPFC was strongly dependent on 4OHT injections with no detectable expression in the absence of 4OHT; rats tolerated IV injections as well as IP injections. We are optimizing experimental conditions to maximize detection of activity-dependent recombination of a Cre-dependent reporter induced by novelty exposure. In future studies, we will use this rat model to label and manipulate drug-cue-specific ensembles during operant drug self-administration and relapse.

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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.17/EE24

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Z1A DA000611

Title: Behavioral and neurochemical assessment of vilazodone and its structural analog, CDV-7-21, as potential atypical dopamine transporter inhibitors in male and female rodents

Authors: *G. TANDA[1], C. D. VOGT[3], Z. FRANGOS[3], M. HERSEY[4], M. K. BARTOLE[5], I. RALPH[6], Z. PURCELL[6], J. MELTON[6], M. MICHAELIDES[7], A. H. NEWMAN[2];
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Abstract: Mental disorders are often comorbid with psychostimulant use disorder (PSUD). Vilazodone (VLZ), a serotonin partial agonist/reuptake inhibitor approved for the treatment of major depression, not only has very high affinity (K_i=0.101 nM) for the serotonin transporter (SERT) and the 5HT1A receptor (K_i=0.20 nM) but also for the dopamine (DA) transporter (DAT; K_i=11.1 nM). DAT plays a primary role in the addictive liability of psychostimulants, like cocaine or methamphetamine, but there are no reports of VLZ misuse, suggesting its affinity for DAT is not associated with rewarding effects, at least in the population of patients to which it is prescribed. An explanation for its lack of rewarding effects might be found in the ~100-fold higher affinity VLZ exhibits for SERT over DAT, and/or in its potential atypical DAT inhibitor actions that would predict reduced reinforcing effects leading to addiction, as compared to typical, cocaine-like, DAT blockers. In this study, we aimed to evaluate the behavioral and

neurochemical effects of VLZ and its structural analog, CDV-7-21, as they relate to their high affinity for DAT. We assessed VLZ and CDV-7-21 behavioral effects in open field activity tests in mice and changes in DA dynamics in the nucleus accumbens shell using fast scan cyclic voltammetry (FSCV) and microdialysis procedures in male and female mice and rats. In the open field tests, administration of VLZ and CDV-7-21 (1, 3, 10, 30 mg/kg i.p.) in Swiss-Webster male mice did not elicit ambulatory activity significantly different from that produced by vehicle, with the only exception of the 10 mg/kg dose of VLZ, which significantly increased ambulatory activity. In voltammetry tests in C57 male and female mice, administration of VLZ (3-30 mg/kg i.p.) did not significantly modify DA dynamics in the nucleus accumbens shell showing no significant changes in evoked DA-max and DA clearance. However, a modest but significant increase in extracellular DA levels was obtained after administration of VLZ and CDV-7-21 (3-30 mg/kg i.p.) in male but not female Sprague Dawley rats implanted with microdialysis probes in the NAS. Our results suggest limited efficacy of VLZ and CDV-7-21 on the behavioral and neurochemical tests performed in this study, indicating their potential atypical DAT inhibitory actions. In conclusion, this study provides valuable information on behavioral and neurochemical effects of compounds that would facilitate the discovery of novel pharmacotherapies for the treatment of PSUD and potentially comorbid neuropsychiatric disorders.

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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.18/EE25

Topic: H.08. Drugs of Abuse and Addiction

Support: The Univers Foundation

Title: Effects of Dextromethorphan and Its Major Metabolites on Monoamine Transporters and High-Dose-Induced Locomotor Activity

Authors: *K. ISHII[1,2], K. TOMIYAMA[2], M. FUNADA[3], G. TSUJI[4], K. OKITA[2], T. MATSUMOTO[2], K. YOSHIZAWA[1];
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Abstract: Overdose cases dextromethorphan (DXM)-containing medications have been emerging as a serious public health issue in Japan. High-dose administration of DXM can induce psychoactive effects such as dissociation and hallucination-like experiences, though its mechanism has yet to be fully elucidated. DXM is metabolized mainly to dextrorphan (DXO) by

CYP2D6 and to 3-methoxymorphinan (3-MM) by CYP3A4, followed by further metabolism to 3-hydroxymorphinan (3-HM) and other metabolites. Although DXM and DXO have been reported to act as NMDA receptor antagonists, their effects on monoaminergic neurotransmission and their relationship to behavioral changes under high-dose exposure, and even the pharmacological profiles of 3-MM and 3-HM remain unclear. The present study compared the effects of DXM and its three metabolites on monoamine transporters in vitro and examined their effects on locomotor activity after high-dose administration in vivo. The inhibitory effects of DXM, DXO, 3-MM, and 3-HM on dopamine transporter (DAT)-, serotonin transporter (SERT)-, and norepinephrine transporter (NET)-mediated uptake were evaluated using calcium fluorescence assays in transporter-expressing cells. Compounds were tested at 0.001-100 μM to determine concentration-response relationships and IC50 values. To assess behavioral effects, mice received each compound at 60 mg/kg, and locomotor activity was measured.DXM and its metabolites showed distinct inhibitory profiles across DAT, SERT, and NET. For SERT, potency was ranked DXM > DXO > 3-MM > 3-HM, with IC50 values of 1.365×10^-7, 9.12×10^-7, 9.549×10^-6, and 4.742×10^-5 M, respectively. For NET, potency was ranked DXO > DXM > 3-MM > 3-HM, with IC50 values of 2.637×10^-6, 9.236×10^-6, 1.694×10^-5, and 3.758×10^-5 M, respectively. For DAT, all compounds significantly inhibited uptake at 100 μM, but IC50 values could not be calculated because clear concentration-response curves were not obtained. In the locomotor assay, DXM and DXO at 60 mg/kg significantly increased spontaneous locomotor activity, whereas 3-MM and 3-HM did not.These findings indicate that DXM, DXO, and 3-MM inhibit SERT and NET, whereas these effects are attenuated in 3-HM, suggesting that monoamine transporter profiles change across metabolic steps. Although monoamine transporter inhibition may contribute to the behavioral effects of high-dose DXM exposure, SERT/NET inhibition alone does not fully explain the observed locomotor activation. Other mechanisms, including NMDA receptor antagonism and pharmacokinetic differences, may contribute to DXM- and DXO-induced behavioral activation.

Disclosures: K. Ishii: None. **K. Okita:** None. **K. Yoshizawa:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.19/EE26

Topic: H.08. Drugs of Abuse and Addiction

Title: The role of the ACC-PPC inhibitory control over alcohol seeking

Authors: *K. WILLIAM[1], H. N. CARLSON[2];
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Abstract: The role of the ACC-PPC inhibitory control over alcohol seekingAuthors Keisha William[1,2] and Hannah Carlson, Ph.D.[1,21]Department of Neuroscience, Lake Forest College, Lake Forest IL 60045[2]Department of Psychology, Lake Forest College, Lake Forest IL

60045**Abstract**Alcohol use disorder (AUD) involves persistent alcohol use despite negative outcomes, dueto impaired inhibitory control and decision-making. Impulsivity has been identified as both avulnerability factor for substance use disorders and a consequence of prolonged alcoholexposure. Although prior studies have investigated the role of the projection from theposterior parietal cortex (PPC) to the anterior cingulate cortex (ACC) in decision-making, fewhave examined the unique role this circuit may play in substance use. The present study isdesigned to assess the potential reciprocal relationship between impulsive behavior andalcohol use, with a focus on the ACC-PPC pathway. To investigate the role of ACC–PPCcircuitry in alcohol-related impairments in inhibitory control, three complementaryexperiments were conducted in male Long-Evans rats. Experiment 1 verifies anatomicalconnectivity between the anterior cingulate cortex (ACC) and posterior parietal cortex (PPC)using viral tracing (n = 6). Experiment 2 examines the effects of chronic alcohol exposure oninhibitory control and neural activity within the ACC and PPC by comparing C-Fosexpression in the ACC and PPC and behavioral performance between rats trained on asucrose-reinforced Go/No-Go task and given intermittent access to alcohol (n=4) or sucrose(n=4) in the home cage. Experiment 3 evaluates the causal role of the ACC–PPC projectionin inhibitory control during alcohol self-administration, using *in vivo* chemogenetics toselectively manipulate ACC-PPC function during behavior. Taken together, these dataelucidate the reciprocal relationship between frontoparietal activity and impulsive behavior inthe context of alcohol self-administration.

Disclosures: K. William: None. **H.N. Carlson:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.20/EE27

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant P50DA046346
NIH Grant R01DA058955

Title: Dynamic interactions between dorsal striatal dopamine and glutamate release predict cognitive flexibility and substance use disorder-like behavior

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Abstract: Cognitive inflexibility is a trait marker that predicts substance use disorder (SUD) development across species. We hypothesized that neural signatures could be measured in the dorsal striatum during a cognitive flexibility test that would distinguish between rats that were flexible versus inflexible. We further hypothesized that these same neural signatures would be able to predict which rats would go on to show SUD-like behavior. We used multi-channel fiber

photometry to measure glutamate (Glut) and dopamine (DA) release in the dorsomedial (DMS) and dorsolateral (DLS) striatum of the same rat during a discrimination learning and strategy switching test. Next, rats were trained to self-administer cocaine and then subjected to a battery of SUD-related tests, including acquisition rate, intake escalation, punishment resistance, progressive ratio, and cue-induced reinstatement. We showed that elevations in Glut release in DLS at trial initiation and DMS prior to a choice, with respective reductions in DA release, predicted both flexibility (fast strategy switching) and reduced SUD-like behavior, while elevations in DLS and DMS DA release at these same behavioral timepoints predicted inflexibility (slow strategy switching) and increased SUD-like behavior. Finally, we used pathway-specific DREADDs to determine where measured Glut release originated and whether each was necessary for the observed effects. We showed that inhibition of the ventral orbital frontal cortex inputs to dorsal striatum reduced the Glut measured in both the DMS and DLS prior to a choice, whereas inhibition of intralaminar thalamus inputs to dorsal striatum reduced Glut measured in both regions at trial initiation. Inhibition of either projection, individually, impaired strategy switching across all rats; however, inhibition of intralaminar thalamus projections produced a stronger impairment. Inhibition of either projection also increased SUD-like behavior, but the strength of these effects differed depending on the SUD behavioral test and whether the rat performed better (fast) or worse (slow) on the strategy switching test. Thus, we propose that elevations in Glut release originating from the ventral orbitofrontal cortex and intralaminar thalamus at specific test epochs represent a “signature” of flexibility that predicts resilience to SUD phenotypes, whereas elevations in DA release at those same test epochs predicts inflexibility and vulnerability to SUD phenotypes.

Disclosures: D.M. Bortz: None. **D.J. Weber:** None. **M.M. Torregrossa:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.21/EE28

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA R01DA039865
NIDA F32DA060613

Title: Diurnal Variations in Cholingeric Interneurons in the Nucleus Accumbens and the Impact of Chronic Nicotine

Authors: *T. A. STOWE[1], Y. H. HUANG[1], M. E. JOFFE[2], C. A. MCCLUNG[3];
[2]Pharmacol., [1]Univ. of Pittsburgh, Pittsburgh, PA; [3]Psychiatry, Univ. of Pittsburgh Med. Sch., Pittsburgh, PA

Abstract: Time-of-day variations are found within psychiatric disorders, including substance use disorders (SUDs). Drug-taking varies throughout the day, indicating that individuals may be

more susceptible to drug use at certain times-of-day. Overall, it is crucial to determine the potential diurnal (light/dark) variations in the mechanisms underlying reward-related behaviors, like drug-taking. Although cholinergic interneurons (CINs) make up 1-2% of the nucleus accumbens (NAc), they are the primary source of acetylcholine (ACh) and play a key role in modulating dopamine (DA) dynamics. CINs are also essential in behaviors like reward-learning and models of relapse-like behaviors. However, limited data exist on the diurnal variations in CINs. Previous studies have found that there are diurnal variations in ACh modulation of DA release in the NAc, but it remains unclear if there are variations in CINs themselves or what potential mechanisms are driving these variations. Here, we measured CIN activity via *ex vivo* electrophysiology in the NAc over the 24 hr cycle. Additionally, we used pharmacological methods to determine what drives variations in CIN activity. Lastly, we have started preliminary studies to determine how chronic nicotine may impact diurnal variations in CIN activity via a chronic drinking paradigm. Our data support that there are both novel diurnal variations and sex differences in CIN activity. Males have higher activity in the dark cycle while females may show other time-of-day differences with peaks and troughs in the light and dark cycle. Our pharmacological data show that targeting nicotinic receptors (nAChRs) decrease CIN activity only in the dark cycle in males. Thus, there may be specific receptors playing a key role in the diurnal variations in CINs that may also vary by sex. Lastly, we have preliminary data showing that chronic nicotine decreases CIN activity in both the light and dark cycle in males, while having little to no effects in females. Given the essential role CINs play in the NAc and reward-related behaviors, the diurnal variations in these cells may influence drug-taking behaviors and play a role in vulnerability to developing SUDs. In the future, we aim to expand on our chronic nicotine exposure model and determine if disrupting the molecular clock of CINs changes reward-taking. Overall, these novel findings collectively bring us closer to characterizing the potential rhythms in the neural mechanisms that drive reward-related behaviors associated with SUDs.

Disclosures: T.A. Stowe: None. **Y.H. Huang:** None. **M.E. Joffe:** None. **C.A. McClung:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.22/EE29

Topic: H.08. Drugs of Abuse and Addiction

Support: UNAM PAPIIT IN213924
UNAM PAPIIT IA201622
DGAPA-UNAM postdoctoral project (CJCA)

Title: Cerebellar volumetric alterations and cellular changes induced by chronic alcohol exposure in male and female Wistar rats

Authors: *C. J. CARRANZA-AGUILAR, J. R. TOLEDO, E. CARDONA ARRIAGA, D. ANGELES-VALDEZ, D. REYES-HARO, E. A. GARZA-VILLARREAL;
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Abstract: The cerebellum is increasingly recognized as a modulator of cognitive, emotional, and reward-related processes. However, although chronic alcohol exposure affects brain regions involved in addiction, its impact on cerebellar structure and cellular organization remains less understood. Here, we evaluated longitudinal cerebellar volumetric changes and cellular alterations induced by chronic alcohol exposure in male and female Wistar rats. Animals were exposed to 20% ethanol using an intermittent access two-bottle choice paradigm (20 EtOH sessions). Longitudinal structural MRI was acquired at baseline (T1, postnatal day 45 (P45)), early exposure (T2, P67), and after completion of the protocol (T3, P90) using a 7 T Bruker scanner. T2-weighted images were analyzed using deformation-based morphometry. Independent cohorts were perfused at T1, T2, or T3, and cerebellar lobules VIII and IX were processed for immunofluorescent labeling of calbindin, GFAP, and Iba1 to quantify Purkinje neurons, astrocytes, and microglia, respectively. Ethanol intake remained stable across sessions, with males consuming approximately 2.3-2.5 g/kg/24 h and females 1.1-1.3 g/kg/24 h. Intake classification identified a high-intake subgroup composed predominantly of males and a low-intake subgroup with a larger proportion of females. Chronic alcohol exposure changes the volume of cerebellar lobule IX, whereas lobule VIII showed no consistent longitudinal changes. At the cellular level, alcohol-exposed rats showed a progressive reduction in Purkinje neuron count in lobule IX, with females displaying marked decreases at T2 and T3 compared with controls, while males showed only modest reductions. Microglial density decreased in exposed females at T2, and astrocyte number increased in exposed females at T3. Males showed minimal glial alterations. These findings reveal a sex-dependent pattern of cerebellar remodeling after chronic alcohol exposure, characterized by earlier and stronger cellular alterations in females despite lower ethanol intake. The combination of lobule IX volumetric alteration, Purkinje neuron loss, reduced microglial counts, and later astrocytic activation suggests that this cerebellar region may be a relevant target for understanding alcohol-related neuroadaptations.

Disclosures: C.J. Carranza-Aguilar: None. **J.R. Toledo:** None. **E. Cardona Arriaga:** None. **D. Angeles-Valdez:** None. **D. Reyes-Haro:** None. **E.A. Garza-Villarreal:** None.

Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.23/EE30

Topic: H.08. Drugs of Abuse and Addiction

Support: DA031695

Title: Altered Cue and Reward Expectancy Signals in the Anterior Insula Following Epigenetic Manipulation

Authors: *S. PERRY[1], X. R. R. SCIARILLO[2], A. T. BROCKETT[3], X. LI[2], M. R. ROESCH[4]; [1]Univ. of Maryland, Washington D.C., DC; [2]Dept. of Psychology, Univ. of Maryland, College Park, MD; [3]Dept. of Psychology, Rollins Col., Winter Park, FL; [4]Dept. of Psychology, Univ. of Maryland at Col. Park, College Park, MD

Abstract: Multiple forms of impulsive behavior may rely on shared or dissociable neural processes involving actions, expected outcomes, and subjective value. The anterior insular cortex (aIC) has been implicated in impulsivity, and overexpression of histone deacetylase 5 (HDAC5), an epigenetic enzyme that generally decreases gene expression, within the aIC increases motor impulsivity and impairs cognitive control. Presently, we examined how HDAC5 overexpression alters neural representations of reward delay and magnitude, key factors underlying impulsive decision-making. Long-Evans rats received aIC injections of HDAC5-overexpressing or control (GFP) virus and were trained on a size/delay task in which reward magnitude and delay varied independently across blocks. Distinct odor cues signaled forced-choice responses to the left or right reward well or a free-choice response to either well. Single-unit recordings yielded 71 neurons from control rats and 132 neurons from HDAC5-overexpressing rats. HDAC5 rats showed intact free-choice preferences but impaired forced-choice performance across both delay and magnitude manipulations. Across population and single-unit analyses, HDAC5 neurons exhibited increased cue-related firing but reduced anticipatory and outcome-related activity for preferred rewards. During error trials, control neurons maintained reward expectancy signals, whereas HDAC5 neurons showed little expectancy-related activity. Instead, they responded more to reward delivery. These results suggest that HDAC5-dependent modulation of aIC function differentially influences dimensions of impulsive behavior. Herein, HDAC5 overexpression shifted aIC encoding toward cue-related signals and away from reward expectancy, potentially disrupting cue-to-outcome mapping during forced-choice performance. In contrast, free-choice behavior, which can rely on relative value comparisons rather than explicit cue-guided responding, may have been less sensitive to this manipulation. Together, these findings suggest that HDAC5 selectively impacts outcome-guided decision processes within the aIC rather than broadly disrupting behavior across decision contexts. Future studies will determine how altered cue and reward expectancy representations contribute to impaired cue-guided behavior and other forms of maladaptive decision-making.

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Poster

PSTR027: Mechanisms of Learning and Memory in the Context of Addiction

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.24/EE31

Topic: H.08. Drugs of Abuse and Addiction

Support: AA026092
AA027552

AA026278
T32AA007565

Title: Epigenetic regulation of alternative splicing of NRXN3 in psychiatric disorders.

Authors: C. LOWE[1], D. ZHU[1], F. MILLER[2], K. ZIMMERMAN[2], A. BUSTABAD[1], K. GRANT[3], ***R. P. CERVERA-JUANES**[4];
[1]Translational Neurosci., Wake Forest Univ., Winston-Salem, NC; [2]Wake Forest Univ., Winston Salem, NC; [3]Div. of Neurosci., Oregon Natl. Primate Res. Ctr., Beaverton, OR; [4]Wake Forest Univ. Sch. of Med., Winston-Salem, NC

Abstract: **Background**: Neurexins are presynaptic cell adhesion molecules critical in regulating synaptic adaptations. Although single nucleotide polymorphisms mapping to *NRXN3* have been linked to substance use disorders, the molecular mechanisms regulating the specific alterations to *NRXN3*'s transcript/protein isoform diversity that accompany risk and consequences to substance misuse remain unknown. **Methods**: Unbiased RNAseq and genome-wide DNA methylation analyses, paired with transcript-specific qPCR were conducted on the dorsolateral prefrontal cortex (dlPFC) of male and female rhesus macaques that remained alcohol-naïve (controls) or self-administered ethanol for 12 months. Immunofluorescence (IF) was used to measure the levels of Nrxn3 isoforms across different cell types in the prelimbic cortex (PLC) of mice following chronic ethanol exposure. Reporter, transcriptional activation and epigenetic editing assays were used to interrogate the role of DNA methylation in regulating alternative splicing. **Results**: DNA methylation analysis identified an intragenic differentially methylated region (DMR) mapping upstream of the first alternative exon 1 of *NRXN3β.* Transcriptome analysis demonstrated that *NRXN3* was downregulated in female macaques. Further evaluation of the different *NRXN3* isoforms demonstrated exclusive downregulation of the short transcript *NRXN3β* across species, that was accompanied by a downregulation of two of its postsynaptic binding partners, neuroligin 2 and *β*-dystroglycan. This downregulation occurred in parvalbumin interneurons and excitatory neurons of the PLC of mice following chronic exposure, although in a sex-specific manner. We further showed that the DMR regulates alternative splicing. **Conclusions:** Our research provides significant insights into the complex adaptations of NRXN3, and its binding partners, by chronic ethanol within different cell types of the PFC/PLC. We hypothesize these changes are modulating synaptic plasticity in parvalbumin interneurons and excitatory neurons.

Disclosures: C. Lowe: None. **D. Zhu:** None. **F. Miller:** None. **K. Zimmerman:** None. **A. Bustabad:** None. **K. Grant:** None. **R.P. Cervera-Juanes:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.01/EE32

Topic: H.08. Drugs of Abuse and Addiction

Title: Ramifications of Adolescent Social Quarantine on Adult Alcohol Consumption in Mice

Authors: *L. ROZEBOOM[1], J. N. BERRY[2];
[1]Butler Univ., Indianapolis, IN, IN; [2]Psychology Dept., Butler Univ., Indianapolis, IN

Abstract: Alcohol is the most commonly abused substance and often plays a dominant role in substance use disorder (SUD), a psychiatric disorder characterized by excessive and disruptive substance use, which has been linked to numerous negative health outcomes. Social isolation (SI), too, has been linked to a myriad of negative health outcomes and has been identified as a risk factor for developing a SUD, but research into SI as it relates to alcohol use is limited, especially in studies using animal models. Using an intermittent access (IA) paradigm, the present study investigated the impact of SI during adolescence on adult alcohol consumption, preference, and anxiety-like behavior following withdrawal in mice. The IA paradigm is commonly used to mimic the pattern of human alcohol consumption and escalation to alcohol use disorder. Adolescent male and female C57BL/6J mice (N=32; 4 weeks of age) were housed either individually or in pairs with a same-sex littermate upon arrival. After 4 weeks of this housing condition, all mice were individually housed and given IA to a 2-bottle choice paradigm containing a secondary bottle of water (control) or 10% alcohol. To evaluate anxiety-like behavior, all mice were given an open field test approximately 6 hours following the final removal of their secondary bottles. A 2-way ANOVA revealed that male, but not female, SI mice exhibited increased alcohol consumption and preference during the first week of the IA paradigm ($p < 0.05$). The open field test revealed that pair-housed mice with access to alcohol displayed significantly worsened withdrawal symptoms than their individual water-exposed counterparts. These results suggest that adolescent SI may result in sex-dependent vulnerability to IA to alcohol, and that these effects extend into early adulthood. This experiment also illustrates the importance of investigating SUD from a multi-faceted perspective, taking into account factors such as age, sex, and SI.

Disclosures: L. rozeboom: None. **J.N. Berry:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.02/FF1

Topic: H.08. Drugs of Abuse and Addiction

Support: NCT03896516
Clinical Psychoneuroendocrinol ogy and Neuropsychopharmacology Section
NIDA Intramural Research Program (IRP) and the NIAAA Division of Intramural Clinical and Biological Research (DICBR)
National Center for Advancing Translational Sciences (NCATS)
NIDA IRP Translational Analytical Core (TAC)

Title: Targeting GOAT to Modulate Ghrelin Signaling in Patients with Alcohol Use Disorder

Authors: *J. VISHWAKARMA;
Translational Addiction Med. Br., Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Our lab investigated whether manipulating ghrelin signaling via the ghrelin O-acyltransferase (GOAT) inhibitor GLWL-01 may represent a promising strategy for alcohol use disorder (AUD), a chronic relapsing condition with limited treatment options. Ghrelin-O-acyltransferase (GOAT) catalyzes the octanoylation of desacyl-ghrelin, converting it to biologically active acyl-ghrelin; thus, GOAT represents a "master switch" for the ghrelin system. Preclinical studies showed that GLWL-01 dose-dependently decreased acyl-ghrelin and increased desacyl-ghrelin without toxicity, and attenuated alcohol-related behaviors. GLWL-01 is a selective GOAT inhibitor that has previously completed a first-in-human safety trial in obesity, type 2 diabetes mellitus and Prader-Willi Syndrome. In the present study, we conducted a Phase 1b/2a proof-of-concept human laboratory investigation to evaluate the safety, pharmacodynamic effects, and early efficacy signals of GLWL-01 in individuals with AUD. Twenty-one participants with AUD were enrolled in a randomized, placebo-controlled crossover design in which participants received GLWL-01 (450 mg twice daily) or placebo during Stage 1, followed by a washout period and crossover to the alternate condition during Stage 2. Blood samples were collected across repeated dosing days (D1-D4) at pre-dose (T1) and post-dose (T2) timepoints, with an additional washout assessment (W1), to evaluate biomarkers and hormonal measures relevant to AUD pathophysiology. GLWL-01 treatment significantly reduced circulating ghrelin concentrations at multiple timepoints compared with placebo, while increasing desacyl-ghrelin, indicating effective inhibition of GOAT activity. Concurrent reductions in LEAP2 levels further supported downstream modulation within the ghrelin signaling pathway. Other neuroendocrine proteins, such as BDNF, insulin, leptin, growth hormone, and cortisol were comparable between GLWL-01 and placebo, supporting maintained metabolic, stress-axis, and pituitary functions. Aldosterone demonstrated a modest transient increase during later treatment days under drug conditions that were partially normalized during washout, consistent with reversible physiological adaptation. Collectively, these findings provide evidence of pharmacological target engagement and support the endocrine-related safety and tolerability of GLWL-01in people with AUD.

Disclosures: J. Vishwakarma: A. Employment/Salary (full or part-time):; full.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.03/FF2

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA Grant 5P50AA017823-17
DNAA T32 Grant 1135235

Title: Investigating the Effect of Adolescent Intermittent Ethanol Exposure and LM11A-31 on Alzheimer's Disease-Related Cognitive Deficits and Pathology in Male and Female TgF344-AD Rats

Authors: *E. L. KERR, L. M. SAVAGE;
Psychology-Behavioral Neurosci., SUNY - Binghamton Univ. Behavioral Neurosci., Binghamton, NY

Abstract: Alcohol use in adolescence has been shown to have a plethora of negative effects on cognitive and behavioral measures, as well as a risk factor for Alzheimer's Disease (AD). This study investigates the effect of LM11A-31, a small molecule modulator of the p75 neurotrophin receptor, on AD-related neural dysfunction in TgF344-AD rats following adolescent intermittent ethanol (AIE). Male and female F344 (WT) and TgF344-AD (AD) rats underwent behavioral assessments of anxiety-like behavior using the open filed test, and spatial learning and memory and behavioral flexibility using the Morris water maze test at 8 months of age (mo). Behavioral tests were followed by immunohistochemical analysis of adult neurogenesis in the sub granular layer of the dentate gyrus within the dorsal hippocampus (dHPC) at 9 mo using staining for doublecortin (DCX). Findings demonstrate that AIE exposure selectively exacerbates behavioral impairments in AD animals in a sex-specific manner, with more pronounced effects in males. Specifically, AIE reduced locomotor activity and increased anxiety-like behavior in AD males, which was rescued by LM11A-31 treatment. While spatial learning did not differ across groups, spatial memory was impaired in AD males exposed to AIE. Additionally, in both males and females, AIE exposure and an AD genotype produced deficits in spatial efficiency and behavioral flexibility. Adult neurogenesis was reduced in AD males exposed to AIE, marked by a decreased number of DCX+ cells in the dHPC. Overall, this reflects a potential interaction between AIE exposure and AD-related cognitive deficits and pathology - with possible recovery through LM11A-31 treatment.

Disclosures: E.L. Kerr: None. **L.M. Savage:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.04/FF3

Topic: H.08. Drugs of Abuse and Addiction

Support: R01 R01AA029386

Title: Sex differences in withdrawal symptom severity and relapse-like behavior in rats following access to oral ethanol during acute withdrawal from ethanol vapor

Authors: *K. BANKSTON[1], R. B. HILL[2], E. HONG[2], M. H. MONFILS[2], R. GONZALES[3], H. J. LEE[2];
[2]Dept. of Psychology, [3]Pharmacol., [1]The Univ. of Texas at Austin, Austin, TX

Abstract: Many individuals with Alcohol Use Disorder (AUD) become physically dependent on alcohol, which entails experiencing withdrawal symptoms in its absence. It is thought that physical dependence contributes to the maintenance of AUD, as individuals will drink alcohol to relieve aversive symptoms of withdrawal— a type of learning known as negative reinforcement. Most rodent models of AUD induce physical dependence via chronic intermittent ethanol (CIE) vapor exposure but do not account for the negative reinforcement learning that is present in human cases. The aim of this experiment was to determine if drinking alcohol during the withdrawal period models negative reinforcement learning and/or impacts relapse risk in rats. Long-Evans rats (n = 78; 46 males, 32 females) were initially trained to drink 15% unsweetened alcohol in their homecages and following a light-cue. To induce physical dependence, rats were exposed to CIE vapor (14 hrs on:10 hrs off daily) 5 days a week for 4 weeks. To model negative reinforcement, rats were given access to a bottle containing 15% alcohol for 2 hrs during withdrawal from CIE vapor (i.e., 6-8 hrs post-vapor cessation). As a control, half of the subjects were exposed to air instead of vapor and half of each vapor/air group were not given alcohol during the withdrawal period. Intoxication was measured with daily behavioral scoring and weekly blood collection. Withdrawal symptom severity was measured with weekly behavioral scoring. Relapse-like behavior was measured as number of sipper licks in the absence of alcohol following an extinguished light-cue. We found that drinking alcohol during the withdrawal period reduced withdrawal symptom severity in males, particularly by the 4th week (Mdiff=1.39±0.41, $t(69)=3.39$, $p=.02$), but not in females. Interestingly, vapor groups drank less during withdrawal than air groups ($F(1,36)=16.22$, $p<0.001$), suggesting alcohol became aversely associated with the withdrawal state. However, this deterrence from alcohol did not persist, as there was no effect of drinking during withdrawal on long-term alcohol consumption nor reactivity to the extinguished light-cue. Yet, males exhibited more relapse-like behavior than females (Mdiff=3.75±1.49 sipper licks, $t(69)=2.51$, $p=.01$). In conclusion, although both male and female rats are deterred from drinking alcohol during acute withdrawal from ethanol vapor, male rats exhibit less acute withdrawal symptoms. In addition, male rats may be more susceptible to relapse-like behavior to alcohol than female rats. Regardless, access to oral ethanol during withdrawal appears to be an insufficient model for negative reinforcement in rats.

Disclosures: K. Bankston: None. **R.B. Hill:** None. **E. Hong:** None. **M.H. Monfils:** None. **R. Gonzales:** None. **H.J. Lee:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.05/FF4

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA 5P50AA017823-17

Title: Galantamine Reverses Habitual Responding Induced by Adolescent Binge Alcohol Exposure in Female Rats

Authors: *A. ROY[1], L. M. SAVAGE[2];
[1]Binghamton Univ., binghamton, NY; [2]Psychology-Behavioral Neurosci., SUNY - Binghamton Univ. Behavioral Neurosci., Binghamton, NY

Abstract: Adolescent heavy binge-type alcohol exposure is known to induce structural brain alterations, particularly affecting late-developing regions such as the orbitofrontal cortex (OFC). In rodent models, adolescent intermittent ethanol (AIE) exposure leads to persistent behavioral and neurobiological changes. The OFC plays a crucial role in reward evaluation and decision-making and is particularly vulnerable to ethanol's neurotoxic effects. One measure of behavioral flexibility is reward devaluation, which assesses an individual's ability to adapt to changes in reward value. Impairments in this domain, often observed following AIE, are linked to the development of habitual behavior. Previous research has demonstrated that AIE suppresses expression of choline acetyltransferase (ChAT) in the nucleus basalis of Meynert (NbM) and reduces vesicular acetylcholine transporter (VAChT) expression in the OFC, suggesting deficits in cholinergic signaling. Enhancing cholinergic tone may reverse these AIE-induced deficits. Galantamine, a cholinesterase inhibitor used clinically to treat Alzheimer's Disease and Related Dementias, has shown promise in restoring cholinergic markers following AIE.
Rats were trained to lever press on a Fixed Ratio schedule for 3 days, then a Random Interval-30 for 2 days, and followed by a Random Interval-60 schedule for 4 days. Rats received either banana or chocolate flavored sucrose pellets during these training sessions. Reward was devalued by a sensory-specific satiation procedure in which rats received access to either the same training flavor for devaluation or a novel flavor ad libitum before an extinction session.Behavior during the extinction session revealed that female saline-treated AIE rats did not decrease responding to the devalued flavor displaying habitual behavior, whereas female galantamine-treated AIE rats and saline-treated control rats showed the traditional suppression of lever pressing for the devalued flavor displaying goal directed behavior. However all male rats, regardless of Exposure and Drug treatment, did not decrease responding to the devalued flavor displaying habitual behavior
ChAT staining was conducted in the NbM region. Preliminary data shows that Galantamine recovered AIE induced suppression of ChAT cells in the NbM. These results suggest that Galantamine rescue AIE-induced impairments in behavioral flexibility by enhancing cholinergic signaling in female rats.

Disclosures: A. Roy: None. **L.M. Savage:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.06/FF5

Topic: H.08. Drugs of Abuse and Addiction

Support: Ciencia de Frontera 2023 (CF-2023-G-893)

Title: Effects of resveratrol on anxiety- and depressive-like behavior in a murine model of binge drinking

Authors: *D. GARCÍA GUERRERO[1], N. L. HERRERA LOZA[1], J. LÓPEZ BARBOSA[1], A. Y. GALVEZ-CONTRERAS[1], O. GONZALEZ-PEREZ[2], Y. RUVALCABA DELGADILLO[1], M. S. LUQUIN DE ANDA[1], R. E. GONZALEZ-CASTAÑEDA[1];
[1]Univ. de Guadalajara, Guadalajara, Mexico; [2]Psicologia/University of Colima, Colima, Mexico

Abstract: Alcohol abstinence after chronic consumption produces anxiety and depressive behaviours related to increased cellular oxidative stress. Resveratrol has been shown to improve anxiety- and depressive-like behaviours in stress models through its antioxidant properties. However, the effects of chronic resveratrol treatment on anxiety- and depressive-like behaviours in a binge-drinking model in juvenile mice have not been evaluated. Here, we aimed to investigate whether chronic resveratrol treatment can ameliorate anxiety- and depressive-like behaviours in a binge-drinking model in juvenile mice. Male C57BL/6J mice (35 days old) were used. To model binge-like alcohol consumption, we employed a modified Drinking in the Dark (DID) protocol: 3 h after lights went off, ethanol-exposed mice had unrestricted access to a 20% (v/v) ethanol solution for 4 h/day over 5 consecutive days. Control mice received only water under the same conditions. Body weight and food intake were recorded daily throughout this period. The following day, animals were given resveratrol (300 mg/kg, p.o.) or vehicle (0.5% carboxymethylcellulose) once daily for 21 days. On the last day of treatment, anxiety- and depressive-like behaviours were assessed using the elevated plus maze (EPM) and splash test (ST), respectively. Ethanol intake remained consistent throughout the exposure period in the alcohol-exposed group. Notably, despite no significant changes in body weight, alcohol exposure was associated with reduced food intake and increased liquid consumption compared with the control group. No significant differences were observed between groups in either the EPM or ST. However, resveratrol treatment significantly increased total grooming duration in the ST in ethanol-exposed mice compared to untreated ethanol-exposed animals. No significant differences were observed in any of the remaining variables.

Disclosures: D. García Guerrero: None. **N.L. Herrera Loza:** None. **J. López Barbosa:** None. **A.Y. Galvez-Contreras:** None. **O. Gonzalez-Perez:** None. **Y. Ruvalcaba Delgadillo:** None. **M.S. Luquin de Anda:** None. **R.E. Gonzalez-Castañeda:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

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Program #/Poster #: PSTR028.07/FF6

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant 5R01DA023281-14

Title: Refining Rodent Model of Comorbid Alcohol Use Disorder and Post-traumatic Stress Disorder

Authors: *K. KEALOHA[1], L. TOLL[2];
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Abstract: Alcohol use disorder (AUD) and mental health disorders like depression and anxiety are positively correlated. Severe anxiety can instigate self-medication with alcohol or other substances, and alcohol withdrawal increases corticotropin-releasing factor (CRF) in the amygdala. This reciprocal relationship leads to a high comorbidity of AUD and post-traumatic stress disorder (PTSD). We model this comorbidity through female and male adult Sprague Dawley rats by combining a noncontingent drinking model and the single-prolonged stress (SPS) paradigm. In this study, we utilize various mixed ethanol-sucrose solutions within a short-access voluntary drinking apparatus to establish AUD-like rodent profiles. PTSDs-like profiles are defined by increases in anxiety-like behaviors and fluctuations in consummatory and appetitive behaviors towards sucrose. These experiments aim to increase the translational value of rodent models of comorbid AUD-PTSD.

Disclosures: K. Kealoha: None. **L. Toll:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.08/FF7

Topic: H.08. Drugs of Abuse and Addiction

Title: Alcohol Exposure Duration and Drinking Continuity Shape Conflict Behavior in Mice

Authors: *D. I. TERRAZAS, M. MINJARES, O. TORRES, R. J. FLORES GARCIA;
Psychology, Univ. of Texas at El Paso, El Paso, TX

Abstract: Alcohol use disorder is characterized by continued drinking despite harmful consequences, suggesting altered integration of reward and threat signals during decision-making. Approach-avoidance conflict resolution depends on balancing reward seeking and threat avoidance; however, how alcohol exposure alters this process remains poorly understood. To address this gap, we examined how alcohol exposure duration and drinking continuity affect approach-avoidance conflict in mice across three experiments using intermittent home-cage two-bottle-choice drinking. C57BL/6J mice were assigned to either a water-only control group or an alcohol group with five days of alcohol access and two alcohol-free days per week. Experiment 1 assessed chronic alcohol exposure using escalating ethanol concentrations (3%, 6%, 12%, 20%), followed by four weeks at 20% ethanol and continued access during testing. Experiment 2 assessed chronic exposure without continued drinking using five weeks of 20% ethanol followed by abstinence during testing. Experiment 3 assessed shorter exposure using one week of 20% ethanol with continued access during testing. All mice were then tested in a platform-mediated

approach-avoidance conflict task. Mice first underwent five days of reward training, learning to nosepoke for a 50% Ensure reward during a light cue across 30 daily trials. They then completed five days of conflict training, in which a 30-s tone co-terminated with a mild 2-s footshock and was presented with the reward-predictive cue at varying overlaps, generating five trial types: light-only, tone-only, full overlap, light-then-tone, and tone-then-light. In partial-overlap trials, the second cue began 15 s later. Footshock was avoidable by stepping onto a platform. Mice then received three days of light-only training with 100% Ensure, followed by five days of conflict testing. In Experiment 1, alcohol-exposed and control mice showed similar reward-seeking during reward and conflict training. However, alcohol-exposed mice showed reduced responding during initial 100% Ensure sessions, normalizing by day 3, and again showed reduced reward-seeking when conflict was reintroduced. These effects were absent in Experiments 2 and 3, where alcohol-exposed and control mice behaved similarly. Thus, approach-avoidance deficits emerged only after chronic escalating alcohol exposure with continued access during testing, suggesting that prolonged exposure and continued drinking are required. Together, these findings indicate that alcohol exposure alters approach-avoidance conflict resolution, and future studies will examine the neural basis underlying these effects.

Disclosures: D.I. Terrazas: None. **M. Minjares:** None. **O. Torres:** None. **R.J. Flores Garcia:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.09/FF8

Topic: H.08. Drugs of Abuse and Addiction

Title: The Effect of Context and Alcohol on Habitual and Goal-Directed Behavior in Rats

Authors: *K. CAGNEY[1], J. NERZ[1], C. PISKURICH[1], S. MILLAR[1], K. J. LEISING[2];
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Abstract: Alcohol consumption can facilitate the transition of operant behavior from goal-directed to habitual, demonstrated through insensitivity to outcome devaluation. This result is relevant to alcohol use disorder, in which alcohol seeking and consumption often persist despite experience with their adverse effects (i.e., outcome devaluation). Studies using non-drug reinforcers have shown that habits may revert to goal-directed actions following a context change. However, little is known about the extent to which habits acquired with alcohol as the reinforcer transfer across contexts. The current study examined the role of context on the expression of behavior (lever pressing) as an action or habit with ethanol or sucrose as the reinforcer. For each experiment, subjects were forty-eight male (n = 24) and female (n = 24) Long-Evans rats aged greater than 90 days, and one response was minimally trained (R1; an action) in one context (A), and another response was extensively trained (R2; a habit) in a different context (B). Subjects were assessed for sensitivity to outcome devaluation (via sensory-

specific satiety) in the same context the response was trained in (R2 in B), a different familiar context (the context the other response was trained in [R2 in A]), or a novel context (R2 in C). Inconsistent with previous research, lever pressing trained as a habit and reinforced with alcohol continued to be expressed as such in the same (B) or different contexts (A and C). Results suggest that non-contextual stimuli, including the response manipulandum or ethanol-associated cues, influenced the expression of habitual behavior.

Disclosures: K. Cagney: None. **J. Nerz:** None. **C. Piskurich:** None. **S. Millar:** None. **K.J. Leising:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.10/Web Only

Topic: H.08. Drugs of Abuse and Addiction

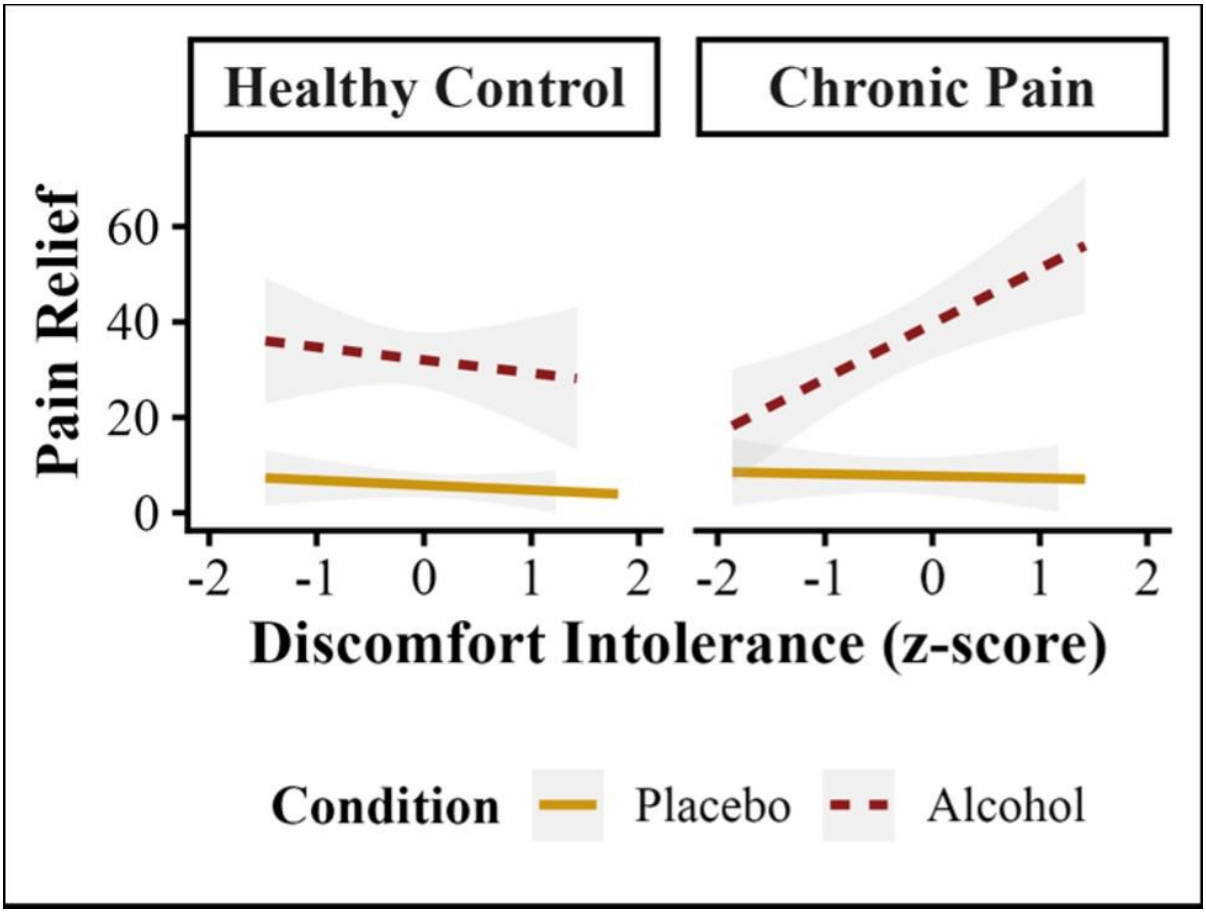
Support: NIH Grant R21AA026805

Title: Intolerance to discomfort moderates the subjective pain-relieving effects of alcohol in people with chronic pain

Authors: *O. D. COSTA[1], J. BOISSONEAULT[2];
[1]Anesthesiol., Univ. of Minnesota - Twin Cities, Minneapolis, MN; [2]Anesthesiol., Univ. of Minnesota, Minneapolis, MN

Abstract: Alcohol is acutely analgesic. Many individuals report using alcohol to self-manage pain, leading to increased risk for alcohol-related consequences. Yet, mechanisms underlying individual differences in perceived pain relief after drinking are not well understood. Discomfort intolerance (DI), or the ability to tolerate discomfort/pain, may contribute to the negative reinforcing effects of alcohol use in the context of pain, increasing risk for alcohol-related consequences.The study consisted of 48 non-problem drinkers, 19 of whom had chronic jaw pain. All participants consumed a placebo (target BrAC: 0.00g/dL) or an alcohol beverage (target BrAC: 0.08g/dl) in a within-subjects design. Following pressure algometry at the masseter, participants rated their perceived pain relief. Participants completed the Discomfort Intolerance Scale (DIS). A linear mixed-effects model examined beverage condition, DI and group as predictors of pain relief.There was a significant main effect of beverage condition ($b = 35.34$, $p<.001$), such that participants reported greater pain relief under alcohol than placebo. In addition, higher discomfort intolerance predicted greater alcohol-induced pain relief ($b=14.72$, $p<0.001$). Overall, there were no differences between the chronic pain and healthy control groups in discomfort intolerance ($t(0.835)) =27.1$, $p=0.411$). A significant three-way interaction emerged between beverage condition, discomfort intolerance, and group ($b = 8.25$, $p=0.04$), such that higher discomfort intolerance predicted higher alcohol-induced pain relief in the chronic pain group.These findings suggest that, among individuals with chronic pain, those with higher

discomfort intolerance maybe more sensitive to alcohol-induced pain relief. Additionally, alcohol intake may attenuate negative affect associated with discomfort intolerance in this population. This raises concerns about increased risk for harmful drinking behaviors and underscores the importance of tailored approaches to pain management.



Disclosures: O.D. Costa: None. **J. Boissoneault:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.11/FF9

Topic: H.08. Drugs of Abuse and Addiction

Support: Dartmouth College Coulter Scholars Funding

Title: Investigating the effects of adolescent alcohol exposure on cognitive flexibility in mice using a novel rule-shifting task

Authors: *A. SHANG[1], Y. PENA[2], K. M. NAUTIYAL[2];
[1]Psychological & Brain Sci., [2]Neurosci., Dartmouth Col., Hanover, NH

Abstract: Despite public-health efforts, alcohol use and abuse are still common among high school and college-aged youth. Adolescence is a critical period during which the brain undergoes rapid structural and neurochemical maturation. Exposure to alcohol at this vulnerable stage can redirect normal developmental trajectories, resulting in persistent behavioral deficits and long-lasting neurochemical alterations. Indeed, some previous rodent studies have shown that adolescent alcohol exposure (AAE) can induce deficits in cognitive flexibility. Using rodent paradigms, we aim to bridge significant knowledge gaps regarding pharmacological interventions capable of reversing adverse effects caused by AAE. To this end, we have developed a novel rule-shifting task (RST) to assess cognitive flexibility in mice. Using operant touch-screen chambers (Bussey-Saksida, Lafayette Instruments), we trained animals on four rules that span two dimensions: image dimension (image 1 correct or image 2 correct) and side dimension (left side correct or right side correct). In a first cohort (n=12), healthy C57 mice spent an average of 14 days learning the four rules (2-5 sessions per rule). During the testing period, they achieved an average of 5-10 rule shifts per 60-minute testing session. To follow up on this, another cohort of mice was exposed to AAE. Periadolescent mice (n=14, PN 28-29) were administered ethanol via intragastric infusions of 4mg/kg on a 2-day on/2-day off schedule. Behavioral testing with RST is underway to assess the effects of AAE on task performance. We anticipate that AAE mice will exhibit an increase in the number of days to learn each rule and fewer rule shifts per testing session. Follow-up studies will probe potential pharmacological interventions for the persisting AAE phenotype. Initial studies show that healthy control mice significantly increased accuracy in task performance 24 hours after 3 mg/kg psilocybin treatment. Ultimately, our studies aim to understand the persistent behavioral deficits resulting from exposure to high levels of alcohol during adolescence. Understanding the behavioral and neural mechanisms can help in developing target behavioral and pharmacological interventions.

Disclosures: A. Shang: None. **Y. Pena:** None. **K.M. Nautiyal:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.12/FF10

Topic: H.08. Drugs of Abuse and Addiction

Support: R01 1R01AA029386-01A1 (HJL)

Title: Context-Dependent Alcohol Seeking Differs by Sex, History of Alcohol Dependence, and Behavioral Modification Method in Rats

Authors: *T. SIMMONS[1], A. PISHARODI[1], A. ANDREWS[1], J. CHAN[1], J. BIJU[1], K. BAJAJ[1], R. GONZALES[3], M. H. MONFILS[4], H. J. LEE[2];

[2]Psychology Dept, [1]Univ. of Texas at Austin, Austin, TX; [3]Pharmacol., The Univ. of Texas at Austin, Austin, TX; [4]Dept. of Psychology, Univ. of Texas At Austin, Austin, TX

Abstract: Purpose: Cues associated with alcohol consumption can trigger relapse after abstinence through context-induced renewal of extinguished alcohol-seeking behavior. Retrieval-extinction involves brief cue-induced memory reactivation before extinction to disrupt reconsolidation of cue-associated memories. Although retrieval-extinction reduces reinstatement and spontaneous recovery of drug-seeking, its ability to attenuate context-induced renewal of alcohol-seeking remains unclear. We tested whether retrieval-extinction reduces renewal of cue-elicited alcohol-seeking in rats with a history of alcohol dependence.**Methods:** Long-Evans rats underwent voluntary alcohol consumption followed by chronic ethanol-vapor or air exposure. Animals were trained in a Pavlovian conditioning paradigm in which a light cue predicted ethanol availability in Context A. Extinction training (light-empty sipper) occurred in Context B under one of three conditions: standard extinction, no retrieval-extinction (brief context exposure 1 h before extinction), or retrieval-extinction (single light presentation 1 h before extinction). Alcohol-seeking (sipper contact) was assessed during long-term memory (LTM) testing in Context B and renewal testing in Context A.**Results:** Females (n = 54) and males (n = 56) exhibited distinct patterns of context-induced renewal following extinction, no-retrieval, and retrieval-extinction procedures. In females, Air- and Vapor-exposed animals in the Extinction condition showed renewal (Air: $p = 0.030$; Vapor: $p = 0.013$). In the No Retrieval condition, Air-exposed females showed renewal ($p = 0.008$), whereas Vapor-exposed females did not ($p = 0.31$). In the Retrieval condition, Vapor-exposed females showed renewal ($p = 0.043$), whereas Air-exposed females did not ($p = 0.050$). In males, Air-exposed animals in the Extinction condition showed renewal ($p = 0.048$), whereas Vapor-exposed animals did not ($p = 0.66$). In the No Retrieval condition, neither Air- nor Vapor-exposed males showed renewal ($ps > 0.05$). In the Retrieval condition, Vapor-exposed males showed renewal ($p < 0.001$), whereas Air-exposed males did not ($p = 0.066$).**Conclusion:** Retrieval-extinction did not reliably prevent context-induced renewal of alcohol-seeking. Although renewal was attenuated in Air males and marginal in Air females, it persisted in Vapor-exposed males and females. Unexpectedly, renewal was absent in both Air and Vapor male no-retrieval groups and in Vapor no-retrieval females, demonstrating important sex- and dependence-related differences in contextual relapse-like responding following extinction.

Disclosures: T. Simmons: A. Employment/Salary (full or part-time):; University of Texas at Austin. **A. Pisharodi:** None. **A. Andrews:** None. **J. Chan:** None. **J. Biju:** None. **K. Bajaj:** None. **R. Gonzales:** A. Employment/Salary (full or part-time):; University of Texas at Austin. **M.H. Monfils:** A. Employment/Salary (full or part-time):; University of Texas at Austin. **H.J. Lee:** A. Employment/Salary (full or part-time):; University of Texas at Austin.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.13/FF11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH grant AA028861

Title: Alcohol-induced morphological changes in mPFC neurons that regulate alcohol seeking

Authors: *Z. CHANG[1], L. VU[2], S. RODRIGUEZ[3], S. KROENER[4];
[1]The Univ. of Texas at Dallas, Richardson, TX; [2]Univ. of Texas at Dallas, Richardson, TX; [3]Univ. of Texas Dallas, Plano, TX; [4]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas Sch. of Behavioral and Brain Sci., Richardson, TX

Abstract: Alcohol use disorder (AUD) is characterized by escalating, compulsive alcohol seeking driven by progressive neuroadaptations in corticolimbic circuits. The medial prefrontal cortex (mPFC) is a critical locus, where the prelimbic (PL) and infralimbic (IL) subregions exert opposing control over relapse through divergent projections to the basolateral amygdala (BLA). PL→BLA pathways promote cue-driven drug seeking, while IL→BLA pathways facilitate extinction and suppress relapse. Chronic intermittent ethanol (CIE) disrupts mPFC executive function and alters glutamatergic transmission, but how these adaptations differ across projection-defined neuronal populations remains unclear. We used a combinatorial viral approach to selectively label PrL and IL pyramidal neurons projecting to the BLA, combined with confocal microscopy and Imaris-based 3D reconstruction. Mice received retrograde AAV-Cre into BLA and Cre-dependent Ruby2 into mPFC, labeling both IL and PL projection neurons. Mice were divided into 5 groups (3mo EtOH/sucrose, CIE+3mo EtOH, 3wk EtOH/sucrose), underwent abstinence and cue-induced reinstatement, then were perfused for morphometric and immunohistochemical analyses of spine density, head diameter, volume, and GluA1 AMPA receptor occupancy. CIE escalated ethanol self-administration, validating our model. Short-term ethanol increased spine density and head diameter in PrL→BLA neurons, while IL→BLA neurons showed reduced density and a shift toward immature morphologies. Long-term CIE selectively reduced IL→BLA spine density and induced hypertrophy. GluA1 analyses revealed a double dissociation: short-term ethanol upregulated GluA1 occupancy at IL→BLA synapses while reducing per-spine GluA1 in PrL→BLA neurons. Ethanol produces bidirectional, circuit-specific synaptic remodeling in mPFC→BLA neurons in an exposure- and subregion-dependent manner.

Disclosures: Z. Chang: None. **L. Vu:** None. **S. Rodriguez:** None. **S. Kroener:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.14/FF12

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH R01 CA284075

Title: The role of 15-lipoxygenase in a mouse model of alcohol use disorder

Authors: *A. LIN[1], Y. DONG[1], C. MILIANO[1], S. GITLIN[1], G. ROBBINS[2], A. GREGUS[3], M. W. BUCZYNSKI[4];
[1]Neurosci., Virginia Tech., Blacksburg, VA; [2]Neurosci., Virginia Tech., Roanoke, VA; [3]Dept. of Neurosci., Virginia Tech., Blacksburg, VA; [4]Sch. of Neurosci., Virginia Polytechnic Inst. and State Universit, Blacksburg, VA

Abstract: Alcohol use disorder (AUD) is characterized by a continuing cycle of excessive alcohol use, withdrawal, and preoccupation with alcohol that produces adverse consequences in the individual's life. Currently, there are three FDA-approved medications to treat AUD; however, the high rate of relapse highlights the need to develop additional treatments. Our previous research identified a correlative role for the pro-inflammatory 12/15-lipoxygenase (12/15-LOX) pathway, as 12/15-LOX metabolites predicted alcohol craving in AUD patients. The present study aims to investigate the potential mechanistic role of 12/15-LOX signaling in AUD. In the present study, we used the chronic intermittent ethanol vapor - two-bottle choice (CIE-2BC) paradigm that mimics different phenotypes in AUD in mice. For this model, male C57BL/6 mice undergo multiple CIE-2BC cycles, with each cycle consisting of one week of CIE (4 days, 16 hours per day) followed by one week of 2BC (5 days, 2 hours per session, 15% ethanol). Alcohol dependence was established in these mice after 4 cycles of CIE-2BC and validated using multiple behavioral output measures, including escalation of alcohol intake from the 2BC test, withdrawal-induced pain-like behavior, increased consumption following alcohol deprivation effect, and compulsive-like drinking behavior from the quinine adulteration. Following treatment with a selective 15-LOX inhibitor (ML351, 0 to 50 mg/kg, IP), we observed a treatment-dependent reduction in the alcohol deprivation effect and compulsive-like drinking behavior. We saw no significant difference in withdrawal-induced pain-like behavior or the escalation of alcohol intake. To investigate if elevated 15-LOX signaling is sufficient to induce behavioral features of dependence, we plan to evaluate the same behavioral output measures during non-dependent alcohol 2BC following intracerebral ventricular administration of 15-HETE (a pro-nociceptive 15-LOX metabolite). Collectively, these findings confirm that 12/15-LOX contributes to the development of AUD, prompting future investigations of this pathway as a potentially viable drug target for treatment.

Disclosures: A. Lin: None. **Y. Dong:** None. **C. Miliano:** None. **S. Gitlin:** None. **G. Robbins:** None. **A. Gregus:** None. **M.W. Buczynski:** None.

Poster

PSTR028: Cognitive and Behavioral Consequences of Alcohol Exposure

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.15/FF13

Topic: H.08. Drugs of Abuse and Addiction

Title: Examining the effects of adolescent alcohol exposure on ethanol-seeking behavior

Authors: *S. PATTERSON[1], K. M. NAUTIYAL[2];
[1]Psychological and Brain Sci., [2]Neurosci., Dartmouth Col., Hanover, NH

Abstract: Alcohol use during adolescence has been associated with persisting behavioral deficits including an increased risk of pathological alcohol consumption. Over 2.9 million adolescents in the US have participated in binge drinking in the past year, making this a large public health concern. In rodents, high levels of alcohol exposure during adolescence is associated with increased impulsivity, and decreased behavioral flexibility and working memory. The present study examined whether ethanol exposure during adolescence alters subsequent ethanol consumption and motivation to obtain ethanol in mice.We administered binge-like levels of ethanol (4g/kg) via oral gavage during either adolescence (PND 21-37) or adulthood (PND 80-96) in a 2 day on 2 day off schedule. Mice were subsequently maintained for 5 weeks in a washout period where they were not exposed to alcohol. Following the washout period, animals were given 24-hour home-cage access to both a 9% EtOH 2% Sucrose solution and water for two weeks. Animals were then trained to lever press for a 9% EtOH 2% Sucrose solution in overnight operant conditioning paradigms, including Fixed Ratio (FR) and Progressive Ratio (PR) schedules.On the FR-20 paradigm, adolescent-exposed mice showed no difference in behavior. However, ethanol-treated adults showed reduced lever pressing for ethanol in sucrose. On a PR+3 schedule, performance was similar across all groups regardless of treatment age, suggesting comparable levels of effort to obtain ethanol reinforcement. Preliminary sex differences were observed with a trend towards greater responding for ethanol on both the FR and PR schedules in ethanol-exposed adolescent females. A similar trend was seen in ethanol-treated adult females only on the PR schedule.Overall, our findings suggest that developmental timing of exposure may differentially influence later ethanol-seeking behaviors. The observed trend toward increased responding among ethanol-treated adolescent females raises the possibility that adolescence represents a sensitive developmental period for long-term alterations in alcohol-related reward processing in a sex-specific manner. Additional analyses about the drinking patterns throughout the night and larger sample sizes are needed to further clarify the effects of adolescent versus adult treatment on later ethanol-seeking behavior.

Disclosures: S. Patterson: None. **K.M. Nautiyal:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.01/FF14

Topic: I.05. Working Memory

Title: Investigating the Role of Prefrontal Somatostatin Interneurons in Functionally Specialized Afferent Pathways During Spatial Working Memory

Authors: *M. HSIANG[1,2,3], A. BAUMAN[2,3], H. A. TEJEDA[4], D. A. KUPFERSCHMIDT[4], J. A. GORDON[2,3];
[1]Brown Univ., Providence, RI; [2]Columbia Univ., New York, NY; [3]New York State Psychiatric Inst., New York, NY; [4]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Afferent pathways from ventral hippocampus (vHPC) and mediodorsal thalamus (MD) to medial prefrontal cortex (mPFC) are functionally specialized for distinct aspects of spatial working memory (SWM) (encoding and maintenance, respectively). To uncover the neural mechanisms underlying this specialization, we investigated how these long-range inputs engage subpopulations of mPFC somatostatin interneurons (SST-INs), a cell type critical for gating afferent information and mediating spatial encoding. We first employed anterograde transsynaptic tracing to characterize the monosynaptic connectivity of these pathways. Anatomically, we discovered that the vHPC targeted a smaller proportion of mPFC SST-INs than the MD, with a preference for the ventral mPFC. However, these long-range inputs demonstrated higher-than-chance convergence onto individual mPFC SST-INs, suggesting a structural substrate for integrating hippocampal and thalamic signals. To assess functional activity of these populations during behavior, we used an intersectional strategy to express the calcium sensor GCaMP in input-defined mPFC SST-INs while mice performed an SWM task on a T-maze. In vivo fiber photometry revealed that while SST-IN activity was robustly modulated by the animal's velocity, it was not differentially modulated by the specific upstream input region. Finally, we tested the functional necessity of mPFC SST neuropeptide signaling in this cognitive behavior using conditional knockout mice and acute microinfusions of the SST receptor antagonist, cyclosomatostatin (c-SST). Crucially, neither local SST peptide ablation nor acute receptor antagonism impaired SWM learning or behavioral performance across short (10-second) or long (60-second) delays. Instead, c-SST administration selectively increased locomotion and reduced local network theta power in both the mPFC and vHPC on a linear track. Together, these findings demonstrate that the specialized functional contributions of the vHPC and MD pathways to spatial working memory operate independently of their anatomical targeting of mPFC SST-INs or the direct signaling role of the SST neuropeptide.

Disclosures: M. Hsiang: None. **A. Bauman:** None. **H.A. Tejeda:** None. **D.A. Kupferschmidt:** None. **J.A. Gordon:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.02/FF15

Topic: I.05. Working Memory

Title: Adolescent stress exacerbates prefrontal-dependent working memory deficits in a mouse model of SETD1A haploinsufficiency

Authors: *A. IKEGAMI[1,2], R. SIRMAUR[1,2], E. PARK[1,2], J. A. GOGOS[3,1], A. Z. HARRIS[1,2], J. A. GORDON[1,2];
[1]Psychiatry, Columbia Univ., New York, NY; [2]New York State Psychiatric Inst., New York, NY; [3]Mortimer B. Zuckerman Mind Brain and Behavior Inst., New York, NY

Abstract: Schizophrenia disrupts core cognitive functions including working memory, which depends on the prefrontal cortex (PFC) circuits. How genetic risk and environmental factors interact to produce persistent cognitive deficits remains unclear. Adolescence is a critical period for the PFC maturation and a window of heightened vulnerability to stress. We tested whether adolescent stress exacerbates cognitive deficits in mice with haploinsufficiency of *SETD1A*, a high-confidence schizophrenia risk gene encoding an epigenetic regulator of synaptic and neurodevelopmental gene programs. Male and female *Setd1a*$^{+/-}$ mice and wild-type (WT) littermates received either daily restraint stress or brief handling from postnatal day 28 to 42. Corticosterone (CORT) was measured during the stress period to assess hypothalamic-pituitary-adrenal (HPA) axis engagement (n=7-13 per group). A month later, mice were tested in a delayed non-match-to-sample T-maze task to assess spatial working memory (SWM) under increasing delay demands (n=13-14 per group). CORT levels were increased by stress in both *Setd1a*$^{+/-}$ and WT mice (rmANOVA, main effect of stress $p<0.0001$). SWM was impaired by stress and genotype, with main effects of genotype at 10s and 30s delays (rmANOVA, $p<0.005$) and a main effect of stress at 30s delays ($p<0.001$). The effects of stress were greater in *Setd1a*$^{+/-}$ mice compared to WT at 30s delay (genotype-by-stress interaction, $p<0.05$). Post-hoc comparisons showed that stressed *Setd1a*$^{+/-}$ mice performed significantly worse than both stressed WT mice and non-stressed *Setd1a*$^{+/-}$ mice at 30s delay. Time to acquisition was not impaired in any group. These findings demonstrate a gene-by-environment interaction in which the combination of *SETD1A* haploinsufficiency and adolescent stress impair SWM performance under higher working memory demand. They are consistent with a two-hit model in which stress during development disrupts PFC maturation in the context of *SETD1A* haploinsufficiency. Ongoing work will test whether this behavioral vulnerability is accompanied by altered PFC synaptic structure and disrupted PFC circuit activity during SWM task.

Disclosures: A. Ikegami: None. **R. Sirmaur:** None. **E. Park:** None. **J.A. Gogos:** None. **A.Z. Harris:** None. **J.A. Gordon:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.03/FF16

Topic: I.05. Working Memory

Title: Inhibition of mPFC VIP interneurons disrupts spatial working memory maintenance

Authors: *M. FRAZER;
Columbia Univ. Vagelos Col. of Physicians and Surgeons, New York, NY

Abstract: Working memory (WM) impairments are a hallmark of neuropsychiatric disorders and predict poor functional outcomes. The medial prefrontal cortex (mPFC) serves as a critical hub for WM. The contribution of mPFC inhibitory microcircuits remains incompletely understood. Vasoactive Intestinal Polypeptide-expressing Interneurons (VIP INs) disinhibit principal cells by targeting other interneurons, but their specific role in WM encoding, maintenance, and retrieval has not been established. To selectively silence VIP INs, we selectively expressed the inhibitory opsin ArchT in mPFC VIP-INs of adult male and female mice via Cre-dependent viral delivery (VIP-ArchT, n=6, VIP-tdTomato controls n=6). Optical inhibition was applied during discrete epochs corresponding to the encoding, maintenance, and retrieval phases of the spatial working memory T-maze task. Variable delay length (10s, 30s) was introduced to manipulate cognitive load. There was no effect of optical inhibition at 10s delays; however, under interleaved delay conditions imposing higher cognitive demand, a significant interaction between Group x Laser was detected during 30s delay periods (Two-way ANOVA, $p = 0.017$). Post-hoc analyses revealed impaired performance in ArchT-expressing mice when the mPFC was illuminated during the maintenance phase (Bonferroni's multiple comparisons test, $p = 0.014$). These results suggest VIP INs play a role in supporting memory maintenance during the delay period of a spatial WM task, particularly under cognitively demanding conditions.

Disclosures: M. Frazer: None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.04/FF17

Topic: I.05. Working Memory

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Title: Internal state dynamically gates task-specific attractor dynamics in mouse prefrontal cortex

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Abstract: Internal states such as motivation and task engagement influence cognitive functions. Working memory, which maintains information over time, is an essential component of cognition and is modulated by motivation. Here, we show motivational states modulated attractor dynamics that supported working memory. Combining population recordings from mouse medial prefrontal cortex (mPFC) with data-constrained recurrent neural network (RNN) modeling, we found task engagement selectively modulated attractor dynamics within a memory-maintenance subspace, while stimulus-evoked responses remained intact. Reverse-engineering the RNNs revealed that task engagement reorganized the dynamical landscape by stabilizing memory-specific attractors. Specifically, task engagement modulated interactions between neurons to change the attractor dynamics. Finally, gradual changes in behavioral engagement were predicted by continuous modulation of attractor geometry in RNNs and mPFC. Together, these results suggest that internal state modulate working memory function by controlling the dynamical regime of mPFC circuits, providing a mechanistic link between internal state, neural dynamics, and cognitive function.

Disclosures: Y. Osako: None. **T. Buschman:** None. **M. Sur:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.05/FF18

Topic: I.05. Working Memory

Support: NIH R01NS120987

Title: Dopaminergic modulation of prefrontal oscillations and D1 ensembles in working memory

Authors: *V. KILONZO[1], Y.-C. KIM[1], M. A. WEBER[1], A. BOVA[1], N. S. NARAYANAN[2];
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Abstract: Working memory is orchestrated by the prefrontal cortex (PFC), which supports persistent activity patterns as a mechanism for temporary storage, maintaining task-relevant information in the absence of external cues. Prefrontal dopamine facilitates the stabilization of prefrontal activity states by binding to D1 dopamine receptors (D1DRs). Prefrontal activity and dopamine signaling work in concert to regulate working memory, yet the mechanisms by which they cooperate are unclear. Advances in GPCR activation-based dopamine (GRAB DA) sensors that fluoresce at low dopamine concentrations enable temporally precise sampling of dopamine dynamics in the mouse PFC. To assess working memory, D1-cre mice were trained on a delayed non-match to position (DNMTP) working memory task and, once trained, underwent stereotaxic

surgery and injection of GRAB DA sensor variant gDA3m and Cre-dependent ChrimsonR into the PFC. Mice were also implanted with a combined optogenetic and multielectrode recording array to simultaneously record prefrontal dopamine dynamics via fiber photometry and prefrontal ensemble activity during the DNMTP task. After recording, prefrontal D1DR-expressing neurons were optogenetically tagged to identify putative D1DR neurons. We examined whether increasing delay intervals during the DNMTP task amplified prefrontal dopamine, as well as low-frequency oscillations that accompany optimal working memory performance. Furthermore, we investigated how prefrontal dopamine input contributes to oscillatory signatures of cognitive control, and neuron spiking activity associated with working memory. Our work highlights how neuromodulatory dopamine signals in the PFC engage specific D1DR populations to orchestrate neuronal activity and network rhythms underlying working memory.

Disclosures: V. Kilonzo: None. **Y. Kim:** None. **M.A. Weber:** None. **A. Bova:** None. **N.S. Narayanan:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.06/FF19

Topic: I.05. Working Memory

Title: Dorsal striatal dopamine dynamics across the sleep-wake cycle

Authors: *M. S. MCMURRIN[1], A. BOVA[2], M. SUMMERFIELD[3], R. LI[4], M. A. WEBER[2], G. F. BUCHANAN[1], N. S. NARAYANAN[1];
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Abstract: Sleep is an essential process and disruptions to sleep can have severe effects on daily life. Dopamine (DA) is a key driver in wakefulness, and DA dysregulation causes changes in sleep/wake. In Parkinson's disease (PD), when the number of DA neurons are reduced, most patients experience at least one comorbid sleep disorder such as insomnia, excessive daytime sleepiness, or restless leg syndrome (RLS). Dorsal striatal dopamine is implicated in sleep, but its moment-to-moment dynamics across sleep-wake states remain undefined. Clinically, several dopaminergic drugs treat both Parkinson's disease and sleep disorders, including Pramipexole, which is effective for PD and restless legs syndrome. Experimentally, manipulating dopamine neurons in the substantia nigra pars compacta or stimulating dopamine terminals in the dorsal striatum alters sleep-wake architecture in rodents. However, it is unknown how dorsal striatal dopamine fluctuates across natural sleep-wake cycles. We recorded dorsal striatum dopamine release dynamics with the genetically-encoded dopamine indicator dLight1.3virus throughout spontaneous sleep-wake cycles in mice. Our preliminary data show highest DA levels during wakefulness, less DA during non-rapid eye movement (NREM) sleep, and the lowest DA levels

during rapid eye movement (REM) sleep. We also recorded dLight dynamics in separate sessions after administration of pramipexole, a D2/D3 agonist at doses of 0.5mg/kg and 0.1mg/kg, and during startle events. This study will inform us about dorsal striatal DA dynamics during sleep and could provide insight into disrupted sleep in PD and RLS.

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Poster

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Program #/Poster #: PSTR029.07/FF20

Topic: I.05. Working Memory

Support: NINDS 2R01NS100849-06A1
NINDS 1RF1NS127809-01A1
NIH T32-NS007421

Title: Insight problem solving in Parkinson's disease

Authors: *C. HUNTER[1], B. E. YEAGER[2], A. I. ESPINOZA[1], V. MAGNOTTA[1], J. DAWSON[1], C. WEBER[1], J. F. CAVANAGH[3], E. UC[1], N. S. NARAYANAN[2]; [2]Neurol., [1]Univ. of Iowa, Iowa City, IA; [3]Dept. of Psychology, Univ. of New Mexico, Albuquerque, NM

Abstract: Creative problem solving is a unique and understudied cognitive process**,** defined as the capacity to generate novel and contextually appropriate solutions. A key component of creative problem solving is insight: a sudden reframing of a problem that allows an individual to escape a fixed interpretation and reach a non-obvious solution. Insight problem solving, like cognition more broadly, is impaired in Parkinson’s disease, with 80% of patients developing clinically significant cognitive symptoms within 20 years of diagnosis. While most cognitive research in Parkinson’s disease emphasizes attention and memory, the capacity to generate and apply new strategies is also important for daily functioning, and cognitive decline in Parkinson’s disease contributes to loss of independence, nursing home placement, and increased mortality. Yet the neural mechanisms of insight problem solving remain poorly understood. Midfrontal low-frequency oscillations in the theta (4-7 Hz) band support executive functions such as working memory and attention and are attenuated in Parkinson’s disease. This project tests the extent to which midfrontal theta rhythms support insight problem solving by studying a population with known deficits in these rhythms. We recruited individuals with Parkinson’s disease and healthy comparison participants from the University of Iowa Hospitals and Clinics. Participants completed an insight problem solving task, the compound remote associates task, while scalp EEG was recorded. We compared task performance (response time and accuracy)

between the Parkinson's disease and comparison cohorts and tested the relationship between theta power and performance within each group. We also assessed whether Parkinson's disease participants exhibited two neural signatures associated with insight solutions: a gamma burst around 300ms before response and an increase in alpha power 1.5s before response that decreased leading up to response. This work contributes to a framework connecting large-scale oscillatory dynamics and insight problem solving, offering a potential pathway toward developing neurophysiological markers and circuit-based interventions to support cognition.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

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Program #/Poster #: PSTR029.08/FF21

Topic: I.05. Working Memory

Support: NINDS R01NS120987

Title: The effect of acute methylphenidate on maternal velocity and latency to retrieve pups in postpartum mice

Authors: *M. M. CONLON[1,2], A. BOVA[2], M. A. WEBER[2], Y.-C. KIM[2], N. S. NARAYANAN[2];
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Abstract: Maternal care is required for offspring survival immediately following birth, and disruptions to maternal responsiveness, including those common in perinatal mood and anxiety disorders, can lead to adverse outcomes for both mothers and their children. There is a critical need to understand the neuronal organization underlying maternal behavior, which will enable a mechanistic understanding of how genetic, environmental, and neuropsychiatric factors disrupt maternal motivation. The medial prefrontal cortex (mPFC) is required for the appropriate sequencing of behavior. mPFC neuronal ensembles encode the temporal dynamics of maternal actions, and how dopaminergic modulation of these ensembles regulates maternal motivation, remains unknown. To probe the role of prefrontal dopamine in maternal behavior, we administered methylphenidate, a dopamine and norepinephrine reuptake inhibitor that preferentially increases dopamine in the prefrontal cortex, to postpartum wild type C57BL/6J dams. We administered either vehicle or 10 mg/ kg methylphenidate (i.p.), then assessed spontaneous maternal behaviors before performing pup retrieval testing. Pup retrieval testing consisted of removing one pup from the nest, placing it in the corner furthest from the nest, and allowing the dam to return it to the nest. Primary outcomes are latency to retrieve the pup and

retrieval success (retrieval or non-retrieval). Secondary outcomes include path efficiency to pup and maternal behavioral sequencing. Other analyzed behaviors include time spent on the nest of pups, nursing, licking or grooming pups, carrying pups, nest-building, self-grooming. Using markerless deep-learning pose estimation with DeepLabCut, we compared measures of velocity and approach kinetics. We studied the effects of methylphenidate on latency to retrieve pups, maternal velocity, and home cage maternal behaviors. Future studies will further interrogate prefrontal circuit mechanisms underlying these effects with the long-term objectives of defining how prefrontal circuits are involved in maternal motivation and ultimately identifying circuit-level biomarkers and therapeutic targets for postpartum mental health disorders.

Disclosures: M.M. Conlon: None. **A. Bova:** None. **M.A. Weber:** None. **Y. Kim:** None. **N.S. Narayanan:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

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Program #/Poster #: PSTR029.09/FF22

Topic: I.05. Working Memory

Support: NIH Gran PD200037

Title: Prefrontal D1 ensemble dynamics predict temporal control

Authors: *Y.-C. KIM[1], M. A. KENNEDY[2], V. KILONZO[1], Y. A. AYALA[3], C. I. PETKOV[3], N. S. NARAYANAN[4];
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Abstract: The prefrontal cortex is critical for temporal control of action, yet how distinct prefrontal cell types contribute to this process remains unclear. Prefrontal neurons expressing D1-type dopamine receptors (D1DRs) have been implicated in timing and related cognitive functions across humans, primates, and mice, suggesting that prefrontal D1 neurons directly encode internal estimates of elapsed time. We tested this idea by recording from human cingulate cortex during a timing task and from mouse medial frontal cortex during a fixed-interval task, in which mice timed responses across a fixed 12-second interval reinforced by reward. Using generalized linear models to rneuronal firing to time, we found that a substantial fraction of prefrontal neurons in both species exhibited time-related ramping activity. To capture population-level dynamics, we performed mesoscale 1-photon calcium imaging of prefrontal ensembles in freely behaving mice, extracting single-neuron activity with constrained nonnegative matrix factorization (CNMF-E). We decoded elapsed time from population activity using multiple cross-validated classifiers—including Bayesian, support-vector, and linear discriminant approaches. Elapsed time was robustly decoded, outperforming time-shuffled

controls, and principal component analysis revealed that this temporal information was largely captured by a ramping activity. We then compared genetically defined D1DR+ and CamKII+ pyramidal populations. While both represented elapsed time, D1DR+ ensembles showed distinct dynamics: trial-by-trial ramping slopes tracked the animals' responses. Complementary deep-learning analyses independently identify ramping as the dominant pattern of activity. These findings provide insight into prefrontal timing networks and have relevance for neuropsychiatric disorders such as ADHD, schizophrenia, and Parkinson's disease.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

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Program #/Poster #: PSTR029.10/FF23

Topic: I.05. Working Memory

Support: NIH Grant EY016407
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Title: Untangling sensory and mnemonic subspaces of working memory in the human cortex

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[2]Psych & CNS, [1]New York Univ., New York, NY; [3]Psychology Dept., The Ohio State Univ., Columbus, OH

Abstract: Working memory has traditionally been viewed as the stable maintenance of sensory representations through persistent neural activity. However, growing evidence suggests that working memory representations dynamically evolve to adapt to task demands. A major challenge in characterizing these dynamics with human neuroimaging has been untangling these multiplexed representations of sensory features and task rules that coexist within neural activity patterns. Here, we applied demixed Principal Component Analysis (dPCA) to fMRI data to isolate independent low-dimensional subspaces encoding stimulus location, task condition, and visualized the temporal dynamics during a spatial working memory task. Following an initial delay, participants received an auditory cue instructing them to either maintain a target location in memory or remap it 180° across the visual field. Using dPCA, we decomposed population activity into stimulus, task, and stimulus-task interaction components. Before the cue, target location representations remained stable within an early subspace, with the stimulus components explaining the majority of the variance and preserving a topological organization throughout the delay. In contrast, after the cue, variance explained by stimulus-task Interaction components increased, revealing a dynamic transformation of target location representations within a late subspace. These representational dynamics were visualized through reconstructed activation

maps in visual field space. In early visual cortex (V1), the transformation appeared as a gradual line-like transition from the original target location toward the remapped location, whereas in higher-order visual areas such as V3AB, activity shifted as a localized hotspot toward the remapped location. Furthermore, representational stability increased along the visual-to-parietal hierarchy during memory maintenance. In contrast, during remapping, later visual regions and early parietal regions showed pronounced dynamics in the representational subspaces. Together, these findings demonstrate that dPCA can successfully resolve the multiplexed dynamics of human working memory, revealing how sensory representations are transformed into task-relevant mnemonic codes across the cortical hierarchy.

Disclosures: Z. Lu: None. **H. Li:** None. **C.E. Curtis:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

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Topic: I.05. Working Memory

Support: NIH R01 EY-016407
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Title: Motor recruitment during visual working memory

Authors: *Z. DUAN[1], C. E. CURTIS[2];
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Abstract: While it is now widely accepted that visual encoding mechanisms for perception are recruited to support visual working memory, the format of our memories undergoes transformations depending on our task goals. Here, we test a new hypothesis that the motor mechanisms housed within the motor system are recruited during working memory to store prospective, memory-guided actions. We predict that such a motor recruitment involves transformations into memory-guided actions that naturally align with our body's mechanics and motor affordances. Human participants (N=16) were scanned with fMRI while they maintained the direction of random dot motion over a short delay. Afterwhich, they reported their memory by adjusting the angle of a freely chosen hand that was tracked using motion capture cameras. Interestingly, participants spontaneously selected the hand that optimized the biomechanical affordance. (e.g., reliably using the left hand for directions pointing towards the upper-right, and vice versa). We examined BOLD activity in frontoparietal circuits during the working memory delay — the period of sensory-to-motor transformation. Activity patterns revealed that the chosen effector could be decoded prior to movement from sensorimotor regions, including primary motor cortex (M1), dorsal pre-motor cortex (PMd), supplementary motor area (SMA), superior parietal lobe (SPL), and intraparietal sulcus (IPS). Remarkably, within each hand, we

could decode the specific directions of dot motion they maintained in these regions, similar to how we could decode them from the visual cortex. Further analyses revealed that the representation structure included information about both the hand used and the angle of the hand, and these motor components, when visualized in a lower-dimensional subspace, formed separable trajectories over the delay and memory-guided response. Rather than simply storing visual information in memory, the goal of working memory is to use memory to optimally prepare for future actions. These results demonstrate that the motor circuits maintain memory-guided, prospective motor affordances.

Disclosures: Z. Duan: None. **C.E. Curtis:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

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Topic: I.05. Working Memory

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NYUAD Global PhD Fellowship (WKHC)

Title: Resolving the paradox of visual cortices' role in working memory

Authors: *W. CHU[1,2], A. PAL[3,4], S. MARTINIANI[4,3], D. J. HEEGER[2,5], K. K. SREENIVASAN[1], C. E. CURTIS[2,5];
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Abstract: Persistent activity is the most established neural mechanism supporting working memory. The averaged univariate signal in human primary visual cortex (V1) rarely persists above the pretrial baseline, despite ample evidence that working-memory content can be decoded from multivariate activity. The apparent contradiction between the absence of persistent univariate activity and the presence of decodable memory representations has led many to conclude that V1 is not involved in working memory storage. Here, we reconcile these conflicting findings by carefully estimating delay-period activity in human V1 from three fMRI studies that successfully decoded spatial working memory content from V1. Leveraging population receptive field (pRF) mapping, we estimated BOLD responses in V1 voxels whose pRFs contained the memory target location (in-RF) and compared these to responses in voxels whose pRFs overlapped a corresponding control location positioned 180° opposite the target, where no stimulus or memory target was present (out-RF). Across all three datasets, the in-RF

response returned to baseline following a transient increase in BOLD activity time-locked to the visual target onset, while the out-RF response dipped below baseline. The below-baseline suppression was widespread and occurred for all voxels that did not overlap the target. The amplitude of BOLD activity in the in-RF voxels was greater than in the out-RF voxels throughout the memory retention interval, demonstrating that working memory content modulated V1 activity. While V1 activity during working memory delays did not exhibit persistent activity in the classic sense, increases in activity were found in the population of voxels which represented the target location relative to voxels that did not. Moreover, we show that these differences explain exactly why one can decode working memory information from V1. Finally, using a three-layer (V1, V4, FEF) hierarchical neural circuit model we identify feedback as a necessary mechanism to reproduce V1's empirical dynamics. According to the model, persistent activity in FEF is fed back to visual cortex (V4 & V1), inducing a difference in neural activity within populations whose RFs match and do not match the memoranda's location, but without an overall increase in persistent activity above baseline. Together these results reveal how selective V1 activity supports robust decoding of working memory features without persistent firing, explaining V1's seemingly paradoxical role in working memory.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

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Title: Does transcutaneous auricular vagus nerve stimulation (taVNS) modulate the balance between interoceptive and exteroceptive attention during working memory?

Authors: *G. TAN[1], T. KARDASHINA[2], H. WANG[4], P. DEMAREST[5], P. BRUNNER[6], J. GORLEWICZ[7], E. C. LEUTHARDT[3];
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Abstract: Transcutaneous auricular vagus nerve stimulation (taVNS) has been shown to improve working memory performance, but the physiological mechanism underlying this cognitive benefit remains unclear. This mechanistic gap limits the targeted use of taVNS as a cognitive intervention. Successful working memory requires efficient maintenance of task information while regulating sensory input from both the external environment and the body. Improved working memory could therefore reflect increased arousal, enhanced processing of task-relevant stimuli, and reduced interference from internal bodily signals. Distinguishing among these possibilities is important because each mechanism predicts a different cognitive context in which taVNS may be most effective.
The vagal afferents convey interoceptive signals from the body and engage brainstem-cortical systems involved in arousal and attention. We therefore ask whether taVNS improves working memory by modulating the balance between interoceptive and exteroceptive attention. To answer this question, we quantified stimulus-evoked potentials (SEPs) and heart-evoked potentials (HEPs) during an N-back working memory task and compared these responses between active taVNS and sham stimulation.
We recorded eye movements, electroencephalogram (EEG), and electrocardiogram (ECG) from 20 healthy participants who completed N-back tasks during baseline, sham stimulation, and active taVNS sessions. We developed a template-matching approach to separate EEG components associated with stimulation artifacts, eye movements, and cardiac activity. We quantified SEPs and HEPs at the sensor level and estimated their cortical sources. We assessed taVNS effects on SEPs and HEPs using time-resolved statistical mapping, threshold-free cluster enhancement, and cluster-based permutation testing. We further explored whether SEP and HEP morphology were associated with working memory performance.
We found robust stimulus-evoked responses and detectable heart-evoked responses during the N-back task. Active taVNS reduced SEPs relative to sham. HEP modulation was weaker but showed a similar direction, with reduced cardiac-related cortical responses during active taVNS. These findings suggest that taVNS does not simply amplify sensory responses during working memory. Instead, active taVNS may shift the balance between interoceptive and exteroceptive attention toward a more efficient task-maintenance state.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

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Program #/Poster #: PSTR029.14/FF27

Topic: I.05. Working Memory

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Title: Gradients of function between sensory drive and working memory regions in human frontal cortex

Authors: *T. POSSIDENTE[1], V. TRIPATHI[2], S. LEE[1], D. C. SOMERS[1];
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Abstract: The coordination of sensory processing and working memory (WM) is fundamental to cognition. Spatial organization of sensory processing and WM is known to be broadly distributed across the cortex (e.g., Christophel et al. 2017; Silver & Kastner, 2009), but finer-scale organization at the interfaces between these functions remains understudied and has important implications for basic and translational research. Although the notion of sharp parcellations of cortex into distinct functional modules dominate the field, a growing body of works support graded changes in function and anatomy in some cortical zones. Based on this and potential advantages of gradient organizational structure in frontal cortex, we hypothesized that sensory-WM interfaces in the frontal cortex are gradient-like, not boundary-like. To test this hypothesis, we examined human visual and auditory WM task fMRI data (N=20) and compared subject-level boundary and gradient models of change in function across five candidate frontal cortical regions. Strong group- and individual-level evidence for visual and auditory sensory-WM gradients was observed in pre-supplementary motor area, inferior lateral frontal cortex, and anterior insula, with 74.6% (203/272) of comparisons favoring gradient-like models over boundary-like models. Only 11.8% of comparisons favored boundary-like models, with 13.6% being inconclusive. Both group and individual analyses revealed that activations for sensory drive and WM activation overlapped but were offset from each other. Sensory-WM gradients were largely in the rostral-caudal direction, mirroring the rostral-caudal theory of abstraction in the frontal cortex, but on a finer scale. These results provide evidence that sensory processing and WM regions in frontal cortex are not distinct with sharp boundaries at their interfaces but instead functionally bleed into each other to form local rostral-caudal sensory-WM gradients. We speculate that these gradients may allow for 1) efficient interfacing between sensory and WM representations, and/or 2) fine-grained, task-dependent shifting between bottom-up sensory and top-down WM influences.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

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Program #/Poster #: PSTR029.15/FF28

Topic: I.05. Working Memory

Title: Domain-specific neurobiological strategies of cognitive reserve: A resting-state EEG network study in older adults

Authors: *O. KATAYAMA[1,2], R. YAMAGUCHI[1], D. YAMAGIWA[1], S. AKAIDA[1], T. SHIMODA[1], C. NAKAJIMA[1], A. KAWAKAMI[1,3], T. KODAMA[2], H. SHIMADA[1,4,5]; [1]Natl. Ctr. for Geriatrics and Gerontology, Obu, Aichi, Japan; [2]Kyoto Tachibana Univ., Kyoto City/Kyoto, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan; [4]Nagoya Univ., Nagoya, Japan; [5]Shinshu Univ., Matsumoto, Japan

Abstract: While age-related cognitive decline follows a universal trajectory, its manifestations across specific domains—including episodic memory, executive function, and processing speed—are remarkably heterogeneous. This divergence stems from distinct neurostructural alterations mediating these functions. This study aimed to determine whether electroencephalography (EEG)-derived brain networks underlying cognitive reserve—the capacity to maintain cognitive function beyond what is predicted by brain volume—differ across distinct cognitive domains. We evaluated resting-state EEG networks in 832 community-dwelling older adults using exact low-resolution brain electromagnetic tomography-independent component analysis (eLORETA-ICA). Cognitive functions were assessed using the National Center for Geriatrics and Gerontology-Functional Assessment Tool (episodic memory, executive function, and processing speed). To isolate the functional networks specific to cognitive reserve, structural brain status was quantified by calculating the MRI volumes of 14 distinct regions, with relevant structural features extracted via Elastic Net regression. Consistent with the guidelines of the Reserve and Resilience Collaboratory, cognitive reserve-associated EEG network activities were modeled by adjusting for these structural metrics. Distinct neurobiological strategies emerged across domains. Episodic memory was associated with high-frequency gamma oscillations in temporoparietal hubs, potentially serving as an active compensatory mechanism that integrates information to bypass structural deficits ($\beta = -0.08$, 95% CI: -0.15 to -0.01, $p = 0.025$). Conversely, executive function involved lower resting-state network loading in the temporoparietal junction and superior parietal lobule, reflecting a highly efficient, "quiet" default state that preserves limited neural resources ($\beta = 0.11$, 95% CI: 0.04 to 0.17, $p = 0.002$). Finally, processing speed was subserved by alpha-band inhibition (gating) centered on the insular cortex, ensuring optimal resource allocation and readiness ($\beta = -0.08$, 95% CI: -0.15 to -0.01, $p = 0.034$). Our findings demonstrate that cognitive reserve does not rely on a unitary mechanism; rather, it manifests through distinct, domain-specific neurobiological strategies—active compensation for memory, neural efficiency for executive function, and dynamic gating for processing speed—depending on specific cognitive demands and their underlying cortical networks.

Disclosures: O. Katayama: None. **R. Yamaguchi:** None. **D. Yamagiwa:** None. **S. Akaida:** None. **T. Shimoda:** None. **C. Nakajima:** None. **A. Kawakami:** None. **T. Kodama:** None. **H. Shimada:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.16/FF29

Topic: I.05. Working Memory

Title: Cognitive demands shape neural variability along the cortical hierarchy in the human brain

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Abstract: Humans flexibly adapt their behavior to changing cognitive demands, yet how this flexibility emerges from continuously evolving patterns of neural activity remains unknown. Recent work has demonstrated that neural variability does not merely reflect random noise, but constitutes a structured feature of neocortical organization that is shaped by recurrent connectivity and increases along the cortical hierarchy from sensorimotor to association regions. Here, we show cognitive demand dynamically reshapes this hierarchy. We analyzed human intracranial electroencephalography (iEEG) recordings from 21 patients with pharmacoresistant epilepsy who performed a working memory (WM) task. In the context-first (CF) condition, participants were cued to the relevant target stimulus before encoding, enabling selective maintenance. In the context-last (CL) condition, this cue was provided only after two visual stimuli had been encoded, requiring both stimuli to be maintained in working memory. Our results extend recent findings of increasing neural variability along the cortical hierarchy. The CL condition exhibited greater neural variability than the CF condition, with this demand-related increase most pronounced in cortical areas implicated in task control and working memory. This suggests that association cortex dynamically adjusts neural variability in response to behavioral demands, while sensory regions preserve stable stimulus representations. This increase in neural variability was also associated with behavioral performance, with higher association areas showing elevated variability on incorrect CL trials. This implies that a surplus of variability under increased cognitive demands reflects a destabilization of mnemonic information. We also test if population variability reflects an expansion of the representational space supporting working memory, or mainly reflects a noisier population state. Together, these findings show WM demands reshape neural variability along the sensory-association hierarchy, balancing representational stability with the flexible use of task-relevant information.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.17/FF30

Topic: I.05. Working Memory

Support: AWARE North Texas Foundation

Title: Task-Based Functional Connectivity of Frontal Regions Across Working Memory Load and Stimulus Domain: An fNIRS Study

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Abstract: Working memory (WM) updating requires maintaining task-relevant information while flexibly shifting the focus of attention as WM load increases (Basak & Verhaeghen, 2011). These control demands are supported by the frontoparietal network (FPN), a network involved in flexible, goal-directed cognitive control (Marek & Dosenbach, 2018). However, most existing studies have focused on regional activation or resting-state functional connectivity (rs-FC), leaving it less clear how prefrontal regions coordinate during task performance. In the current study, we examined task-state FC (task-FC) of prefrontal regions across WM load and stimulus domain using fNIRS. We developed a random N-Match WM task crossing three WM loads (0-, 2-, and 3-match) with verbal stimuli (digits, words) and visual stimuli (scenes, birds), with stimulus complexity varying within each domain. Thirty-one young adults (aged 18-30 years, M = 23.48, SD = 3.42, Male: 12, Female: 17, Non-binary: 2) completed the task while prefrontal fNIRS data were recorded. fNIRS data were preprocessed with standard motion, filtering, hemoglobin-conversion, channel-quality, and short-channel correction procedures. Block-wise task-FC was estimated using Fisher-z-transformed correlations, and WM load × domain effects were tested as within-subject changes in connectivity strength across WM load.Behavioral results showed that as WM load increased, participants became less accurate and slower to respond across stimulus types ($p < .001$). Analyses for reaction time (RT) showed both a significant main effect for stimulus type and a WM load × stimulus type interaction, indicating that RT differences varied across WM loads and across verbal and visual domains ($p < .001$).For task-FC, the strength of prefrontal coupling showed a WM load × stimulus domain interaction ($p = .004$). At 0-match, verbal stimuli elicited marginally stronger prefrontal coupling than visual stimuli ($p = .06$); this domain difference was absent at 2-match but reversed at 3-match, where visual coupling exceeded verbal ($p = .02$), as visual-domain coupling increased with WM load while verbal-domain coupling decreased. The interaction was consistent across both temporal and spatial graph-theoretic connectivity measures, reflecting a common change in overall

coupling strength, and was most pronounced for the more complex type within each domain (words; birds). These preliminary results suggest a perceptual-level domain difference at low WM load that is reorganized under WM demand, with visual domain recruiting increasing prefrontal coordination at the highest WM load.

Disclosures: A. Nik Khah: None. **Y. Liu:** None. **F. Sierra:** None. **R. Prakash:** None. **C. Basak:** None.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.18/FF31

Topic: I.05. Working Memory

Support: JSPS Grant 23K17458
JSPS Grant 24K02955

Title: Differential Sensitivity of Auditory Cognitive and Perceptual Functions to Early Aging

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Abstract: Speech perception in challenging acoustic environments declines from middle adulthood, hindering daily communication and elevating the risk of progressive cognitive impairment, including dementia. Extensive research has linked speech perception in such environments to a constellation of cognitive and perceptual functions, notably working memory (WM) capacity, phonemic restoration, and temporal processing. WM capacity, essential for temporary storage and manipulation of information, declines with aging, concurrent with a degradation of temporal fine structure processing at the brainstem level. In contrast, phonemic restoration remains largely intact in older adults, highlighting the differential impact of aging across distinct cognitive and perceptual domains. However, these functions have primarily been examined separately, and their relative susceptibility to aging remains unclear. To address this gap, the present study employed a within-subject design to comprehensively evaluate the effect of aging on this functional spectrum ranging from the brainstem to the cerebral cortex. Fourteen young (aged 21-25 years) and eight middle-aged (aged 50-62 years) normal-hearing adults participated in this study. Speech perception in competing sound environments was assessed using the Coordinate Response Measure (CRM) task. Cognitive and perceptual functions were further quantified using a battery of behavioral assessments: a listening span test for WM capacity, an interaural time difference (ITD) discrimination task for temporal fine structure processing, and a noise superposition/replacement discrimination task for phonemic restoration. In the CRM task, age-related deterioration was most pronounced under challenging listening

conditions characterized by low signal-to-noise ratios and maximal informational masking where target and masker phrases were produced by the same talker. The middle-aged group also exhibited diminished listening span scores and elevated ITD discrimination thresholds. The results indicate that both cognitive and perceptual functions—specifically WM capacity and temporal processing—begin to decline during the early stages of aging. In contrast, no significant age-related differences were observed in phonemic restoration. This disparate sensitivity to aging suggests that preserved restorative processes may provide a functional scaffold to mitigate the impact of reduced cognitive and perceptual functions.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.19/FF32

Topic: I.05. Working Memory

Support: St. Jude Cancer Center Developmental Funds Award
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Title: Identifying Working Memory Mental Strategies for DLPFC Activation: A Preparatory rt-fMRI Neurofeedback Study in Healthy Adults

Authors: *S. SAXENA[1,2], C. TORRES ROJAS[3], P. PANDEY[3], J. DALBONI DA ROCHA[3], J. VALLEY[3], Y. PANG[3], S. S. MCAFEE[3], S. STATEN[3], J. ASHFORD[4], R. GILES[5], Y. LI[6], A. BAG[3], H. CONKLIN[4], R. SITARAM[3];
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Abstract: Real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback is a closed-loop brain-training approach that enables voluntary modulation of neural activity through real-time feedback of Blood Oxygenation Level-Dependent (BOLD) signals. This reinforcement based mechanism allows individuals to learn control over specific brain regions, including the dorsolateral prefrontal cortex (DLPFC), a core hub for working memory and executive function. Identifying mental strategies that reliably activate target brain regions is essential before applying rt-fMRI neurofeedback in pediatric medulloblastoma survivors, who often exhibit long-term impairments in working memory, attention, and processing speed following treatment. Healthy participants provide a controlled setting to evaluate the effectiveness of strategies and individual differences without disease-related confounds, thereby enabling the optimization of

neurofeedback approaches for future clinical use. We evaluated working memory-based mental strategies in ten healthy adults to determine their ability to modulate DLPFC activity based on a gamified real-time fMRI neurofeedback. Participants performed strategies during rt-fMRI runs: a structured verbal working memory task ("picnic game"), and mental arithmetic or song, using a block design with alternating task and rest periods. Functional images were preprocessed using SPM12 and analyzed using custom MATLAB algorithms, and task-related activation was assessed using beta and Percentage Signal Change (PSC) estimates for the contrast Task > Rest in bilateral DLPFC, primary auditory cortex (PAC), and primary motor cortex (PMC). Preliminary General Linear Model and PSC analyses suggest math and picnic strategies produce the largest DLPFC activation relative to rest. In the DLPFC, math produced higher mean beta and PSC values (0.81 ± 0.16, $n = 4$) compared to picnic game (0.60 ± 0.09, $n = 9$) and song (0.37 ± 0.17, $n = 5$), while PAC and PMC areas were not strongly recruited by these tasks, indicating stronger engagement of DLPFC-related networks during working memory strategies. Despite variability across participants, math and picnic strategies consistently increased DLPFC activity compared to baseline and other strategies. These findings demonstrate that working memory-based mental strategies can effectively modulate DLPFC activity, with mental arithmetic showing the strongest activation. Identifying reliable strategies for DLPFC up-regulation provides an important methodological foundation for future rt-fMRI neurofeedback studies aimed at improving cognitive function in pediatric medulloblastoma survivors.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.20/GG1

Topic: I.05. Working Memory

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Picower Institute for Learning and Memory
Swartz Foundation Fellowship for Theory in Neuroscience

Title: Emergent Traveling Waves in Neural Circuits

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Abstract: Artificial neural networks achieve striking performance but do not capture a prominent neural property. Cortical activity is organized by structured spatiotemporal dynamics, traveling waves (TW), which have been implicated in a wide range of functions. Existing computational models often rely on hand-crafted connectivity and imposed dynamics, offering insight into their impact but less into how the waves naturally emerge in biological circuits. Here, we found that TWs emerge in models under biologically plausible constraints (spatially organized, directionally biased connectivity). Under an empirical neural manifold constraint, these wiring principles naturally emerge to support traveling wave dynamics in the recurrent model. We further show that wave propagation provides a robust mechanism for maintaining working memory in the presence of visual distractors. We compared these model predictions to non-human primate prefrontal cortex recordings, revealing a similar mechanism. Together, these results advance our understanding of traveling waves as a substrate for cognition and offer a framework for mechanistic accounts of cortical computation.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

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Program #/Poster #: PSTR029.21/GG2

Topic: I.05. Working Memory

Support: NIH Grant R01 EY017077
NIH Grant F31 EY035546

Title: Dorsolateral prefrontal cortex preserves shape-space geometry during visual working memory

Authors: *W. DANG[1], R. JAFFE[4], D. MENDOZA[2], C. CONSTANTINIDIS[3];
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Abstract: The prefrontal cortex (PFC) plays a central role in working memory. Studies of spatial working memory have revealed how neural activity represents the locations of remembered stimuli, but how PFC represents nonspatial visual features, such as shape, remains less well understood. Prior work using morphed shape stimuli showed that PFC activity can reflect shape category rather than individual shape identity when category membership is behaviorally relevant. However, it is less clear how PFC represents shape information when explicit

categorization is not required. To address this question, we trained two macaque monkeys to perform a delayed match-to-sample task using two stimulus sets. In the first set, four pairs of shapes were linearly morphed at different levels to create four linear morph axes. In the second set, 360 shapes formed a perceptually circular shape axis. Both stimulus sets allowed us to test whether mnemonic activity in PFC preserves continuous similarity relationships among shapes, rather than encoding each shape as an unrelated discrete identity. We recorded extracellular spiking activity from neurons in dorsolateral PFC while the animals maintained individual shapes in working memory. In the linear morph dataset, we recorded 1,809 neurons, of which 20.6% were responsive during the delay period. In the circular morph dataset, we recorded 1,100 neurons, of which 21.5% were responsive during the delay period. During the memory delay, PFC population activity showed robust persistent signals encoding the remembered shape's position along the morph axis in both stimulus sets. Low-dimensional population analyses revealed that delay-period representations preserved the perceptual similarity structure of the stimulus space in low-dimensional neural activity. Importantly, for the circular stimulus set, the organized ring-like structure was substantially degraded on error trials, suggesting that preservation of stimulus-space geometry in PFC population activity is behaviorally relevant for accurate working memory performance. Together, these findings indicate that PFC does not represent remembered shapes merely as arbitrary, unrelated "pointers." Instead, PFC population activity preserves the relational structure of shape space, supporting a geometry-preserving code for nonspatial visual working memory. These results extend prior work beyond spatial and categorical representations and suggest that dorsolateral PFC can maintain continuous, structured representations of complex visual features.

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Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.22/GG3

Topic: I.05. Working Memory

Support: NIH 5 R01 NS 119519-03

Title: Relational coding of multiple objects in macaque prefrontal cortex

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Abstract: When we remember the location of an object, what coordinate system is that memory expressed in? An object's location can be remembered relative to the current direction of gaze (retinotopic), relative to the body (egocentric), relative to a reference frame in the world

(allocentric), or relative to other objects in the scene (object-centric). Behavioral studies suggest that spatial working memory combines these cues: Remembered locations are biased not only by where objects appeared in space, but also by the locations of other remembered objects. However, the neural basis of this cue combination remains unknown. Here, we address this question by combining a novel multi-object working memory task with electrophysiology in the frontal eye field (FEF) and supplementary eye field (SEF), brain areas that have been associated with retinotopic and allocentric coordinate systems, respectively.
We trained nonhuman primates (NHPs, macaque monkeys) to perform a task in which they must keep in working memory a scene consisting of up to three objects. We found relational effects in the animals' behavior: The remembered location of each object was systematically biased by the location of the other objects, consistent with a prior over relative object positions coming from the stimulus distribution. While they performed this task, we recorded large-scale neural activity from FEF and SEF using Neuropixels probes. We found that most neurons showed receptive field responses to a single visual object in retinotopic coordinates. However, under multi-object conditions, many neurons adopted an object-centric coordinate system, tuned to the relative position of objects. This relational coding was amplified in the working memory phase of the task when the stimulus objects were no longer visible. This relational response was also most prevalent in SEF, where the majority of neurons reflected an object-centric coordinate system. This finding reveals a neural substrate for relational effects in multi-object working memory.

Disclosures: N. Watters: A. Employment/Salary (full or part-time):; Massachusetts Institute of Technology. **J. Gabel:** A. Employment/Salary (full or part-time):; Massachusetts Institute of Technology. **M. Jazayeri:** A. Employment/Salary (full or part-time):; Massachusetts Institute of Technology, Howard Hughes Medical Institute.

Poster

PSTR029: Central and Prefrontal Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.23/GG4

Topic: I.05. Working Memory

Title: Neural substrates of working memory capacity in the common marmosets

Authors: *T. LO[1], S. VIJAYRAGHAVAN[2], J. PIMIENTO CAICEDO[5], L. E. MULLER[3], J. C. MARTINEZ-TRUJILLO[4];
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Abstract: Working memory (WM) is a crucial cognitive function supporting the temporary retention and manipulation of information essential for goal-directed behavior. However, this system is bound by strict physiological capacity limits. To investigate the behavioral and neural

constraints of WM capacity, we recorded electrophysiological activity from marmosets performing a delayed non-match-to-position (DNMP) span touchscreen task. In each trial, subjects were required to maintain an initial spatial location in memory. Following a delay, they were presented with the original stimulus and another stimulus at a novel location. Subjects had to select the novel spatial target. This process iteratively repeated to sequentially increase the memory load up to four locations. Behavioral performance across all subjects systematically declined with increasing memory load, reflecting robust capacity limitations. To uncover the underlying prefrontal dynamics, we utilized a multiscale electrophysiological approach. First, freely moving marmosets were implanted with wireless multi-shank microelectrode arrays (N-Form) targeting the lateral prefrontal cortex (LPFC, area 46). To complement this, we performed high-density Neuropixels recordings from marmosets engaged ina head-fixed, oculomotor variant of the task. Both recording modalities yielded highly consistent results, revealing single-unit spiking profiles with robust persistent delay activity tuned to individual spatial locations. Leveraging these spatially selective populations, we evaluated multi-item representations against summation, winner-take-all, and normalization models of WM capacity. We identified divisive normalization as the canonical computation governing capacity at the population level; firing rates for multi-item arrays (e.g., maintaining two items versus one) exhibited significant sublinear compression. To map the state-space geometry of the LPFC network, we applied principal component analysis (PCA). Population activity occupied distinct low-dimensional manifolds determined by remembered location and memory load. These load-dependent shifts in neural manifold geometry demonstrate that prefrontal ensembles flexibly reconfigure as maintenance demands increase. Together, these complementary datasets—exploring WM performance in both naturalistic and highly controlled oculomotor contexts—provide a multiscale foundation for understanding the mechanistic boundaries of working memory.

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Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.01/GG5

Topic: I.07. Long-Term Memory

Support: NIH Grant 1R15EY033512-01A1

Title: What makes an image of material memorable?

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Abstract: We see and interact with numerous materials every day. Remembering material appearances and later recognizing them when encountered again supports our decisions to

interact with the environment. Here, we ask what makes an image of material memorable? Memorability has been conceptualized as an intrinsic property of images that predicts human visual memory. We probe material memorability by having participants play a memory game using stimuli sampled from the STUFF dataset, which comprises 3,514 images across 200 specific material categories. Participants (N = 37) viewed a continuous stream of images and pressed a key whenever they recognized an image they had encountered; over the course of the experiment, each participant viewed the entire dataset. We compute material memorability for an image as the difference between the hit rate and false alarm rate. Participants show moderate accuracy (mean memorability: 56.46%; false alarms: 10.70%) with consistent patterns (Spearman correlations between randomly split groups: r=0.64), demonstrating that material memorability is a property consistent across observers. We further organize the 200 specific material categories (e.g., flint) into 10 broad categories by physical origin (e.g., rock). Results from the Bayesian regression model show that material categories predict memorability, with images containing certain materials (e.g., metals; mean memorability = 0.60) more memorable than those containing others (e.g., rocks; mean memorability = 0.45). We further explore whether material memorability could be predicted from image feature representations. Using features derived from a pretrained neural network (e.g., DreamSim), we train an SVM to classify a small set of high- vs. low memorability samples. The resulting model predicts memorability scores across the full dataset (Spearman R2 = 0.5). Together, we show that memorability is an intrinsic feature of material images and that features related to material categories contribute to their memorability. Image memorability, which reflects statistical regularities of the material appearances, can serve as a critical dimension in constructing human mental representations of materials.

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Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.02/GG6

Topic: I.07. Long-Term Memory

Support: NIH Grant R01MH133637

Title: What is common to memory retrieval and relational reasoning? Testing neural overlap in anterior prefrontal cortex

Authors: *A. CHEN[1,3], M. VASHEL[1], M. ALY[1], S. A. BUNGE[1,2];
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Abstract: Anterior lateral prefrontal cortex (aLPFC) has been consistently implicated in retrieval monitoring and relational reasoning. However, it is unknown whether aLPFC supports a

cognitive process that is common to memory retrieval and reasoning tasks. To inform this question, a first step is to ascertain whether there is, within individuals, spatial overlap in aLPFC between tasks. A prior study found overlap in activation of left aLPFC between verbal analogy and source memory retrieval tasks, using tightly matched word stimuli (Westphal et al., 2016). To assess whether this overlap in activation extends to other stimulus types and task designs, we collected fMRI data from 35 healthy young adults who completed an associative memory task and a relational reasoning paradigm that reliably engages left aLPFC. We included four variants of the reasoning paradigm, involving visual/auditory stimuli factorially combined with spatial/featural relations. During memory encoding, participants studied word pairs and decided whether the two words were related. At retrieval, they viewed pairs of previously seen words and judged whether the pair was Intact (words paired together at encoding) or Recombined (previously seen words recombined into new pairs). Response times were slower for Recombined vs. Intact pairs, consistent with heightened retrieval monitoring. As predicted, aLPFC was more active for Recombined than Intact pairs, as well as for the manipulation of relational complexity across the four reasoning tasks. A group-level conjunction analysis demonstrated overlap between memory and reasoning activations in all four Glasser parcels of interest in left aLPFC: a47r, p47r, a10p, and p10p. Clusters in the target parcels defined from the reasoning task manipulation were more active on Recombined vs. Intact memory retrieval trials. Further, there was overlap in the pattern of active vertices, as measured with Dice coefficients. Bayes factor testing within each parcel of interest, as well as the broader aLPFC region, demonstrated greater vertex-level overlap than expected by chance, particularly in p47r. Moreover, exploratory results showed that both cluster-level activation and vertex overlap in p47r, but not the other parcels, correlated with memory discriminability (d'). We hypothesize that neural overlap in this area reflects engagement in relational thinking during memory retrieval. Together, these results move beyond general characterizations of aLPFC function by meeting a precondition—individual-level neural overlap—of a unified neurocognitive function in support of reasoning and memory, such as relational thinking.

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Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

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Program #/Poster #: PSTR030.03/GG7

Topic: I.07. Long-Term Memory

Support: NIH Grant U01NS117838

Title: Neural Reinstatement During Repeated Viewing of Real-World Autobiographical Memories in Humans

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Abstract: Autobiographical memories are revisited throughout life, yet little is known about how repeated viewing influences the neural representations of personal experiences over time. Here, we investigated whether neural activity elicited during first-person capture of real-world autobiographical events is reinstated during subsequent viewing and how repeated viewing alters these representations over four months. Eight participants with treatment-resistant epilepsy implanted with the NeuroPace Responsive Neurostimulation (RNS) System captured autobiographical experiences using camera-equipped smart glasses that recorded synchronized first-person audio and video. Over four months, participants viewed recordings of their autobiographical experiences through a smartphone application [1] while simultaneous medial temporal lobe (MTL) intracranial EEG (iEEG) was acquired using a wearable electromagnet-triggered recording platform [2]. Before each viewing, a 2-second textual event cue (e.g., "Making salsa") was presented, followed by the original 24-second recording played at three times normal speed. Events were randomly assigned to either a light viewing condition (10 sessions) or a heavy viewing condition (20 sessions). Representational similarity analysis quantified event-specific neural reinstatement, and spectral power changes were examined. Event-specific neural representations showed robust reinstatement during viewing. However, the number of reinstatement episodes declined with increasing viewing frequency, suggesting that repeated viewing may alter the neural expression of autobiographical memories over time. Neural reinstatement was also observed during the textual event cue preceding viewing, suggesting rapid retrieval of event-specific representations from the description alone. Furthermore, theta (3-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz) power increased with repeated viewing across cue and viewing sessions. Behaviorally, heavily viewed memories maintained higher vividness ratings over four months. These findings demonstrate that neural representations of real-world autobiographical experiences are reinstated during both cue-triggered retrieval and viewing in the MTL and that repeated memory reactivation reshapes oscillatory dynamics while preserving subjective vividness. This work establishes a framework for studying the evolution of autobiographical memory with chronic intracranial recordings in naturalistic settings. **References:** [1] Martin, C.B. et al. (2022). *PNAS*, *119*(51), e2214285119. [2] Topalovic, U. et al.(2020). *Neuron*, *108*(2), 322-334.

Disclosures: W. Jiang: None. **U. Topalovic:** None. **B. Hong:** None. **E. Popescu:** None. **G. Vilchez:** None. **N. Hasulak:** None. **M. Dilbeck:** None. **C. Oragwam:** None. **S. Hiller:** None. **T. He:** None. **R. Mustapha:** None. **J. Baham:** None. **B. Guzman:** None. **A.I. Jang:** None. **C.S. Inman:** None. **M. Seeber:** None. **P. Parikh:** None. **B. Frauscher:** None. **V.R. Rao:** None. **D. Eliashiv:** None. **M.D. Barense:** None. **N.A. Suthana:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.04/GG8

Topic: I.07. Long-Term Memory

Support: European Research Council grant, no. 647954
European Research Council grant, no 101200478

Title: Theta phase reset in memory: linking spike-time alignment and oscillatory phase consistency in human single-neuron recordings

Authors: *Y. YAO[1], L. D. KOLIBIUS[2,3,1], F. ROUX[3], G. PARISH[3], M. TER WAL[3], M. VAN DER PLAS[1,3], R. CHELVARAJAH[3,4], D. ROLLINGS[4], K. WALTHER[5], R. HOPFENGAERTNER[5], H. HAMER[5], B. P. STARESINA[6,7], M. WIMBER[1,3], H. BOWMAN[3,8], S. HANSLMAYR[1,3];
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Abstract: Theta phase reset has been proposed as a mechanism for separating memory encoding and retrieval, yet direct evidence linking phase alignment to neuronal firing dynamics remains limited. We tested whether stimulus-related phase consistency is associated with transient alignment of neuronal spike timing in human medial temporal lobe recordings. To investigate this possibility, we analysed human single-unit and local field potential (LFP) recordings from medial temporal lobe regions during episodic memory tasks. Because phase-reset mechanisms presuppose an underlying oscillatory substrate, we first identified rhythmic neurons using oscillation-based criteria and subsequently identified candidate phase-reset (PR) neurons exhibiting reliable trial-to-trial spike-time alignment relative to task events, without increasing their firing rate. We then tested whether trial-by-trial variability in spike-time alignment predicted event-related phase consistency and replicated the analysis across three independent associative-memory datasets. Across three independent associative-memory datasets (>1,200 recorded units), theta-rhythmic neurons represented the dominant oscillatory subtype, consistent with the proposed role of theta oscillations in memory processing. Within candidate PR neurons, trials exhibiting stronger spike-time alignment were consistently associated with greater event-related LFP phase consistency. This relationship was most prominent within memory-relevant theta and alpha frequency ranges and was reproducible across datasets despite differences in participants, recording sessions, and task implementations. Importantly, when trials were realigned to the estimated spike-alignment peak, phase-consistency effects became more temporally concentrated than in conventional stimulus-locked analyses, suggesting that enhanced

phase consistency was temporally linked to transient spike-alignment events rather than solely to stimulus onset.Together, these findings link transient neuronal spike-time alignment to event-related phase consistency and support spike-timing dynamics as a potential contributor to phase-reset mechanisms beyond explanations based solely on evoked firing-rate changes. Future analyses will establish the extent to which this relationship generalizes across neuronal populations and evaluate whether rhythmic neurons make a disproportionate contribution to memory-related phase consistency.

Disclosures: Y. Yao: None. **L.D. Kolibius:** None. **F. Roux:** None. **G. Parish:** None. **M. Ter Wal:** None. **M. Van Der Plas:** None. **R. Chelvarajah:** None. **D. Rollings:** None. **K. Walther:** None. **R. Hopfengaertner:** None. **H. Hamer:** None. **B.P. Staresina:** None. **M. Wimber:** None. **H. Bowman:** None. **S. Hanslmayr:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.05/GG9

Topic: I.07. Long-Term Memory

Support: BYU MRI Facility - RF Seed Grant

Title: Mind's Eye Memory: Individual differences predict neural activity during memory retrieval for concrete words

Authors: *A. SCHMIDT[1], S. R. ASHBY[2];
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Abstract: Visual imagery processes in human beings have been shown to vary from person to person. These individual differences can deviate into extremes, such that some individuals report a complete absence of visual imagery experiences altogether (aphantasia). The concreteness effect is a replicable phenomenon where words referring to imageable objects (dog, apple, tree) are easier to retrieve than abstract words (lie, love, injustice). Dual-coding theory would suggest that memories are composed of visual and verbal elements separately. We chose to explore the possible functionality of visual imagery on episodic memory using an fMRI study. Participants were tasked to perform a recognition memory task on words (categorized as concrete or abstract) and faces. We collected survey data from these participants using the Internal Representations Questionnaire and the Vividness of Visual Imagery Questionnaire 2. Our current results suggest a correlation exists between concrete word memory retrieval and VVIQ-2 survey scores. We observed significant neural differences, but no significant behavioral differences. When participants remembered concrete words versus abstract words, there was greater activation in the parietal lobe and right dorsomedial frontal lobe, such that participants with greater visual imagery vividness showed a greater difference in activity remembering concrete words over

abstract words. As well, when participants remembered concrete words, we observed occipital activation positively correlating with participant VVIQ-2 scores, suggesting that visual imagery vividness predicts greater activation for concrete words. Conversely, VVIQ-2 scores did not predict actual memory test performance. Additionally, when comparing abstract and concrete word memory the VVIQ-2 and IRQ did not predict the concreteness effect. These findings suggest that word concreteness may induce a visual imagery component to the memory process, while participants' self-reported imagery ability influences the magnitude of neural activation, this does not appear to impact memory performance.

Disclosures: A. Schmidt: None. **S.R. Ashby:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.06/GG10

Topic: I.07. Long-Term Memory

Title: Tracking Memory Representations with fMRI: Optimising Decoding to Detect Wake-Rest Replay

Authors: *E. L. KOLBE[1,2], M. PETZKA[1], C. F. DOELLER[2,3], N. W. SCHUCK[1,4];
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Abstract: How do memory traces evolve over time, and what neural processes drive their transformation into longer lasting memories? Memory consolidation transforms newly encoded experiences into stable long-term traces, a process thought to depend on spontaneous offline reactivation of experience-related neural activity patterns. Studying memory reactivation with fMRI usually pursues multivariate pattern analysis, in which classifiers are often trained on stimulus-specific neural patterns, typically from a separate localiser task. The classifiers are then used to track memory processes during encoding, retrieval, or wake-rest in an independent main task. This approach carries the implicit but largely untested assumption that memory representations remain stable across task contexts and brain states. To address this assumption empirically, we designed a localiser task mirroring the structure of an associative memory paradigm,comprising both an encoding and a retrieval phase. This enabled a systematic comparison of classifiers during different testing conditions at retrieval: trained on encoding data (*cross*-decoding), trained on retrieval data (*match*), or trained on data from both phases jointly (*joint*). Performance was either evaluated on retrieval data of a held-out localiser testing set or on retrieval data of an independent sequential memory task (n=35). Our results show that regions were differently affected by task context transfer (i.e. tested on retrieval data of localiser vs. sequential memory task) and testing conditions (i.e. *cross* vs. *match* vs. *joint*). Visual cortex and

posterior-parietal cortex maintained stable object representations across task contexts and testing conditions, supporting robust cross-context and cross-condition generalisation. In contrast, memory-related regions such as medio-temporal lobe and precuneus show a significant reduction in classifier generalisation during task context transfer. Moreover, object representations in precuneus seem to be retrieval-specific: classifiers trained on retrieval data outperform those trained on encoding when tested at main task retrieval, pointing to active memory reformatting rather than simple reinstatement of encoding patterns. These findings demonstrate that localiser design critically shapes classifier sensitivity for detecting memory reactivation in an ROI-specific memory. Building up on this, optimised classifiers will be applied across four rest periods interspersed throughout a sequential memory task. A time-resolved fMRI approach offers the possibility to detect wake-rest replay and examine how replay evolves across early memory consolidation.

Disclosures: E.L. Kolbe: None. **M. Petzka:** None. **C.F. Doeller:** None. **N.W. Schuck:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.07/GG11

Topic: I.07. Long-Term Memory

Title: Effects of Familiarity and Preference on Musical Memory Retrieval and Salience

Authors: *C. G. MARSHALL, E. L. STEGEMOLLER;
Kinesiology and Hlth., Iowa State Univ., Ames, IA

Abstract: Alzheimer's disease (AD) is a neurological disorder characterized by abnormal protein deposits in the brain, leading to a decline in cognition. Case studies have shown that individuals with AD can retain the ability to recall musical memories despite broader episodic memory impairments (Cuddy & Duffin, 2005). These findings suggest that pathways that mediate recall of musical memories may differ from those that support traditional episodic memory recall (Groussard et al., 2019). This dissociation may be more robust for personally meaningful music, supporting the idea that emotions can strengthen the durability of musical memories (Carr & Rickard, 2016). While these effects have been hypothesized to reflect music's interaction with dopaminergic mechanisms in the brain, the underlying qualitative mechanisms remain underexplored (Peck et al., 2016). To address this gap, this study examines musical memory in a healthy population as a step toward future clinical translation. We assessed subjective ratings of musical preference, familiarity, and the presence and salience of personal memories across genres, artists, and time periods to characterize patterns of musical memory recall. Data were collected from a virtual survey completed by healthy adults (ages 20-24; n = 35) to examine how songs are represented in long-term memory. Participants reported whether each song was remembered (yes/no), rated familiarity and preference on 7-point scales, and rated vividness of the memory on a 5-point scale. A mixed-effects logistic regression examined

whether familiarity and preference predicted the likelihood of memory association while accounting for variability across participants and songs. Both familiarity, $b = 0.71$, $SE = 0.06$, $t(2711) = 12.05$, $p < 0.0001$, and preference, $b = 0.40$, $SE = 0.04$, $t(2711) = 9.62$, $p < 0.0001$, were significant predictors, with familiarity showing the stronger effect. A linear mixed model tested whether these factors also predicted memory vividness. Both familiarity, $F(1, 678.4) = 12.07$, $p = 0.0005$, and preference ratings, $F(1, 846.3) = 43.50$, $p < 0.0001$, predicted vividness, with preference emerging as the stronger predictor. Together, these results suggest that familiarity and preference differentially contribute to musical memory processes, with familiarity more strongly predicting whether a memory is retrieved and preference more strongly shaping how vividly it is experienced. Future work will evaluate these qualitative findings through behavioral and neuroimaging assessments in a larger sample, further characterizing how familiarity, preference, and musical memory interact across individuals and disease states.

Disclosures: C.G. Marshall: None. **E.L. Stegemoller:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.08/GG12

Topic: I.07. Long-Term Memory

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EMPIRIS foundation
Synapsis foundation
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Title: Sense of agency enhances object-spatial memory binding: an MEG study

Authors: *Q. REN[1], F. BERNASCONI[1], L. ZHANG[2], B. HERBELIN[1], O. BLANKE[1];
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Abstract: Why do some experiences remain vivid while others fade? One factor may be the sense of agency (SoA), the feeling of controlling one's actions and their outcomes, which shares self-referential mechanisms with episodic memory. We investigated whether SoA during encoding modulates item and spatial memory and the underlying neural mechanisms. During MEG recording, participants performed an intentional encoding task in which keypresses moved objects either congruently or incongruently with the intended direction. After each trial, participants rated their SoA. One hour later, item recognition and spatial (object-location) memory were tested. Participants reported higher SoA for congruent than incongruent trials. Congruency improved spatial memory, while item recognition remained unaffected. This benefit was partially mediated by SoA ratings and increased with higher trait SoA. At the neural level,

incongruent trials elicited stronger responses in sensorimotor and prefrontal regions, consistent with increased conflict processing, and weaker hippocampal theta desynchronization, with the weakest engagement observed for incongruent trials that were later forgotten. Additionally, in congruent trials, later-remembered trials showed stronger activity in the posterior cingulate cortex, precuneus, and parahippocampal gyrus, consistent with engagement of a posterior midline episodic memory network. In contrast, incongruent trials showed the opposite pattern. A similar pattern was observed during retrieval, where this network showed stronger responses for correctly remembered congruent trials, whereas incongruent trials showed the reverse pattern. Together, these findings suggest that the SoA selectively supports object-spatial memory binding and is associated with enhanced engagement of hippocampal-posterior midline memory networks during encoding.

Disclosures: Q. Ren: None. **F. Bernasconi:** None. **L. Zhang:** None. **B. Herbelin:** None. **O. Blanke:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.09/GG13

Topic: I.07. Long-Term Memory

Title: Effects of Emotion on Mnemonic Discrimination

Authors: *J. SUN, D. TALMI;
Dept. of Psychology, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Emotional events are often remembered vividly, but there are conflicting views as to whether emotion improves or impairs memory specificity. To address this problem, we combined a systematic review with a frequency-tagged emotional Mnemonic Similarity Task (emoMST).
The review identified 48 human adult studies testing recognition memory of emotional stimuli where lures included items that were more and less similar to studied items. We identified a number of methodological differences between studies, including in stimulus control, response format, and outcome measures. We observed that in experiments that employed naturalistic scene stimuli the conguency between foreground objects and background context was rarely controlled, despite its potential theoretical significance. Furthermore, in most published studies the memory measures were vulnerable to response bias.
We addressed these methodological weaknesses in two experiments. Our emotional Mnemonic Similarity Task improved on previous research by controlling object-background congruency, stimulus similarity, familiarity, and object-scene congruency. In Experiment 1 (33 adults) participants incidentally encoded neutral backgrounds containing either negative or neutral objects. In Experiment 2 (52 adults) objects and backgrounds flickered at distinct frequencies to separately quantify visuocortical processing with steady-state visual evoked potentials (ssVEPs).

At test, participants made 6-point confidence old/new judgments for old objects, similar object lures, and new object foils. Recognition memory (novel-old) and mnemonic discrimination (lure-old) were estimated using receiver-operating-characteristic-derived d_a, a recommended signal-detection metric for situations where criterion differences are expected, as is the case for emotional stimuli.
We found that negative emotion enhanced both mnemonic discrimination and recognition. Frequency tagging produced robust occipital ssVEPs at 8.6 and 12 Hz. ssVEP amplitude showed a significant Emotion × Scene Element interaction, indicating that negative objects increased object-related visuocortical processing.
Together, these findings show that negative emotion improves memory specificity when measured with rigorous signal-detection methods. This finding aligns with attentional encoding mechanisms that prioritizes emotionally salient objects over neutral context, consistent with the Negative Emotional Valence Enhances Recapitulation (NEVER) model.

Disclosures: J. Sun: None. **D. Talmi:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.10/GG14

Topic: I.07. Long-Term Memory

Support: European Research Council grant no. 647954
European Research Council grant no 101200478

Title: Episodic-specific neurons temporally link retrieval cues to reinstated target representations during human episodic memory retrieval

Authors: *X. WU[1,2], L. D. KOLIBIUS[3], F. ROUX[4], G. PARISH[5], M. TER WAL[6], M. VAN DER PLAS[7,5], R. CHELVARAJAH[5,10], D. ROLLINGS[10], K. WALTHER[11], H. HAMER[12,13], B. P. STARESINA[14], M. WIMBER[8], H. BOWMAN[5,15], S. HANSLMAYR[9];
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Abstract: The hippocampal indexing theory proposes that sparse hippocampal neurons bind distributed cortical representations into episodic memories and reactivate them during retrieval from partial cues. Prior analyses of intracranial single-unit recordings from epilepsy patients

identified episodic-specific neurons (ESNs) in the hippocampus that selectively respond to individual episodic memories (Luca et al., 2023). However, it remains unclear whether ESNs participate in the transition from externally presented retrieval cues to internally reinstated memory representations during episodic retrieval. Here, we tested whether ESN activity temporally bridges cue-related cortical representations and reinstated target representations. Activity was recorded from 216 hippocampal neurons together with macro-scale intracranial EEG contacts while patients (N = 12) performed an associative episodic memory task. Using the ESN identification procedure from previous studies, we identified 46 ESNs from the recorded hippocampal population. During retrieval, participants were presented with retrieval cues and asked to recall associated target memories. Neural representations related to retrieval cues and recalled targets were quantified from extra-hippocampal intracranial EEG activity using multivariate pattern analysis (MVPA). We first observed that target-related reinstatement emerged after cue-related cortical representations during retrieval. We then used cross-correlation analyses to examine the temporal relationship between ESN activity and classifier evidence. Results showed that cue-related cortical representations preceded ESN activity, whereas target-related reinstatement followed ESN activity, indicating that ESN activity emerged between externally presented retrieval cues and reinstated target representations. Together, these findings suggest that ESNs may reflect a hippocampal memory mechanism linking externally presented retrieval cues to internally reinstated memory representations during episodic retrieval, as predicted by hippocampal indexing theory.

Disclosures: X. Wu: None. **L.D. Kolibius:** None. **F. Roux:** None. **G. Parish:** None. **M. Ter Wal:** None. **M. Van Der Plas:** None. **R. Chelvarajah:** None. **K. Walther:** None. **H. Hamer:** None. **M. Wimber:** None. **H. Bowman:** None. **S. Hanslmayr:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.11/GG15

Topic: I.07. Long-Term Memory

Support: NIH P50MH136296
NIH F32MH140486

Title: Enhancing memory control ability through real-time fMRI neurofeedback

Authors: *A. C. HENNINGS[1], R. IYER[2], Y. NIV[2], K. NORMAN[2];
[1]Princeton Neurosci. Institue, Princeton Univ., Princeton, NJ, NJ; [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: The suppression of memory retrieval is adaptive, allowing us to filter irrelevant or distressing memories from our awareness. Repeatedly suppressing memory retrieval can lead to a lasting impairment in recall, known as suppression-induced forgetting (SIF). Converging

evidence from human neuroimaging suggests that the neural mechanisms of SIF include top-down inhibitory control from the dorsolateral prefrontal cortex (dlPFC) over the hippocampus (HC). Dysfunction of this neural circuit has clinical relevance, as individuals with anxiety- and trauma-related disorders exhibit impaired SIF. Here, we tested whether healthy adults could be trained to strengthen their ability to intentionally suppress intrusive memories by strengthening inhibitory dlPFC-HC functional connectivity. We designed a novel double-blind real-time fMRI neurofeedback (NFB) intervention, in which participants received visual feedback (i.e., points) based on their observed dlPFC-HC functional connectivity during fMRI. Feedback was embedded into a movie watching task, designed to maximize opportunities for memory suppression. On each NFB session (2 days) participants first encoded short (~30s) movie clips with highly memorable endings outside of the scanner. Then, during fMRI, participants watched the same clips again and were explicitly instructed to suppress their memories of the clip endings. Critically, participants were assigned to one of two groups in a double-blind fashion. In the active NFB group (N=12), NFB scores were directly related to each participant's dlPFC-HC functional connectivity during suppress trials, such that greater negative connectivity corresponded to a higher score. In the control group (N=10), participants received NFB scores that belonged to a participant in the active group (i.e., "yoked" NFB). Transfer was assessed using a think/no-think task with novel stimuli, completed on a subsequent day under fMRI. SIF was measured using a surprise visual priming task. Following NFB training, the active group exhibited significant SIF as evidenced by slower reaction times to no-think vs. baseline items. In contrast, the control NFB group did not exhibit significant SIF, and the magnitude of SIF observed in the active group was significantly larger than the control group. Additionally, the active group exhibited significant suppression-related inhibition in the HC during the post-NFB think/no-think task, while the control group did not. These initial results suggest that it is possible for individuals to enhance their own memory control ability and may represent a novel avenue for psychiatric treatment; data collection is ongoing.

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Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

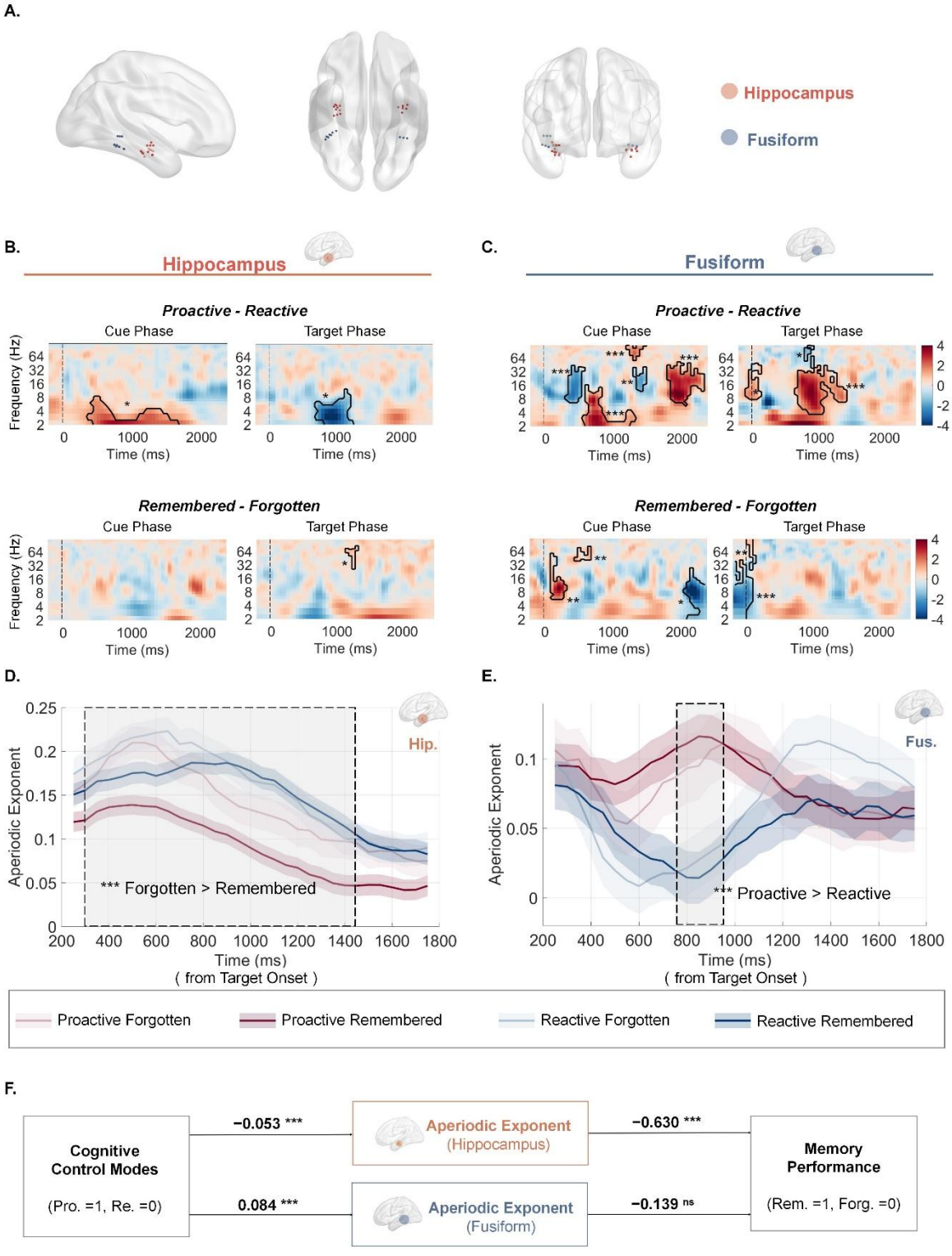
Program #/Poster #: PSTR030.12/GG16

Topic: I.07. Long-Term Memory

Title: Proactive control promotes an excitation-dominant hippocampal state that supports memory encoding: evidence from human intracranial recordings

Authors: *Y. HU[1,2], C. GAO[1], H. ZHOU[2], W. XU[3], F. GENG[4];
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Abstract: The hippocampus has a well-established role in memory encoding, but how this activity is shaped by different modes of cognitive control remains unclear. Cognitive control operates in two modes (Braver, 2012): proactive, which prepares goals before a stimulus arrives, and reactive, which engages goals only after a stimulus appears. Because memory-trace formation depends on neuronal excitability, these modes may shape encoding by placing the hippocampus in different excitation-inhibition (E/I) states. The aperiodic (1/f-like) component of the local field potential indexes this balance. A lower exponent reflects a more excitation-dominant state. To capture this directly, we used stereo-electroencephalography (sEEG) in six patients during presurgical monitoring (3 females, 3 males; mean age 30.2 years). Participants performed a cue-guided classification task under proactive and reactive control, followed by a surprise recognition test. We analyzed contacts within hippocampus and fusiform gyrus, computing time-frequency power and trial-wise 1/f fits. Effects were tested with mixed-effects models and cluster permutation. We first found that proactive control improved memory performance ($t(5) = 2.82$, $p = .037$). Time-frequency analyses then showed that proactive control temporally segregated cue and target processing. Crucially, we found that hippocampal aperiodic exponents were lower under proactive than reactive control ($\beta = -0.053$, $p < .001$). Lower exponents, in turn, predicted successful encoding ($\beta = -0.63$, $p < .001$). In the fusiform gyrus, by contrast, control mode shaped the exponent but did not predict memory. We propose that proactive control resolves the cue before the target, shifting the hippocampus into an excitation-dominant state, preserving item-specific signals. Together, these findings identify hippocampal excitability as a state-level mechanism linking cognitive control to memory encoding.



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Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.13/GG17

Topic: I.07. Long-Term Memory

Support: BMBF; 01GQ2402A
European Union's Horizon 2020 (grant agreement no. 101001121)

Title: Aperiodic Neural Activity During Encoding Tags Cortical Networks for Spindle-Mediated Memory Consolidation

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Abstract: Memory formation depends on initial encoding and subsequent consolidation of new experiences. How do these processes interact to determine which experiences ultimately persist? Sleep plays an active role in memory consolidation, particularly through neural oscillations such as sleep spindles. Previous work suggests that sleep spindles are preferentially expressed at sites of prior cortical excitation, however, the neural signatures during wake that tag these sites for later spindle-mediated consolidation remain elusive. We therefore examined whether aperiodic activity during encoding—thought to reflect levels of neural excitation—predicts trial-by-trial memory success and marks neural sites later recruited by sleep spindles to support memory consolidation. During pre-sleep learning, participants encoded a sequence of 50 images, followed by a two-hour nap and post-sleep retrieval, while we recorded high-density electroencephalography. Spectral parameterization revealed that flatter aperiodic slopes and decreases in alpha/beta power during encoding predicted subsequent memory success. Flatter aperiodic slopes, which have been shown to index increased neuronal excitation, emerged at temporoparietal electrodes, with source localization suggesting medial temporal lobe involvement. Further, the topographic correspondence between encoding-success-related aperiodic activity and fast sleep spindle expression during the subsequent nap predicted memory retention across participants. These findings indicate aperiodic dynamics as a neural marker of effective memory encoding and suggest that sleep spindles recruit tagged learning networks to promote consolidation.

Disclosures: P. Büchel: None. **J. Klingspohr:** None. **M.S. Kehl:** None. **L. Kunz:** None. **B. Staresina:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.14/GG18

Topic: I.07. Long-Term Memory

Support: 1ZIANS003144-11

Title: Neural spike sequence fidelity in the anterior temporal lobe supports successful episodic memory formation

Authors: *R. P. KIRKPATRICK[1], J. ZHANG[2], E. JITENDRAN[3], S. INATI[1], K. A. ZAGHLOUL[1];
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Abstract: Recent experimental work has found that neurons fire in a sequential pattern during episodic memory encoding. These sequential patterns are subsequently replayed during memory retrieval, and this replay is associated with successful memory outcomes. It is still unclear why these sequences fluctuate across varying task conditions. We designed an experiment where human epilepsy patients performed a semantic categorization and recall task. The patients completed this taske while the patients were implanted with electrodes in the anterior temporal lobe for seizure monitoring. We isolated single neurons from the microelectrode contacts and examined these sequences of neural firing. We find that neuronal sequences reliably represent semantic information when participants are actively encoding the stimulus into memory. Memory performance and sequence fidelity are strongest when remembering images, but the relationship between sequence fidelity and memory performance persists with textual stimuli. These results elucidate the role of single neuron sequences in the anterior temporal lobe in episodic memory performance.

Disclosures: R.P. Kirkpatrick: None. **J. Zhang:** None. **S. Inati:** None. **K.A. Zaghloul:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.15/GG19

Topic: I.07. Long-Term Memory

Support: NIH/NINDS R01NS132872

Title: The relationship between external attention and the encoding state

Authors: *S. HAN, N. M. LONG;
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Abstract: Although substantial evidence indicates that memory and attention are interdependent, there is no unified theory on how attention and memory are related. A growing body of behavioral, computational, and neural work suggests that the retrieval state is linked with internal attention, the focusing of the mind's eye inward toward stored information. Our aim in the present study is to determine the extent to which the encoding state is linked with external attention, focusing on sensory information in the environment. Our hypothesis is that the encoding state reflects the degree to which attention is directed externally. The alternative hypothesis is that the encoding state specifically tracks successful memory formation. We collected scalp electroencephalography data during a recognition memory task in which participants intentionally studied words and images in anticipation of a later memory test. Half of the target trials were modality matched (i.e., the same item was presented in the same modality in both study and test), and the other half of the targets were modality mismatched (i.e., an item was presented in a different modality across study and test). We used cross-study multivariate pattern analysis (MVPA) to assess the degree to which study modality (word, image) impacts mnemonic brain state engagement. We used within-study MVPA to develop a classifier that distinguishes trials in which study items were subsequently remembered vs. trials in which study items were subsequently forgotten at test. Our preliminary results replicate the picture superiority effect in that we find greater recognition accuracy for images compared to words. Consistent with the encoding specificity principle, we find greater recognition accuracy for study-test modality matched compared to mismatched items. We find greater study-phase encoding state engagement for images compared to words. Encoding state engagement during study does not predict subsequent memory. We find no linear relationship between evidence for encoding state engagement and evidence for subsequent memory effects. Together, these findings suggest that the encoding state reflects the degree to which attention is directed externally, rather than specifically tracking successful memory formation.

Disclosures: S. Han: None. **N.M. Long:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.16/GG20

Topic: I.07. Long-Term Memory

Title: Baseline memory ability gates the neural response to hippocampal electrical stimulation in patients with epilepsy

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Abstract: Direct hippocampal electrical stimulation (ES) is being developed for memory disorders, yet the same stimulation can improve or impair recall, and it remains unresolved which patients benefit and at which frequency. We tested whether baseline memory ability moderates the response to ES, dissociating patients who improve from those who decline. Nine patients with bilateral hippocampal head and tail electrodes performed verbal free recall while receiving 5 Hz ES (theta-band, matching the endogenous encoding rhythm) and 50 Hz ES (clinical gamma-range), and were classified by no-stimulation recall as high (≥50%, n=7) or low (<50%, n=2) baseline performers. In the stimulation-artifact-free post-stimulation interval (700-5700 ms), we computed power spectral density and theta- and alpha-gamma phase-amplitude coupling (PAC; Tort modulation index and mean vector length) in grey-matter channels, stratified within region, and compared stimulation-induced changes (ES minus no-ES) between groups at the patient level. Pooled across all patients, recall did not differ between frequencies (Cohen's d=0.27, p-value=0.611), and the two frequencies left dissociable post-stimulation coupling fingerprints: 5 Hz ES increased amygdala alpha-low-gamma coupling during encoding (Cohen's d=0.80, p-value=0.008, n=8), whereas 50 Hz ES increased hippocampal-head theta-low-gamma coupling during retrieval (Cohen's d=1.12, p-value=0.031, n=6), yet neither neural change tracked behavior. The interaction emerged only after stratification by baseline ability. ES reversed the group difference in recall accuracy (proportion of items recalled): the large no-stimulation gap (high 85.7% vs low 20.0%) closed under stimulation, as high performers declined (to ~64% under 5 Hz and ~51% under 50 Hz) while low performers improved (to ~35% under 5 Hz and ~55% under 50 Hz). Neurally, low performers showed the larger ES-induced coupling increases across regions and bands in a consistent direction, though with only two low-baseline patients these group comparisons are descriptive. These exploratory findings indicate a performance-group-by-frequency interaction in which baseline ability, not frequency alone, shapes the neural response to ES, motivating a charge-matched, adequately powered confirmatory study.

Disclosures: X. Shao: None. **R. Martin Del Campo Vera:** None. **M. Parra:** None. **J. Cavaleri:** None. **R. Chung:** None. **C. Liu:** None. **J.T. Kuo:** None. **R. McGinn:** None. **S. Kellis:** None. **B. Lee:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

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Program #/Poster #: PSTR030.17/GG21

Topic: I.07. Long-Term Memory

Support: NIH R01 MH125990

Title: Encoding minds: How mental state inference shapes episodic memory

Authors: *N. CURKO[1], M. ZHANG[2], E. A. KENSINGER[1], M. RITCHEY[3];
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Abstract: Studies of memory encoding have commonly focused on memory for concrete features of an event. However, understanding and remembering social events also involves attending to others' thoughts and feelings, a process known as mentalizing. It is unknown how mentalizing affects the brain processes involved in memory encoding. We hypothesized that mentalizing would enhance memory encoding while shifting hippocampal interactions toward dorsal default mode network (DMN) areas associated with social cognition. To test this hypothesis, we scanned participants (current N=24) as they viewed images depicting individuals performing everyday actions (e.g., jogging, baking). Mentalizing was manipulated at encoding using the Why-How paradigm, a validated mentalizing localizer: for each picture, participants answered a question about why the person was performing the action ("Why" mentalizing condition) or how the action was being performed ("How" non-mentalizing condition). Following scanning, participants completed a free recall task, and one day later completed a delayed old/new recognition task. Behaviorally, participants were equally likely to freely recall Why and How items, and marginally more likely to recognize Why items after a delay. Neurally, Why encoding elicited greater activation in DMN regions compared to How trials, particularly in dorsomedial prefrontal cortex, precuneus, inferior parietal lobule, and temporal regions. Furthermore, activity in the lateral prefrontal cortex, superior parietal lobule, and occipitotemporal cortex predicted subsequent memory for the images, but these effects did not appear to be modulated by mentalizing during encoding. Together, these preliminary findings suggest that mentalizing during encoding recruits DMN areas, but this process may be differentiated from the processes supporting episodic memory encoding success. Planned analyses will examine how functional connectivity among DMN regions varies as a function of mentalizing at encoding and whether these connectivity patterns predict subsequent memory outcomes. We expect that memory success in the Why condition will be associated with increased functional connectivity between the dorsal DMN and memory-related areas, such as the hippocampus.

Disclosures: N. Curko: None. **M. Zhang:** None. **E.A. Kensinger:** None. **M. Ritchey:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.18/GG22

Topic: I.07. Long-Term Memory

Support: NIH R01MH133732

Title: Causal Structure of a Narrative Shapes Individual Event Representations Independently of Event Semantics

Authors: *A. DRISSI[1,2], S. TAVASSOLI[2], J. CHEN[3];
[1]Johns Hopkins Univ., Catonsville, MD; [3]Psychological and Brain Sci., [2]Johns Hopkins Univ., Baltimore, MD

Abstract: Our perception and memory of an event depends not only on the event itself, but also its causal and semantic relationships to other events we have experienced (Antony et al., 2024; Lee et. al, 2022). However, the causal structure of an event series and the semantic content of individual events are often intertwined. In this study, we aim to isolate how the causal properties of an event influence how it is neurally represented and recalled independent of its semantic content. We predict that a given event's causal connections to others in a narrative will modulate its neural representation and the brain's functional integration at its encoding, as well as its recall likelihood (Park et al., 2026). To test this, we created three different versions of a story by re-ordering the events while keeping the literal text of each event the same. Independent ratings confirmed that these versions were identical in perceived comprehensibility, chronologicity, cohesiveness, surprisingness, and immersiveness, but differed in terms of the causal connections perceived between individual events. While undergoing fMRI, participants (n = 31) were randomly assigned to listen to only one of the three versions of the story (~20 minutes), then recalled the story aloud. We compared the event-level pattern ISC (pISC) across participants who listened to the same story against pISC across participants who listened to different story versions. We chose four ROIs for analysis: PMC, mPFC, angular gyrus, and early visual cortex (control). Randomization tests revealed pISC in all ROIs was significantly greater than zero, regardless of an event's condition (all ps < 0.05). Moreover, pISC was significantly greater within condition vs. between conditions only in bilateral mPFC (p = 0.0362) and marginally in right PMC (p = 0.054). These preliminary results reinforce the findings that perception of individual events is influenced by both event content and by the surrounding context. Now, we are investigating how differences in the causal interconnectedness and emotional throughlines of each story version may influence event perception, memory, and event-specific functional integration.

Disclosures: A. drissi: None. **S. Tavassoli:** None. **J. Chen:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.19/GG23

Topic: I.07. Long-Term Memory

Support: University of Delaware Research Foundation

Title: Investigating category-selective familiarity signals within the parietal memory network

Authors: *M. AYYILDIZ, A. F. HOLT, H. DIXON, A. W. GILMORE;
Univ. of Delaware, Newark, DE

Abstract: Familiarity is one of the primary processes underlying recognition memory. Neuroimaging studies in humans have identified a parietal memory network (PMN) that exhibits increased activity in response to familiar, relative to novel, stimuli. Activity within this network appears to be automatic and agnostic to the type of stimulus being processed. However, the latter conclusion is primarily supported by large, group-averaged studies and may not reflect patterns observable at the level of individual participants. The current study examined whether PMN activity is differentially modulated by encoding and retrieving stimuli across different semantic categories. Multi-echo precision-MRI data were collected from 2 participants, across 3 sessions each, with participants performing separate encoding and retrieval tasks in each session. Participants initially encoded 120 stimuli (40 faces, 40 scenes, and 40 words) in each session while making binary semantic decisions for each stimulus category. 240 stimuli were then presented in a recognition memory task (half old, half new) in each session, where participants made binary old/new decisions. Recognition memory scans included only one stimulus category at a time. Retrieval success (old > new) effects were calculated separately for each stimulus category, and identified regions were subsequently binarized and combined to identify the degree to which separate clusters responded to familiar stimuli in a category-selective manner. Overlapping clusters, in which retrieval success effects were present across all stimulus categories, were observed in canonical PMN regions. However, these were adjacent to clusters that appeared sensitive to specific categories. These data, collected within precision-mapped subjects, suggest that functional heterogeneity may be present in PMN regions in a manner that was not easily appreciated in earlier, group-averaged results.

Disclosures: M. Ayyildiz: None. **A.F. Holt:** None. **H. Dixon:** None. **A.W. Gilmore:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.20/GG24

Topic: I.07. Long-Term Memory

Support: University of Delaware Research Foundation

Title: Separating Familiarity and Attention Signals in the Parietal Memory Network

Authors: *A. HOLT[1], M. AYYILDIZ[1], H. DIXON[1], N. M. LONG[2], A. W. GILMORE[1]; [1]Univ. of Delaware, Newark, DE; [2]Univ. of Virginia, Charlottesville, VA.

Abstract: Recognition memory decisions rely on the brain's ability to distinguish between novel and familiar stimuli. Previous neuroimaging research has identified a group of brain regions, known as the parietal memory network (PMN), that appear particularly sensitive to stimulus familiarity. Across numerous task conditions, activity within this network is consistently greater for familiar ("old") items than for novel ("new") items. However, the degree to which activity in the PMN reflects familiarity per se, or attentional capture by familiar stimuli, remains unclear.

This distinction is particularly relevant because recent work has associated the PMN with another functional network, the salience network, which supports the allocation of attention to salient stimuli. To better understand the meaning of activity differences within the PMN, the present study manipulated attentional orientation during a recognition memory task. Participants (N=21) encoded 160 words while undergoing fMRI, then completed two types of old/new recognition memory tasks: one where they were instructed to focus on detecting familiar items and another where they focused on detecting novel items. Task order was counterbalanced across participants. During retrieval, participants saw a total of 320 words, half old and half new. This approach directly examines how PMN responses change when target selection is consistent with, or in opposition to, stimulus familiarity. Across all PMN regions, there was a significant Old > New effect. This effect was observed across task conditions, and did not reverse in cases where the salient target category was “new” instead of “old.” Effects were similarly robust to task order across participants. Overall, the results support the view that stimulus familiarity, rather than target selection, is a primary determinant of activity within the PMN during recognition memory.

Disclosures: A. Holt: None. **M. Ayyildiz:** None. **H. Dixon:** None. **A.W. Gilmore:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.21/HH1

Topic: I.07. Long-Term Memory

Support: NSF Grant 2145172

Title: Tracking multiple contexts in naturalistic events

Authors: *X. XU, J. R. MANNING;
Dartmouth Col., Hanover, NH

Abstract: Naturalistic events have hierarchical structure: items/scenes grouped into events, events into storylines/topics. Episodic memory should track multiple interleaving threads and bridge information within a thread. Classical retrieved-context models assume a single drifting context. It remains unknown how episodic memory maintains multiple interleaving higher-level contexts and what computational mechanism supports it. Here, participants watched 30-minute movies with multiple storylines either interleaved or grouped, then they were later cued with short clips from the film. For each cue, participants first rated its vividness, then recalled what happened either immediately before or after the clip, within the same storyline. We found that there was no cost in memory associations when inserting events from other storylines in between two consecutive events within the same storyline. We propose the Multi-Thread Context Maintenance and Retrieval (MT-CMR) model that extends Cornell & Zhang's (2025) hierarchical CMR with a per-storyline cache. Each storyline has its own context vector, written when the storyline departs and restored when it returns. Simulations show that the MT-CMR

model can account for the experimental results and shed light on how we track multiple contexts in everyday life.

Disclosures: X. Xu: None. **J.R. Manning:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

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Program #/Poster #: PSTR030.22/HH2

Topic: I.07. Long-Term Memory

Support: RF1MH055687

Title: The subsequent memory effect largely reflects experimental structure rather than endogenous mnemonic variability

Authors: *R. DEHAAN[1], D. HALPERN[3], M. J. KAHANA[2];
[2]Psychology, [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Columbia Univ., New York, NY

Abstract: The subsequent memory effect (SME) — the difference in neural activity between subsequently recalled and forgotten items — has been interpreted as an indicator of subjects' "readiness to learn," independent of the properties of memorized items. However, it is known that items at the beginnings and ends of lists are recalled most often, that some items are more memorable than others, and that both of these factors modulate brain activity. This suggests the SME may reflect the effects of experimental stimuli rather than internal fluctuations in mnemonic function. Here we estimate the SME adjusting for factors including serial position and item identity in 377 patients recorded intracranially during a free recall task. After adjustment, multivariate neural decoders still reliably predict recall but only explain 1.4% of recall variance beyond what stimulus factors explain, suggesting the SME largely reflects experimental structure rather than endogenous activity. Moreover, adjusting regional SMEs attenuates effects by 40% on average across brain regions, implying widespread confounding. Sensitivity analyses suggest small amounts of additional unmeasured confounding could explain these residual signals. Our findings indicate that isolating activity corresponding to endogenous states of memory requires careful consideration of experimental confounds.

Disclosures: R. DeHaan: None. **D. Halpern:** None. **M.J. Kahana:** A. Employment/Salary (full or part-time):; Nia Therapeutics.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.23/HH3

Topic: I.07. Long-Term Memory

Title: Slow-theta oscillations play a retrieval-specific causal role in human hippocampal memory

Authors: *R. CAO[1], N. HERZ[2];
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Abstract: Hippocampal theta oscillations have long been implicated in human memory, yet their causal contribution to memory performance, and whether they serve distinct functions during encoding and retrieval, remains unresolved. Here, we combined intracranial recordings and direct brain stimulation to test the frequency-specific role of hippocampal oscillations in memory. 28 participants with intracranial electrodes in the hippocampus performed a hybrid verbal-spatial memory task. To dissociate rhythmic oscillations from broadband spectral changes, we applied Irregular-Resampling Auto-Spectral Analysis (IRASA). In line with canonical memory effects in free recall paradigms, successful cued recall was characterized by increased theta (2-5 Hz) and gamma (> 40 Hz) power together with reduced alpha power (6-12 Hz) relative to unsuccessful recall. The theta effect was driven primarily by the oscillatory component and was found during retrieval rather than during encoding, suggesting that oscillatory theta is particularly linked to the recovery of stored memories. We next tested the causal role of these dynamics in a separate cohort of 16 participants using direct electrical stimulation during either encoding or retrieval. Stimulation at 3 Hz, corresponding to the dominant slow-theta frequency observed during successful retrieval, significantly enhanced the probability of correctly recalling items when delivered during retrieval. In contrast, the same stimulation failed to improve memory when delivered during encoding. Stimulation at 8 Hz, a frequency outside the retrieval-related theta range, did not enhance retrieval and instead impaired memory when applied during encoding. Together, these findings identify a retrieval-specific role for slow-theta oscillations in human memory and demonstrate that memory enhancement depends on frequency- and phase-specific engagement of endogenous hippocampal dynamics.

Disclosures: R. Cao: None. **N. Herz:** None.

Poster

PSTR030: Memory Encoding and Retrieval in the Human Brain

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.24/HH4

Topic: I.07. Long-Term Memory

Title: The Impact of the Method of Loci as a Forgetting Curve Intervention: Effects on Delayed Recall and Serial Position Accuracy

Authors: J. R. PIKE[1], A. M. PIKE[2], *A. J. PAYNE[1];
[1]Biomed. Sci., Noorda Col. of Osteo. Med., Provo, UT; [2]Salt Lake Community Col., Salt Lake City, UT

Abstract: Purpose:
Hermann Ebbinghaus's work on memory loss over time helped define what is now called the forgetting curve. The Method of Loci (MoL), or "memory palace," is a spatial mnemonic technique with evidence supporting improved recall. However, prior studies are often limited by sample size, inconsistent methods, and short follow-up periods, limiting conclusions about its effect on forgetting over time. This study evaluated whether a standardized MoL protocol improves recall across classic forgetting-curve intervals compared with self-selected memorization strategies.
Methods:
Participants were randomized into either a standardized MoL training group or a control group using self-selected memorization strategies. All participants studied the same 25-word list and completed recall assessments at five intervals: immediate recall, 1 hour, 1 day, 7 days, and 31 days. The primary outcome was the percentage of total words recalled. The percentage of words recalled in the correct serial position was a secondary outcome. These outcomes were analyzed using a mixed-effects model with pairwise group comparisons at each recall interval. Control participants were categorized by apparent strategy selection into three subgroups for post-hoc analysis: repetition, hook-based association, and image-based association.
Results:
The MoL group demonstrated significantly greater total recall than the control group at every interval. The between-group difference widened over time, from 25.9 percentage points at immediate recall to 57.7 percentage points at 31 days. MoL also produced gains in serial-position accuracy, ranging from 37.5 percentage points at immediate recall to 71.5 percentage points at 31 days. These findings suggest that MoL improved both item retention and ordered recall across delayed intervals when compared to the control group. The control group's strategy selection of either image, hook, or repetition methods was also associated with differences in recall performance. Both the hook and image subgroups significantly outperformed the repetition subgroup at every recall interval. However, the MoL group outperformed all control subgroups.
Conclusions:
A brief standardized MoL intervention substantially improved word-list recall and serial position accuracy compared with self-selected memorization strategies. The effect persisted through 31 days and appeared to increase as recall delay lengthened, suggesting that MoL may attenuated forgetting over time. Future studies should test MoL under more demanding learning conditions, including shorter encoding periods, larger information loads, and applied educational content.

Disclosures: J.R. Pike: None. **A.M. Pike:** None. **A.J. Payne:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.01/HH5

Topic: I.08. Learning and Memory

Title: Recognition memory in young pigs is associated with hippocampal volume and fornix microstructure

Authors: *Z. LI[1], R. N. DILGER[2];
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Abstract: Recognition memory is an important component of cognitive development and is supported by a network of brain regions that includes the hippocampus and its associated white matter pathways. Although recognition memory has been extensively studied in rodents and humans, the neuroanatomical substrates underlying individual differences in recognition memory during early postnatal development remain poorly understood. The domestic pig represents a valuable translational model due to its gyrencephalic brain and similar neurodevelopmental trajectory with human. The objective of this study was to identify neuroanatomical correlates of recognition memory in young pigs across multiple spatial scales.Artificially reared pigs (N = 31; 17 male, 14 female) underwent novel object recognition testing at approximately 4 weeks of age. Cognitive performance was quantified using the recognition index (RI), where higher RI reflects better recognition memory. Following behavioral testing, pigs underwent structural and diffusion MRI. Associations between RI and regional brain volumes, regional diffusion tensor imaging (DTI) metrics, white matter tract microstructure, and structural connectivity measures were evaluated using linear models controlling for sex and genetics, with false discovery rate correction applied within each analysis level.Higher RI was associated with larger relative left hippocampal volume ($P < 0.05$). At the white matter tract level, higher fractional anisotropy and lower radial diffusivity within the left fornix were associated with improved RI ($P < 0.05$). However, no significant associations were observed between RI and whole-brain structural connectivity measures.These findings suggest that individual differences in recognition memory in young pigs are associated with structural variation within the hippocampus-fornix circuit. The convergence of volumetric and diffusion MRI findings across grey and white matter supports a role for hippocampal circuitry in early cognitive performance and further establishes the domestic pig as a translational model for studying brain-behavior relationships during neurodevelopment.

Disclosures: Z. Li: None. **R.N. Dilger:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.02/HH6

Topic: I.08. Learning and Memory

Support: R01DA062018

Title: Temporally Distinct Dorsal CA1 Computations Support Associative Learning Across Delays

Authors: ***M. ZHOU**[1], B. WU[2], M. KHEIRBEK[3], V. K. NAMBOODIRI[4];
[1]Neurosci., Univ. of California, San Francisco, San Francisco, CA; [2]Neurosci., [3]Psychiatry, UCSF, San Francisco, CA; [4]Neurol., Univ. of California San Francisco, San Francisco, CA

Abstract: The hippocampus is crucial for associative learning, yet the specific neural computations supporting this role remain elusive. A key clue is that an intact hippocampus is specifically required for trace conditioning—when a temporal gap separates the conditioned stimulus (CS) from the unconditioned stimulus (US)—but not when they overlap. To explain this, one hypothesis is that hippocampal activity maintains a memory of the CS during the trace interval, thereby bridging the temporal gap. Alternatively, hippocampal computations occurring after the US, such as replay of preceding CS-related activity, may retrospectively link reward with earlier cue representations. While previous studies suggest that either mechanism is plausible, a rigorous test of both hypotheses has not been performed for appetitive trace learning. In this study, we combined optogenetic inhibition, longitudinal two-photon calcium imaging, high-density electrophysiology, and dopamine recording to determine how dCA1 computations during distinct periods support appetitive trace learning. Specifically, we used temporally precise optogenetic inhibition of dCA1 during either the cue-trace interval or immediately following reward in an appetitive trace conditioning task. Inhibition during either epoch impaired learning but produced distinct effects on cue-reward association formation and behavioral performance: cue-trace interval inhibition produced a generalized learning deficit across cues predicting the same reward, while post-reward inhibition produced cue-specific learning deficits. Two-photon calcium imaging then revealed the emergence and strengthening of distinct dCA1 ensembles during both epochs as learning progressed. Consistent with the optogenetic results, many neurons exhibited generalized trace period responses across cues predicting the same reward, whereas others displayed cue-specific post-reward activity. To assess whether cue-specific post-reward activity coincides with sharp-wave ripples (SWRs) or dopamine signals, we performed simultaneous Neuropixels recordings of dCA1 spiking activity and SWRs alongside dopamine monitoring in the nucleus accumbens. Preliminary studies show that cue-specific post-reward activity was not coincident with ripples and was unlikely to reflect replays. Moreover, mesolimbic dopamine cue responses emerged sooner than hippocampal SWR responses to reward. Together, these complementary approaches provide new insights into how distinct hippocampal computations contribute to cue-outcome binding across temporal gaps and interact with mesolimbic reward circuits to support associative learning.

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Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.03/HH7

Topic: I.08. Learning and Memory

Support: NIH Grant R01AG013622
HSFP Grant LT 0004/2023-L

Title: Hippocampal O-LM Interneuron Activity is Modulated by Cognitive Demand

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[3]Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Hippocampal neuronal networks encode goal-driven variables and are modulated by behavioral state and cognitive demand. Yet, the hippocampal neuronal mechanisms underlying the encoding of distinct behavioral and spatial variables as cognitive demands increase are poorly understood. Distinct interneuron types have important roles in shaping principal cell dynamics by inhibiting different regions along the somatodendritic axis of pyramidal neurons. Oriens-Lacunosum Moleculare (O-LM) interneurons target distal dendrites and modulate local field potential (LFP) theta frequency (4-12 Hz), an electrophysiological rhythm linked to memory encoding during active behavior. Because of its role in distal dendritic excitability during active states, we hypothesize that this neuronal type plays a critical role in modulating hippocampal activity during periods of increased cognitive demand. To address this question we expressed the genetically encoded voltage sensor pAce specifically in O-LM cells and tracked their activity in head-fixed mice. To test the influence of cognitive demand, we developed a linear treadmill track behavioral paradigm. Mice were first imaged after habituation during a random foraging session where rewards were released at random locations. Then, to increase cognitive demand, we fixed the location of the reward for every lap and we imaged mice after they learned to lick at the location. Preliminary data suggests that intracellular theta power and firing rates are differentially modulated by cognitive demand. This implicates a causal relationship between O-LM population dynamics and cognitively demanding behaviors.

Disclosures: D.R. Espino: None. **L. Sheintuch:** None. **M. Kannan:** None. **P. Golshani:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.04/HH8

Topic: I.08. Learning and Memory

Support: NSERC
CFI

Title: Spatial memory network reorganization following distributed learning

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Abstract: Learning distributed across multiple sessions produces more durable and interference-resistant memories than equivalent massed training, likely by promoting incremental network reorganization that distributes memory representations across brain regions. Spatial memory in the Morris Water Task (MWT) critically depends on the hippocampus, particularly during the acquisition and retrieval of precise spatial representations. The present study tested whether distributed MWT acquisition enhances memory strength and alters hippocampal engagement relative to massed acquisition. Nineteen rats were assigned to either a massed (MASS; n = 10) or distributed (DIST; n = 9) training condition. MASS rats completed 20 acquisition trials in a single session, whereas DIST rats completed the same number of trials across five consecutive days (4 trials/day). The final DIST session occurred on the same day as MASS training to control for retention interval effects. Memory was assessed 7 days later using a 30-s probe trial followed by reacquisition training. Acquisition performance was comparable across groups. However, at the 7-day test, MASS rats exhibited poor retention, whereas DIST rats showed a clear preference for the target location, indicating stronger memory. During reacquisition, both groups showed better performance than during initial learning, suggesting that the MASS group did retain some spatial memory. Critically, the superior probe performance in DIST rats indicates that distributed learning produced a stronger and more precise spatial representation. To assess hippocampal engagement, c-Fos expression was quantified in CA1 using unbiased stereological methods in a subset of animals (MASS: n = 6; DIST: n = 6). DIST rats exhibited reduced CA1 c-Fos expression relative to MASS rats. These findings demonstrate that distributed learning enhances spatial memory persistence while reducing hippocampal recruitment, consistent with a shift toward more distributed neural representations, potentially extending beyond the hippocampus. Ongoing c-Fos mapping aims to identify the neural circuits that increasingly support spatial memory following distributed learning, reflecting a reorganization of memory representations.

Disclosures: J.A. Webb: None. **B. Dow:** None. **H. Lehmann:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

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Program #/Poster #: PSTR031.05/HH9

Topic: I.08. Learning and Memory

Support: NINDS 5R01NS125250-05
NINDS 1R01NS125250
NINDS 1R01NS107357-03

Title: Single-unit mechanisms of temporal context representation and recovery in the human medial temporal lobe

Authors: *S. E. SEGER[1], A. DULANEY[1], O. ARAIZA CARRANZA[2], B. C. LEGA[3]; [1]Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [2]Univ. of Texas Southwestern Med. Canter, Dallas, TX; [3]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX

Abstract: Episodic memory depends on representing temporal context as events unfold and recovering that context at retrieval to cue recall. Time cells, which fire at characteristic moments within structured intervals, and ramping cells, which fire with monotonically changing rates over longer windows, have both been proposed as cellular substrates of temporal context. We recorded single units from the human medial temporal lobe in neurosurgical epilepsy patients performing two verbal memory tasks — free recall, in which item information must be generated internally, and serial reconstruction, in which item information is provided at retrieval. We characterize how time cells and ramping cells represent temporal information through their firing rates across paradigms, and how the tuning of these populations relates to task demands. We further investigate whether temporal information is embedded in the phase of theta oscillations, and how phase coding differs based on task demands. During retrieval, we examine the timing of time-cell firing relative to the broader cell-assembly population and to multi-neuron reactivation sequences, motivated by the recovery of temporal context predicted by behavioral models of episodic memory, and we relate these dynamics to behavioral measures of contextually organized recall. Together, this work probes the cellular mechanisms by which the human medial temporal lobe represents temporal context during encoding and recovers it during retrieval.

Disclosures: S.E. Seger: None. **A. Dulaney:** None. **O. Araiza Carranza:** None. **B.C. Lega:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.06/HH10

Topic: I.08. Learning and Memory

Support: MRC Grant MR/Z504476/1

Title: Behavioral timescale synaptic plasticity facilitates learning-dependent emergence of conjunctive non-spatial representations in the hippocampus

Authors: *D. DOBOLYI[1,2], E. J. BÄUMLER[2], M. BUCHHOLZ[2], N. T. ROBINSON[1], D. NITU[1], A. PRODAN[1], A. ROTH[1], A. MACASKILL[1], M. HAUSSER[3,1], B. A. CLARK[2]; [2]Wolfson Inst. for Biomed. Res., [1]Univ. Col. London, London, United Kingdom; [3]Univ. of Hong Kong (HKU), Hong Kong, Hong Kong

Abstract: Adaptive decision-making critically depends on neural representations that integrate stimulus information with context. The hippocampus is central to generating and storing such representations, yet how they are formed and dynamically organized during learning remains poorly understood. Behavioral timescale synaptic plasticity is a rapid learning mechanism that

underlies the formation of new place fields, but whether it contributes to the emergence of conjunctive stimulus-context representations during non-spatial associative learning is unknown. To address these questions, we performed longitudinal two-photon calcium imaging in dorsal CA1 as mice learned a hippocampus-dependent, olfactory temporal association task. With learning, CA1 population activity progressively decorrelated to incorporate the contextual information required to solve the task. This was supported by the emergence of a distinct subpopulation of CA1 neurons which conjunctively integrated information about stimulus identity and context. These previously silent neurons acquired feature selectivity after a single large, 'plateau-like' calcium event, consistent with BTSP. To probe the causal role of BTSP in this process, we employed an 'all-optical' approach combining two-photon imaging with two-photon holographic optogenetics to drive 'plateau-like' events, rapidly inducing task-relevant tuning in individual CA1 neurons. As mice learned the task, the induced tuning profiles gradually shifted from encoding individual stimuli in isolation towards encoding stimulus and context conjunctively. Together, these findings establish BTSP as a fundamental mechanism by which the hippocampus supports non-spatial learning and acquires flexible, context-dependent representations that guide behavior.

Disclosures: D. Dobolyi: None. **E.J. Bäumler:** None. **M. Buchholz:** None. **N.T. Robinson:** None. **D. Nitu:** None. **A. Prodan:** None. **A. Roth:** None. **A. Macaskill:** None. **M. Hausser:** None. **B.A. Clark:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.07/HH11

Topic: I.08. Learning and Memory

Title: Visual discrimination substantially enhances place cells in head-fixed mice

Authors: *L. ZHONG[1], S. BAPTISTA[2], G. MICHEL[1], N. P. SPRUSTON[3], C. STRINGER[3], M. PACHITARIU[4];
[1]Janelia Res. Campus, Ashburn, VA; [2]Janelia Res. Campus, Herndon, VA; [3]HHMI Janelia Res. Campus, Ashburn, VA; [4]Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA

Abstract: Neural responses to stimuli in the mouse visual cortex are plastic and change when animals explore the same visual environments over several days, regardless of whether a visual discrimination task is learned or not (Zhong et al 2025). This plasticity may form the basis of "unsupervised pretraining", a type of latent learning that enables faster subsequent task learning. However, it remains unclear whether unsupervised pretraining alters neural activity in brain regions beyond the visual cortex. In this study, we investigate neural plasticity in hippocampal CA1, a neural region that is critically involved in encoding and maintaining spatial information in familiar environments. We recorded more than 10,000 neurons simultaneously from CA1 in head-fixed mice that navigated in a virtual reality (VR) environment consisting of two distinct

linear corridors (Zhong et al, 2025). Following unrewarded exploration of the VR environments, we observed a small increase in weakly- but not in strongly- selective neurons, corresponding to encoding levels substantially below those of visual cortex. However, during task learning we observed substantial increases in both weakly- and in strongly- selective neurons, reaching selectivity levels similar to those of visual cortex after training. In task-trained mice, we also found that the same corridor can possess multiple sequence maps that are mutually exclusive but lead to the same behavioral outcomes, suggesting a flexible, rich, and strongly-selective code in CA1 for encoding sequential basis functions for reward-driven learning. In conclusion, we find that neural plasticity in CA1 is mainly task-driven in head-fixed mice navigating through vision-based VR.

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Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.08/HH12

Topic: I.08. Learning and Memory

Title: Evaluating the effects of $Ca_V1.2$ overexpression in a novel spatial learning and memory test

Authors: *J. ZHANG[1], K. STANGIS[2], Y. DAS[3], G. G. MURPHY[4];
[1]Univ. of Michigan Neurosci. Grad. Program, Ann Arbor, MI; [2]MNI, Univ. of Michigan, MNI, Ann Arbor, MI; [3]MNI, [4]MNI/MIP, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: The Global Burden of Disease (GBD) 2023 study estimated that psychiatric disorders affect more than 1 billion people and are the leading cause of years living with disability. The diathesis-stress model posits that an individual's genetic vulnerability interacts with external stress to promote disease development. Genome wide association studies (GWAS) across a broad range of psychiatric disorders have implicated risk-associated single nucleotide polymorphisms (SNPs) in *CACNA1C* which encodes for the alpha subunit of L-type voltage-gated calcium channel $Ca_V1.2$. Studies in human patients have linked *CACNA1C* SNPs to increased *CACNA1C* mRNA expression. On the protein level, $Ca_V1.2$ is enriched in the hippocampus and amygdala and serves an important role in synaptic plasticity, hippocampal-dependent spatial memory, and stress-coping behavior. To determine the effects of increased $Ca_V1.2$ expression, our lab has generated a mouse model (OE- $Ca_V1.2$HA) by inserting a full-length rat *Cacna1c* transgene with a hemagglutinin (HA) epitope downstream of a CAG promoter and a Lox-stop-Lox cassette. Mice were subsequently crossed with Syn-cre mice to achieve pan neuronal expression. Because of reported difficulties with probing $Ca_V1.2$ protein, a mouse line (E- $Ca_V1.2$HA) in which the endogenous $Ca_V1.2$ tagged with HA was generated via CRISPR-Cas9 editing. Previous studies from our lab have shown that OE- $Ca_V1.2$HA mice are

mildly anxiolytic and have impaired contextual fear memory consolidation but intact tone-cued fear memory. Given that all types of fear conditioning require an intact amygdala but only contextual fear conditioning also requires spatial information from the hippocampus, this suggests that $Ca_V1.2$ overexpression specifically impacts hippocampal-dependent spatial memory under stress. To determine if this impairment persists in a stress-free context, we are currently using the novel "Colosseum Maze" which was recently developed in our lab and validated with the 5xFAD mouse model which has well-known deficits in spatial memory. Compared to the Morris Water Maze which requires mice to swim under duress or the Barnes maze which requires mice to navigate vertical holes, the Colosseum Maze provides a more ethologically relevant task for mice with minimal aversive stimuli.

Disclosures: J. Zhang: None. **K. Stangis:** None. **Y. Das:** None. **G.G. Murphy:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

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Program #/Poster #: PSTR031.09/HH13

Topic: I.08. Learning and Memory

Support: NIH R01 MH123466

Title: Encoding and reactivation of odor cues and their associated valenced outcomes along the dorsoventral hippocampal axis

Authors: *E. F. B. GIBBENS, M. A. JANSSEN, J. SUN, M. A. A. VAN DER MEER; Dartmouth Col., Hanover, NH

Abstract: Many psychiatric disorders, including PTSD and anxiety, involve the maladaptive reactivation of emotionally valenced experiences. Yet, the neural mechanisms underlying such biased reactivation remain poorly understood. The ventral hippocampus (vHC) is extensively connected with emotion-related regions and plays a key role in affective processing, making it a promising target for investigating the origin of these biases. While reactivation has been relatively well studied in the dorsal hippocampus (dHC), its structure and content in vHC remain poorly characterized. Moreover, most existing rodent studies have employed spatial tasks in freely moving animals, limiting control over valenced experiences and translatability to human research. To address these gaps, we use a head-fixed, odor-based paradigm that balances rewarding and aversive experiences within a single session, enabling us to examine the reactivation of discrete, non-spatial cues along the dorsoventral axis of the hippocampus. Five mice (3M, 2F) were trained on an associative learning task in which sequentially presented odor pairs cued either neutral (nothing), aversive (airpuff), or appetitive (chocolate milk) outcomes. Once mice reached criterion performance, measured by anticipatory licking, we used acute Neuropixels recordings to capture neural activity in dorsal and ventral CA1 during task performance. We first characterized awake sharp-wave ripple (SWR) activity. Full inter-trial

interval (ITI) SWR rates were lower for rewarded trials; however, excluding a post-trial buffer eliminated this effect, suggesting suppressed SWR activity during reward consumption rather than experience-dependent modulation. At the single-neuron level, preliminary analysis (n = 119 neurons) suggests roughly 20% of neurons per subregion encoded single odors, ~10% encoded reward outcomes, and airpuff outcomes were encoded by 41% of dCA1 and 13% of vCA1 neurons. Proportionally fewer odor-selective neurons in vCA1 encoded neutral outcome-associated odors than in dCA1. These stimulus-encoding neurons were active during SWRs, motivating analysis of whether valence shapes reactivation content. Comparing SWR participation rates between reward-encoding and aversive-encoding neurons (odors and outcomes), we found that aversive-encoding neurons participated in a significantly greater proportion of SWRs ($p < .01$), driven primarily by vCA1 ($p = .027$) rather than dCA1 ($p = .12$). Ongoing data collection will further clarify how affective valence shapes reactivation along the dorsoventral axis, advancing our understanding of the neural mechanisms underlying biased memory reactivation.

Disclosures: E.F.B. Gibbens: None. **M.A. Janssen:** None. **J. Sun:** None. **M.A.A. van der Meer:** None.

Poster

PSTR031: Hippocampal Circuit I

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Title: Behaviorally driven increased glutamatergic activity from lateral entorhinal cortex to hippocampus supports object and spatial memory recall.

Authors: *T. SAMCHOK[1,3], M. HERNANDEZ FRAUSTO[5], C. JOHNSON[4], J. TAI[2], J. BASU[6];
[1]NYU Langone Hlth., Maspeth, NY; [2]NYU Langone Hlth., New York, NY; [3]Neurosci. and Physiol., [4]NYU Grossman Sch. of Med., New York, NY; [5]Neurosci. and Physiol., NYU Grossman Sch. of Medicine; NYU Neurosci. Institute; NYU Langone Hlth., New York, NY; [6]Dept. of Neurosci. and Physiol., New York Univ., New York, NY

Abstract: Functional interactions between the entorhinal cortex (EC) and area CA1, the major output area of the hippocampus, are crucial for forming episodic memories of people, places, objects, and events. However, their role in memory recall is less well defined. Canonically, within the EC, the medial entorhinal cortex (MEC) primarily codes for spatial information, particularly global environmental cues, whereas the lateral entorhinal cortex (LEC) processes non-spatial sensory information about local contextual cues, including objects, odors, rewards, and novelty. Although these functionally distinct inputs from MEC and LEC remain largely anatomically segregated within area CA1, multidimensional memory processing requires integrating spatial and contextual information. Recent studies have, in fact, put these strict functional divisions into question, suggesting greater crosstalk between these systems. Global LEC silencing via lesions, or combined suppression of both glutamatergic and GABAergic LEC neurons, impairs associational learning in goal-oriented navigation and multi-object-cued behaviors. However, we know little about the in vivo functional role of LEC glutamatergic projections to CA1 in episodic memory recall during object recognition and spatial navigation. In this research study, we used fiber photometry-based calcium imaging of LEC axon terminals within CA1 during freely moving, hippocampal-dependent novel object recognition (NOR) and Barnes maze (BM) tasks. We expressed a red-shifted RGeCO1a-mCherry, in LEC glutamatergic neurons. We observed that in both tasks, LEC glutamatergic axonal activity was selectively increased during recall compared to encoding. Moreover, in the spatial BM task, LEC-CA1 input activity progressively increased as animals learned the escape location guided by global cues, peaking at the late stages of training and during recall. Accordingly, local chemogenetic silencing of LEC glutamatergic inputs into CA1 via an infusion cannula after learning these behaviors impaired recall performance in both the object recognition and Barnes maze tasks. This unmasks the role of direct glutamatergic input from LEC into CA1 as crucial for memory recall beyond learning, supporting goal-oriented spatial behavior in addition to object recognition. This helps us to better understand how LEC glutamatergic inputs into area CA1 are involved not only during learning features but also a specific functional role during learning remains to be determined. Nevertheless, functional role of LEC glutamatergic inputs into area CA1 during encoding remains to be elucidated.

Disclosures: T. Samchok: None. **M. Hernandez Frausto:** None. **C. Johnson:** None. **J. Tai:** None. **J. Basu:** None.

Poster

PSTR031: Hippocampal Circuit I

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Topic: I.08. Learning and Memory

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Whitehead Foundation
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Title: Anatomy and function of dendrite-targeting inhibitory neurons in CA3 of the mouse hippocampus

Authors: *J. J. MOORE[1,2], J. BASU[3,1];
[1]NYU Sch. of Med., New York, NY; [2]Ctr. for Computat. Neurosci., Flatiron Inst., New York, NY; [3]Dept. of Neurosci. and Physiol., New York Univ., New York, NY

Abstract: Inhibitory neurons (INs) expressing somatostatin (SST) preferentially target the dendrites of pyramidal neurons. Later stages of Alzheimer's Disease (AD) are associated with a reduction in the number and activity of SST^+ INs, implicating their role in impaired memory. While the hippocampus in mice is crucial for spatial memory, the contribution of hippocampal SST^+ IN activity to this functionality is unknown. This project aims to test the hypothesis that SST^+ INs are key modulators of spatial selectivity and remapping and that this role is impaired in AD. First, we present anatomical data quantifying morphology and overall cell counts of SST-positive neurons in the different subfields of the hippocampus. Typically, apical dendritic inhibition is balanced by excitatory input from Entorhinal Cortex, but both of these inputs are degraded in AD. We quantify changes of the density, dendritic arborization, and projection patterns of inhibitory SST^+ INs in wild type and AD model mice (amyloid precursor protein knock in, APP-KI), at a wide span of ages. Second, to characterize SST^+ IN activity, we expressed GCaMP6f, a fluorescent indicator of neural activity, in SST+ INs of adult SST-Cre mice. Headfixed mice were trained to run on a treadmill belt and discriminate two environments by licking to one of two water ports. Imaging was performed through a cannula implanted over area CA3 of the hippocampus for 8 consecutive days. SST^+ INs showed a variety of response properties, including modulation by speed and reward. A large proportion of neurons showed overall activity modulation by the environment, preferring one environment over the other, without specific spatial modulation. A subset of cells also showed spatial modulation like the traditional place cell activity observed in pyramidal neurons. Response properties were highly stable across days, far more stable than typical pyramidal neuron responses. We quantify these

response properties in young and aged mice in both WT and APP-KI mice. This demonstrates that SST^+ INs can convey important spatial information. Our quantification of SST^+ IN distribution, morphology, and activity demonstrates the varied roles that SST^+ INs can play in spatial memory, particularly in discriminating between different environments. It is likely that alterations in these properties may underlie some of the behavioral and cognitive deficits observed in AD model mice with impaired spatial memory. We are currently exploring if rescuing deficits in SST^+ INs activity may ameliorate spatial memory deficits, providing a potential future therapeutic pathway.

Disclosures: J.J. Moore: None. **J. Basu:** None.

Poster

PSTR031: Hippocampal Circuit I

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ALZHEIMERS ASSOCIATION grant AARGD-NTF-23-1151101

Title: Studying the Role of Inhibition in Behavioral Timescale Synaptic Plasticity in Hippocampal CA1

Authors: *S. WANG[1], R. W. TSIEN[2], J. BASU[3];
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Abstract: Behavioral Timescale Synaptic Plasticity (BTSP) enables rapid, one-shot formation of hippocampal place fields through dendritic calcium plateau potentials, but the involvement of inhibition in this process remains poorly understood. Originally, BTSP has been induced in acute slices with pharmacological blockage of inhibition. However, *in vivo*, inhibition is intact and is actively modulated during place cell tuning, which is mechanistically linked to BTSP. This poses the question whether BTSP can be induced in the presence of inhibition *ex vivo*, and if so, whether BTSP modulates inhibitory activity. To address these questions, we performed whole-cell current clamp recording in CA1 of acute hippocampal slices from C57BL/6 male and female mice. We were able to induce BTSP under more physiological conditions with intact inhibition. In the presence of inhibition, potentiation of postsynaptic potentials (PSPs, a combination of excitatory and inhibitory inputs) was reduced compared to when inhibition was blocked. We hypothesized that inhibition gates potentiation of excitatory inputs to suppress BTSP. To test this, we isolated excitatory postsynaptic currents (EPSCs) using whole-cell voltage clamp recordings. Surprisingly, we found that EPSCs were equally potentiated with or without intact

inhibition, suggesting that BTSP induces a purely excitatory component (e-BTSP) that persists in the presence of inhibition. To test whether inhibitory transmission is co-modulated during BTSP (i-BTSP), we recorded EPSCs and inhibitory postsynaptic currents (IPSCs) from the same cell using alternating holding potentials in voltage clamp recordings to isolate each synaptic current. We found that, indeed, IPSCs were potentiated along with EPSCs in a correlated manner. Together, our results demonstrate behavioral timescale synaptic plasticity at inhibitory synapses, which is poised to modulate the input-output functions of pyramidal cell.

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Poster

PSTR031: Hippocampal Circuit I

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Program #/Poster #: PSTR031.13/HH17

Topic: I.08. Learning and Memory

Support: NIH G10004321

Title: Parallel Hippocampal Remapping Across Behavioral and Population Burst Timescales

Authors: *D. D. LUO[1], B. K. GIRI[2], K. DIBA[3], C. KEMERE[1];
[1]Rice Univ., Houston, TX; [2]Anesthesiol., [3]Dept of Anesthesiol., Univ. of Michigan, Ann Arbor, MI

Abstract: When animals actively explore novel environments, their hippocampal neural representations rapidly reorganize to form a cognitive map at the behavioral timescale. Complementing this online processing, hippocampal population burst events (PBEs)—which always co-occur with sharp-wave ripples (SWRs) during sleep or quiet wakefulness—replay neural sequences from recent experiences at a compressed timescale. While this offline process aids memory consolidation, it remains unclear how this offline PBE map adapts to the rapidly shifting online cognitive map.
To investigate this, the Extended Poisson Gaussian-Process Latent Variable Model (eP-GPLVM) was applied to hippocampal spike trains from rats exploring novel mazes. This dimensionality reduction technique reveals underlying latent neural structures without relying on pre-defined tuning variables, enabling the observation of single-trial population dynamics.
First, we assess whether both online and offline maps undergo remapping. By tracking manifold drift in the latent space over moving time windows, we observe the rapid evolution of the RUN map (online). At the population-burst timescale, parallel evolution is also observed in the latent manifolds of PBEs during immobility (immobile PBE map).
Next, we investigate whether the neural remapping is in a consistent direction and is temporally aligned across these distinct timescales. By inferring the latents of the immobile PBEs in the latent space learned from the RUN data, we compare their trajectory evolution. Our results demonstrate that immobile PBEs remap in a direction consistent with the RUN map. And this

parallel remapping across the two brain states is temporally aligned, revealing the close temporal coupling between active spatial updating and offline memory consolidation.

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Poster

PSTR031: Hippocampal Circuit I

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Program #/Poster #: PSTR031.14/HH18

Topic: I.08. Learning and Memory

Support: 5R01MH139216-02

Title: Sleep protects against retroactive memory interference

Authors: *E. CUI[1], N. R. KINSKY[1], C. KEMERE[2], K. DIBA[1];
[1]Anesthesiol., Univ. of Michigan-Ann Arbor, Ann Arbor, MI; [2]Rice Univ., Houston, TX

Abstract: The capacity to continuously acquire information from the environment carries an inherent cost as the new memories could potentially interfere with earlier ones. We and others have hypothesized that sleep stabilizes memories and protects against retroactive interference. To test this hypothesis, we used and modified the previously published Object-in-Context task that reliably elicits retroactive interference [1]. We replicated the previously reported result using both the original and a shortened experimental paradigm to show that rats display significantly impaired memory with 1-h, but not 4-h, uninterrupted rest/sleep between the learning sessions. To dissociate the contributions of rest and sleep, we performed gentle-handling sleep deprivation during this 4-hour period, and found that sleep-deprived rats showed impaired memory compared to non-sleep-deprived rats, indicating that sleep itself, instead of passage of time, confers protection. These findings define a critical temporal window required for sleep-dependent memory consolidation, providing an efficient behavioral framework for investigating the underlying neural circuitry of memory protection in the future.
[1] Martínez, M. C., Villar, M. E., Ballarini, F., & Viola, H. (2014). Retroactive interference of object-in-context long-term memory: role of dorsal hippocampus and medial prefrontal cortex. Hippocampus, 24(12), 1482-1492.

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Poster

PSTR031: Hippocampal Circuit I

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Program #/Poster #: PSTR031.15/HH19

Topic: I.08. Learning and Memory

Support: NSF Grant 2423995 (CRCNS)

Title: Sleep-Dependent Remodeling of Hippocampal CA1 Connectivity Inferred from Spike Train Statistics

Authors: *S. Y. LI[1,2], N. R. KINSKY[1], B. K. GIRI[1], A. AMARASINGHAM[3], K. DIBA[1]; [1]Anesthesiol., [2]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI; [3]Mathematics and Neuroscience, City Col. and the Grad. Ctr., City Univ. of New York, New York, NY

Abstract: Sleep is essential to memory consolidation, likely by supporting local network processes such as hippocampal replay and oscillations. Disruption of these neuronal activities correlates with memory deficits under sleep deprivation. However, the precise patterns of synaptic modification underlying memory formation during sleep remain elusive. Here, we utilized cross-correlogram (CCG) analysis to identify thousands of *in vivo* synaptic connections and examine their functional reorganization during spatial memory consolidation at the network level. We analyzed large-scale, long-duration electrophysiology recordings from the hippocampus CA1 of seven rats, capturing both sleep and sleep deprivation before and after novel maze exploration. We hypothesized that learning would cause both enhancement and pruning within selected neuronal subpopulations. Through a computational approach featuring CCG analysis validated by timescale separation, we identified thousands of putative synaptic connections across four connection types: Pyramidal-interneuron, Interneuron-Pyramidal, Interneuron-Interneuron, and putative Pyramidal-pyramidal connections, as validated by a jittered baseline. Connection strengths are defined by measures of synaptic efficacy, including jitter-based synchrony index and synaptic transmission gain, and tracked for high-quality Pyramidal-Interneuron pairs. Preliminary results revealed that while individual synapses can either strengthen or weaken; however, overall connection strength demonstrated an increase during unrestricted sleep but decreased during recovery sleep after deprivation. Monosynaptic connections coincided with a rich variety of sub-millisecond co-firing patterns. In addition, We developed a visual interface flexible for integrating CCG-based methods and new datasets to support analysis. These results indicate that sleep-dependent synaptic changes include both upscaling and downscaling, potentially corresponding to their involvement in learning, and contributing to large-scale network reorganization during memory consolidation.

Disclosures: S.Y. Li: None. **N.R. Kinsky:** None. **B.K. Giri:** None. **A. Amarasingham:** None. **K. Diba:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.16/HH20

Topic: I.08. Learning and Memory

Support: NIH/NINDS 1F32NS117732
NIH/NINDS R01NS115233

Title: Acute effects of psilocybin on hippocampal sharp wave ripples

Authors: I. KAYIKCIOGLU BOZKIR[1], **R. LASHIN**[2], T. LIU[5], D. PAL[3], K. DIBA[4], *N. R. KINSKY[2];
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Abstract: Psilocybin is a psychedelic compound with potential therapeutic effects for the treatment of depression and anxiety. Previous studies have shown that psilocybin can promote both structural and functional neuroplasticity in cortical and hippocampal circuits, however, the cellular and network-level mechanisms underlying these changes remain poorly understood. Sharp wave ripples (SWRs) are transient, high frequency (150-250Hz) oscillations observable in the hippocampal local field potential coincident with population burst spiking which is hypothesized to broadcast memory-related information throughout the cortex. SWRs have been causally linked to memory consolidation and have been shown to induce long-term potentiation in hippocampal neurons. Moreover, coordination between SWRs and prefrontal cortex during sleep has been shown to produce alterations in the prefrontal cortex network. SWRs could therefore provide a potential mechanism for instilling memory-related plasticity in cortical circuits. In this study in rodents chronically implanted with linear silicon probes we investigated the acute and lasting effects of psilocybin on SWRs. We found that psilocybin infusion (10 mg / kg) acutely decreased the peak frequency of SWRs compared to control (saline) infusions the day before or after psilocybin administration. We found that psilocybin also acutely lengthened SWRs, which is associated with stronger memory consolidation. Although animals remained essentially motionless following psilocybin administration, they rarely entered sleep. These results indicate that psilocybin produces an acute modification to hippocampal dynamic activity important for cognition, memory, and coordination with cortical circuits.

Disclosures: I. kayikcioglu bozkir: None. **R. Lashin:** None. **T. Liu:** None. **D. Pal:** None. **K. Diba:** None. **N.R. Kinsky:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.17/HH21

Topic: I.08. Learning and Memory

Support: R00MH129565
Whitehall Foundation Research Grant

Alfred P. Sloan Neuroscience Award
Klingenstein Fellowship Award in Neuroscience

Title: A seed-and-expand circuit architecture underlies CA3 attractor dynamics in the hippocampus

Authors: *B. KANG[1,2,3], G. HENZE[1,2,3], K. STACHOWICZ[1,4,3,2], S. QIU[1,2,3], T. GEILLER[1,2,3]; [1]Neurosci., Yale Univ., New Haven, CT; [2]Wu Tsai Inst., New Haven, CT; [3]Kavli Inst. for Neurosci., New Haven, CT; [4]Yale Univ. Interdepartmental Neurosci. Program, New Haven, CT

Abstract: Hippocampal area CA3 has long been modeled as a uniform recurrent attractor network supporting autoassociative memory, yet how such dynamics arise within a heterogeneous cellular population remains unknown. Here we identify a stratified solution rooted in the two morphologically distinct CA3 pyramidal cell types. Using subtype-resolved two-photon imaging, post hoc morphological registration, and single-neuron and pathway-specific optogenetics in navigating mice, we show that dentate gyrus (DG)-recipient thorny neurons act as early memory seeds. They form sparse, stable place fields within the first laps of a new environment and maintain them across days. Athorny neurons, in contrast, are recruited later, are more dynamic, and progressively expand the spatial map. Focal DG activation was sufficient to drive this cascade, producing new fields in thorny neurons first and athorny neurons thereafter. In a separate test of map retrieval, silencing DG during the first laps of a familiar environment delayed thorny re-engagement and was accompanied by athorny neurons forming fields at incorrect locations, whereas silencing later in the session had limited effect, establishing that DG drive is most critical for re-initiating CA3 representations. A two-stage computational model built on this architecture reproduced these dynamics and outperformed homogeneous recurrent networks at both pattern completion and resistance to interference. CA3 attractor dynamics are thus implemented not through a homogeneous network but a heterogeneous, stratified circuit in which dentate-driven thorny neurons anchor a stable index and athorny neurons carry its flexible expansion.

Disclosures: B. Kang: None. **G. Henze:** None. **K. Stachowicz:** None. **S. Qiu:** None. **T. Geiller:** None.

Poster

PSTR031: Hippocampal Circuit I

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Topic: I.08. Learning and Memory

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NIH Grant T32NS041228
Sloan Foundation
Whitehall Foundation

Klingenstein Fund
Thomas Kingsley Lawrence '19 Program in Brain Research

Title: Integration and reorganization of excitatory inputs at single-spine resolution in the hippocampal output pathway during spatial learning

Authors: *K. M. STACHOWICZ, S. QIU, G. HENZE, T. GEILLER;
Dept. of Neurosci., Yale Univ., New Haven, CT

Abstract: Hippocampal place cells provide spatial representations required for navigation and memory-guided behaviors in rodents, but how downstream circuits transform these encodings remains poorly understood. The subiculum, the principal output node of the hippocampus, is uniquely positioned to address this question, yet remains one of the least studied regions of the hippocampal formation. Resolving how the subiculum performs this transformation requires understanding how individual neurons integrate spatially structured synaptic inputs and convert them into somatic output. Dendrites and spines are the cellular substrates of this input-output transformation, yet how excitatory inputs onto subicular neurons are organized and modified during learning remains unknown. To address this gap, we developed an in vivo two-photon imaging approach to record and track calcium and glutamate signals at the single-spine level in the mouse subiculum during a spatial learning task. In this task, head-fixed mice run on a one-dimensional belt patterned with somatosensory cues and a hidden fixed reward zone. Over days, mice learn to restrict licking to the reward zone. We tracked the same subicular spines and dendrites across days during both task performance and post-task rest, a behavioral state associated with reactivation and memory consolidation. Across learning, excitatory inputs onto subicular neurons became progressively aligned with the spatial activity of the postsynaptic neuron, indicating that subicular input-output coupling is refined over experience. This form of progressive co-tuning differs from canonical models of single-trial place field formation based on dendritic plateau events, suggesting that the subiculum may use CA1-derived spatial inputs to gradually construct and stabilize a downstream output code. To identify activity patterns that precede this co-tuning, we analyzed spine activity during post-task rest. Spines that became co-tuned on the following day exhibited unusually high-amplitude activity during the preceding rest epoch, suggesting that rest-associated input activity may predict subsequent incorporation into the subicular spatial code. Ongoing experiments are testing whether these high-amplitude spine events coincide with sharp-wave ripples and whether co-tuned spines arise from distinct presynaptic sources, including CA1, recurrent subicular inputs, and other afferent pathways. Together, these results reveal a spine-level mechanism by which subicular neurons reorganize excitatory inputs to generate spatially derived representations during spatial learning.

Disclosures: K.M. Stachowicz: None. **S. Qiu:** None. **G. Henze:** None. **T. Geiller:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

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Topic: I.08. Learning and Memory

Support: National Institutes of Health R00MH129565
Alfred P. Sloan Foundation
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Whitehall Foundation
Kavli Institute for Neuroscience, Yale School of Medicine

Title: Input convergence gates the transmission of CA1 reactivations to downstream circuits

Authors: *M. CUM[1], B. KANG[2], S. QIU[2], K. STACHOWICZ[2], T. GEILLER[2];
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Abstract: Hippocampal offline reactivations are thought to support memory consolidation by replaying recent experience and driving plasticity in downstream circuits. Although CA1 reactivates frequently during post-task quiescence, only some reactivations engage output pathways and propagate beyond the hippocampus. The circuit mechanisms that determine whether a given CA1 reactivation propagates remain unknown. Using the subiculum, the principal output region of the hippocampus, as a model pathway, we performed mesoscale two-photon imaging across the CA1-subiculum projection during spatial learning. We found that learning increased the downstream impact of hippocampal reactivations without changing their rate or amplitude in CA1. Instead, learning reorganized the structure of reactivation events: CA1 recruited increasingly reproducible neuronal assemblies, and subicular activity became progressively time-locked to them. Distinct CA1 reactivation patterns recruited distinct subicular ensembles, indicating that the subiculum develops an assembly-specific readout of CA1 activity. To link this functional routing to the circuit architecture, we developed a "record-and-tag" approach combining population imaging with single-cell monosynaptic input tracing from individual subicular neurons. CA1 neurons converging onto the same subicular target formed functionally co-active ensembles during reactivations, and their co-participation strengthened with learning. We define reactivations in which a subicular neuron's convergent CA1 inputs are co-active above chance as "convergent reactivations" and find that the proportion of reactivations that are convergent, rather than the overall reactivation rate, predicts that neuron's recruitment during offline reactivations. Thus, these results identify a circuit mechanism by which CA1 reactivations are routed to downstream regions through cross-regional coactivation.

Disclosures: M. Cum: None. **B. Kang:** None. **S. Qiu:** None. **K. Stachowicz:** None. **T. Geiller:** None.

Poster

PSTR031: Hippocampal Circuit I

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.20/HH24

Topic: I.08. Learning and Memory

Support: Restracomp Scholarship

Title: BTSP generates and stabilizes hippocampal representations of associative memory

Authors: *J. DUDA;
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Abstract: Hippocampal pyramidal neurons quickly become tuned to different environmental cues and contexts, such as space (place cells) or delays (time cells). Though this tuning to specific behavioural features is critical for memory formation, the mechanisms underlying its rapid formation remain unclear. A novel candidate mechanism is "behavioral time-scale synaptic plasticity" (BTSP) whereby hippocampal neurons undergo a large depolarization, known as a 'plateau potential', while a mouse is in a specific location, followed by the emergence of stable tuned spiking at that location. However, beyond place cell formation, it is unclear if time cells can also be tuned by BTSP. To address this, we utilized 2-photon calcium imaging to record thousands of CA1 pyramidal neurons across days while mice learnt a non-spatial delayed odour discrimination task. After training, we find an increased number of time cells, with temporal tuning to the delay period, compared to naïve exposure to the task, many of which were tuned through putative BTSP events. Additionally, a higher rate of time cell tuning and associated BTSP events were observed after the rewarded odour versus non-rewarded. The number of tuned cells, and their tuning strength, correlated with task performance. Finally, using 2-photon holographic optogenetics, we simulated plateau potentials in pyramidal neurons during the same task. Confirming our above results, we found that artificial plateaus were able to yield tuned cells as well as stabilize already tuned cells, potentially supporting memory formation. Overall, we present novel learning-related dynamics of time cell formation in the hippocampus, as well as a potential mechanism behind this tuning.

Disclosures: J. Duda: None.

Poster

PSTR032: Hippocampal Circuit II

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.01/HH25

Topic: I.08. Learning and Memory

Support: CZI CP2-1-0000000614
R01MH132204

Title: Covariance clustering analysis of multi-omics data reveals complex relationships between co-expression modules, protein networks, and behavior in an active place avoidance task

Authors: *J. HAN[1], C. GARCIA JOU[2], J. HAN[4], H. A. HOFMANN[5], S. MARTINIANI[1], A. A. FENTON[3];
[1]New York Univ., New York, NY; [2]New York Univ., Brooklyn, NY; [3]Ctr. for Neural Sci., New

York Univ., New York, NY; [4]Univ. of Texas at Austin, Austin, TX; [5]Integrative Biol., The Univ. of Texas at Austin, Austin, TX

Abstract: Synaptic plasticity underlying long-term memory persistence requires coordination of diverse molecular substrates, yet direct gene-protein-behavior connections remain difficult to identify with conventional analysis tools. Although diverse multi-omics approaches have been developed, they typically miss molecules known to be crucial for memory biology. Here we collected matched transcriptomic and proteomic data from 32 wild-type (WT) and 14 Fmr1 knockout (KO) mouse hippocampi a week after memory or control training in the active place avoidance task (KO mice lack FMRP, a synaptic translation regulator). Then we applied C-SCoRe (Correlation Signal Co-Cluster Reduction), which exploits within-subject molecular correlations, to identify low-dimension co-expression modules and how they change with memory training.

Before applying C-SCoRe to multi-omics data, we validated it using model datasets for three scenarios of increasing gene-protein relationship complexity: linear, nonlinear, and gain control, mimicking transcription factor regulation. Each dataset included pre-defined co-expression modules and gene/protein importance rankings for predicting memory behavior. We assessed module recovery and whether summary vectors outperform raw expression in predicting model protein expression and behavior. C-SCoRe detected pre-set modules under the simpler conditions. Under complex scenarios, combining the modules across conditions outperformed using memory-associated module alone, suggesting that cross-treatment consensus stabilizes module structure. Module summary vectors outperformed raw gene expression values in both predicting protein and memory behavior. Unlike gene expression, the raw protein expression values better predicted memory behavior than the summary protein modules.

In the real dataset, we hypothesized that synaptic plasticity-related gene and/or protein module structure is reorganized by FMRP loss and/or training. Conventional differential expression analyses revealed strong genotype effects but weak training-dependent effects. However, C-SCoRe identified co-expression modules with functionally related synaptic plasticity genes in transcriptomes. While individual mRNA levels did not predict corresponding protein expression, gene modules can predict protein modules that contribute to WT and KO memory behavior, with the simulations providing interpretive benchmarks. Taken together, our results suggest that co-expression module structure captures gene-protein-behavior relationships underlying memory that conventional differential expression analyses fail to identify.

Disclosures: J. Han: None. **C. Garcia Jou:** None. **J. Han:** None. **H.A. Hofmann:** None. **S. Martiniani:** None. **A.A. Fenton:** None.

Poster

PSTR032: Hippocampal Circuit II

Location: WCC Halls A-C

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Program #/Poster #: PSTR032.02/HH26

Topic: I.08. Learning and Memory

Support: R01MH132204
T32MH019524

Title: Towards quantifying a PKMζ long-term memory trace

Authors: *A. GARCIA[1], A. PATEL[1], A. MANU[1], T. C. SACKTOR[2], A. A. FENTON[1]; [1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]Dept Physiol. & Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY

Abstract: Does memory require a memory trace, the enduring physical change in the brain hypothesized by Richard Semon's concept of an "engram?" In our search for an active place avoidance memory trace we have identified enhanced fEPSP changes persisting over 1 month in both excitatory and inhibitory synaptic pathways within the mouse hippocampus. Using ArcCreERT2 x STOPflChR2-eYFP TRAP2 mice to tag memory-activated neurons, we also discovered that 1-mo memory causes 200% increases of protein kinase M zeta (PKMζ) selectively in memory-tagged neurons at the identified potentiated postsynaptic compartments of the tri-synaptic pathway. PKMζ is a persistently active kinase, atypical PKC isoform with no inactivating regulatory subunit, that forms an enduring complex with the scaffolding protein KIBRA at potentiated synapses. Inhibition of either PKMζ kinase action or the KIBRA-PKMζ complex depotentiates established LTP and memory, even after 1 month. Here we used the TRAP2 mice to identify and quantify the subcellular locations of the 1-mo PKMζ memory trace, hypothesising that memory persistence will cause persistently increased PKMζ at dendritic spines of potentiated synaptic compartments. Mice that acquired either a strong or weak place active place avoidance (APA) memory expressed similar numbers of eYFP-tagged CA1 neurons, respectively 17.8% ± 3.2% vs 13.7% ± 3.2%. This highlights that activity alone is insufficient to mark memory strength. One possibility is that these tagged cells differentially express PKMζ depending on learning. We find that PKMζ in the upper blade of the dentate gyrus is increased in tagged cells of mice with strong memory ($p < 0.05$), consistent with our previous finding that this region is physiologically altered with APA training. This result can appear surprising in light of the observation that only 2% of spines express PKMζ in tagged cells. We therefore aim to next investigate the spatial distribution of the PKMζ-expressing memory-tagged spines. Such a finding promises to determine whether the dendritic localization of this putative memory trace supports or challenges computational and biophysical models for optimizing synaptic transmission.

Disclosures: A. Garcia: None. **A. Patel:** None. **A. Manu:** None. **T.C. Sacktor:** None. **A.A. Fenton:** None.

Poster

PSTR032: Hippocampal Circuit II

Location: WCC Halls A-C

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Topic: I.08. Learning and Memory

Support: R01 AG070094
NIA K99/R00 AG049090
FL DOH 20A09
FL DOH 21K12

Title: Anterior Thalamic-Parietal Circuits Support Spatial Reference-Frame Transformation During Navigation

Authors: *Y. CHEN[1], B. J. CLARK[2], A. A. WILBER[3];
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Abstract: Understanding how rodents navigate space requires disentangling the use of different spatial reference frames, including allocentric (map-based) and egocentric (body-centered) strategies. Although extensive theoretical and computational work suggests that both the anterior thalamic nuclei (ATN) and parietal cortex (PC) contribute to transofrmation/coordination between allocentric and egocentric reference frames, the actual neural computations performed by these regions in reference-frame processing remains unclear. Because rodents will frequently shift reference frames even when random foraging, determining which reference frame animals rely on in a given context or moment in time remains challenging.To address this issue, we developed the Map-Action Transformation Task (MATT), a novel behavioral paradigm designed to dissociate reference-frame use during navigation. The task allows systematic examination of how animals use egocentric, allocentric and transform between these representations when navigating toward a fixed reward location. First, I present several data sets validating this paradigm. Next, using this paradigm, we examined the effects of temporary muscimol inactivation targeting either the ATN or PC on navigation behavior. Preliminary analyses revealed distinct behavioral deficits following inhibition of the two regions in transformation condition of MATT. Both Bilateral PC and ATN inactivation significantly decreased correct responses; however, for bilateral ATN inactivation this was due to increased incorrect arm selections, consistent with a lack of a head direction input necessary for a transformation. While bilateral PC inactivation increased no-selection trials and hesitation time, indicating deficits in the transformation and/or the egocentric action output of this transformation. These findings suggest that ATN and PC contribute differently to successful navigation. We are performing the same inactivation experiments in both allocentric and egocentric versions of MATT to further disentangle how ATN and PC support the use of different reference frames versus transformations. Work is also underway to extend these findings in two directions 1) inactivating the ATN-PC pathway using retrograde DREADDs in PC and CNO infused into ATN (assess a potential pathway) and 2) recording from PC during paired random foraging to identify head direction cells and how PC cells might be affected if paired with ATN inhibition during MATT transformation trials. These experiments will more precisely resolve how interactions between these regions support spatial reference-frame transformations.

Disclosures: Y. Chen: None. **B.J. Clark:** None. **A.A. Wilber:** None.

Poster

PSTR032: Hippocampal Circuit II

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Program #/Poster #: PSTR032.04/HH28

Topic: I.08. Learning and Memory

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NINDSR01NS131728
NIARF1AG080818
the Brain and Behavior Research Roundation
Human Frontier Science Program

Title: Parallel independent voltage computing along dendrites of hippocampal pyramidal neurons

Authors: *A. NOGUCHI[1], S. TERADA[1], G. ZAKKA[2], C. O'TOOLE[3], L. REYNOLDS[3], M. LAND[4], B. ROZSA[5], F. ST-PIERRE[4], A. LOSONCZY[2];
[1]Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [2]Neurosci., [3]Columbia Univ., New York, NY; [4]Baylor Col. of Med., Houston, TX; [5]BrainVisionCenter Res. Inst. and Competence Ctr., Budapest, Hungary

Abstract: Dendrites of pyramidal neurons are proposed to be active computational units capable of processing synaptic inputs in parallel across their arbors to shape somatic output. Hippocampal CA3 pyramidal neurons, a central hub for rapid memory encoding during spatial learning, receive powerful mossy fiber inputs, recurrent/associational-commissural excitation, and entorhinal cortical inputs across distinct dendritic domains. However, *in vivo* dendritic mechanisms governing information processing during learning remain largely unknown. To address this gap, we leveraged ultra-fast, motion-stabilized, three-dimensional voltage imaging to record voltage dynamics from dendrites and somata of individual CA3 pyramidal neurons in behaving mice during virtual-reality-guided spatial navigation. In familiar environments, somato-dendritic coupling in place cells was spatially organized and associated with temporally asymmetric subthreshold dendritic dynamics that preceded the somatic place field. Distinct patterns of somato-dendritic decoupling emerged across different remapping processes. Reward translocation within the same environment induced transient decoupling between the soma and its dendrites, characterized by rapid reorganization of somatic place fields while dendritic representations remained more stable, followed by their gradual, centrifugal realignment toward the soma. In contrast, during exposure to novel environments, place field formation first emerged in distal dendrites and progressed centripetally toward proximal dendrites and the soma. Subthreshold dendritic dynamics further contained latent representations of upcoming somatic tuning, positioning subthreshold voltage dynamics as an additional high-dimensional layer of neuronal computation. Together, these results indicate that dendritic voltage dynamics constitute a multi-timescale substrate that integrates past, ongoing, and prospective representations,

dynamically organizing these signals to shape somatic output while preserving flexibility. This flexible organization expands the computational capacity of single hippocampal pyramidal neurons by enabling parallel input processing and context-dependent reorganization during learning.

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Poster

PSTR032: Hippocampal Circuit II

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.05/HH29

Topic: I.08. Learning and Memory

Support: R01 MH132204
R01 DA059220
T32 NS086750

Title: Reregistering the CA1 place code: LTP and context-dependent alignment of population geometry

Authors: *J. R. HURTADO, Jr[1], A. A. FENTON[2], S. CHUNG[3];
[1]New York Univ., New York City, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY; [3]Harvard Univ., Cambridge, MA

Abstract: Hippocampal place-cell activity changes across experience, but it remains unclear whether changes reflect alterations in the coactivity patterns or transformations that preserve representational geometry. We analyzed CA1 population activity using a geometric framework that separates manifold shape from manifold alignment. For each recording epoch, trial-averaged activity was represented as a neuron-by-place tuning matrix. These representations can be analyzed in terms of neural coordinates or coactivity relationships between neurons or places, allowing us to distinguish coordinate rotations from shape changes.We reanalyzed a published calcium imaging dataset in which rats explored a circular cylinder and square box across nine days. Shape-based measures showed comparable variability within and across environments and did not distinguish SAME (circle-circle, square-square) from DIFF (circle-square) comparisons. In contrast, alignment measures revealed strong environmental specificity. Coordinate misalignment distinguished SAME and DIFF environments. Across repeated exposure, misalignment within SAME environments decreased with familiarity, whereas DIFF comparisons remained highly misaligned.To test whether this stability depends on synaptic plasticity, we reanalyzed electrophysiological recordings from animals receiving saline or the atypical protein kinase C inhibitor ZIP, which reverses established LTP. ZIP had little effect on place coactivity, modest effects on neural coactivity, and large effects on geometric alignment. We additionally analyzed published calcium imaging studies in VR tasks with two-choice

structure and found robust shape changes, suggesting that task demands or VR learning may influence manifold shape.These findings suggest that experience in the absence of task structure primarily stabilizes mappings between neural activity and spatial coordinates rather than the underlying coactivity structure of the representational manifold. Persistent synaptic plasticity is required for maintaining this alignment. This geometric dissociation separates intrinsic fluctuations in manifold shape from experience-dependent representational stability and provides a new interpretation of CA1 remapping as representational misalignment.

Disclosures: J.R. Hurtado: None. **A.A. Fenton:** None. **S. Chung:** None.

Poster

PSTR032: Hippocampal Circuit II

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.06/HH30

Topic: I.08. Learning and Memory

Support: NIMH NRSA F32MH135680
NIMH Grant R01MH132204

Title: Representational similarity within the hippocampus and anterior cingulate cortex during cognitive control

Authors: *G. J. BLAIR, A. A. FENTON;
Ctr. for Neural Sci., NYU, New York, NY

Abstract: Our research addresses how information is dynamically represented across distinct brain regions. Navigating our daily lives requires cognitive control, the judicious use of limited cognitive resources to yield preferred outcomes, which is known in humans and animals to depend on the medial prefrontal cortex (mPFC), including the anterior cingulate cortex (ACC). Our studies of rats and mice performing an active place avoidance task have also demonstrated the importance of hippocampus (HPC) for cognitive control. We performed simultaneous imaging using miniscopes in the ACC and HPC of freely-behaving rats to determine how information is separately represented in these two areas. Rats were transfected with GCaMP8m in HPC dorsal CA1 and ACC, then gradient refractive index lenses were implanted above the injection sites. Rats were trained to perform an Active Allocentric Place Avoidance (AAPA) task or an appetitive Spatial Memory and Allocentric Reinforcement Training (SMART) task. Complementing AAPA, SMART is a novel spatial decision-making behavior for which we can modulate cognitive control demands. Both tasks are conducted on a rotating circular arena, which dissociates the local arena cues from the stationary distal room cues. Rats must suppress the local distractor cues while using the distal room cues to guide either avoidance (in AAPA) or appetitive navigation (in SMART). Because room and arena cues continuously change their relationships, both tasks require cognitive control to utilize the appropriate task-relevant cues. Ensemble recordings of ACC and of CA1 demonstrate that cells in both regions are significantly

modulated by position, though CA1 activity is more location-specific (greater mutual information). This room-specific spatial information develops slower than the hippocampal representation. Analysis of the momentary (200 ms) positional information (Ipos) and Bayesian decoding of room position reveals a highly coordinated spatial representation within HPC and ACC for the reinforced room frame of reference. While each area's representation is often local to the current position, sometimes it is not, especially when the rat is not at a location crucial to the current task. Furthermore, the similarity of the two representations increases as rats become proficient in both tasks. This appears most prominent either at the point of avoidance (in AAPA) or at the decision location (in SMART). These features of the task and associated HPC and ACC representations provide a paradigm for investigating mechanisms of how two distinct brain circuits coordinate the information needed to guide behavior.

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Poster

PSTR032: Hippocampal Circuit II

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.07/HH31

Topic: I.08. Learning and Memory

Support: NIH Grant R01MH132204

Title: Testing the role of PKMzeta in long-term stability of hippocampal spatial representations

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Abstract: Long-term memories are thought to reside at synapses that are modified by altered protein expression during learning and maintained by de novo protein synthesis. Protein kinase M Zeta (PKMζ) is a persistent kinase, atypical PKC isoform that localizes at postsynaptic sites by forming a complex with the postsynaptic scaffolding protein KIBRA, a process called persistent synaptic tagging. PKMζ is crucial for maintaining long-term memories, but its genetic deletion is compensated by upregulated expression of PKCι/λ, the other atypical PKC. Here, we tested the role of PKMζ in the long-term maintenance of hippocampal CA1 spatial representations, a process thought to be maintained by synaptic plasticity. We allowed *CaMKIIa-CreER^{T2}-Prkcz-floxed*, and *Gad2-CreER^{T2}-Prkcz-floxed* mice to freely explore a circular rotating arena while recording hippocampal CA1 neuronal activity with Miniscope calcium imaging. In this environment, arena-bound cues rotate while room-bound cues are stable, allowing us to

measure the stability and interactions between arena- and room-frame spatial representations. We then administered tamoxifen to conditionally knock out (cKO) PKMζ in the Cre-expressing excitatory (*CaMKIIa)* or inhibitory (*Gad2*) neurons. After two weeks, we returned mice to the environment to measure how PKMζ cKO affected hippocampal representations. If PKMζ uniquely maintains potentiated synapses then cKO should destabilize the established representations. Alternatively, these representations should maintain if PKMζ loss is compensated by PKCι/λ at the previously potentiated synapses by KIBRA mediated persistent synaptic tagging. Hippocampal representations should also be disrupted if PKCι/λ upregulation is not specifically targeted to the previously PKMζ-maintained synapses. PKMζ cKO in CaMKII-expressing neurons reduced cofiring of the hippocampal population, whereas place cell number, coherence, and information content remained unaffected. PKMζ cKO in Gad2-expressing neurons had no effect on these measures. We next tested the effects of PKMζ cKO on the persistence of a specific spatial representation in two distinct environments (A and B). Using *Arc-CreER^{T2}* mice, environment-specific cKO of PKMζ was achieved in neurons expressing Arc while mice explored environment A. After two weeks, we recorded CA1 calcium dynamics while mice explored both environments to compare the environment-specific CA1 representations. These experiments should allow us to determine the roles of PKMζ-mediated synaptic plasticity for establishing and maintaining hippocampal population dynamics, topology, and place cell representations across weeks.

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Poster

PSTR032: Hippocampal Circuit II

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.08/HH32

Topic: I.08. Learning and Memory

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Title: Place, context, taste and ambient sounds are encoded in the CA1 population topography

Authors: *A. A. FENTON[1], S. CARRILLO SEGURA[4], E. R. LEVY[2], J. HURTADO[3], E. PARK[5];
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Abstract: The location-specific activity of single hippocampal neurons identifies that ~20% of hippocampal cells discharge robustly in locations called “place fields,” but such analyses explicitly ignore cofiring amongst cells. Cofiring patterns define an information-rich, time-

evolving population code that cannot be observed by time-averaged firing field-based analyses. We investigated cofiring by recording GCaMP6f activity in dorsal CA1 using UCLA miniscopes during separate spatial and non-spatial behaviors, each characterized by classes of distinct, simultaneously useful information. The spatial experiment used a 1-rpm rotating disk with a parallel-rod floor. Mice (n = 5) explored freely in the "*neutral*" condition with a clear plastic film on the floor and they avoided a stationary shock zone without the plastic in the "*avoidance*" condition. The cofiring hypothesis predicts that despite indifferent place fields, conjoint ensemble activity distinguishes the *neutral* and *avoidance* conditions. The non-spatial experiment also used a single environment, a cage in which mice consume their daily ration of water during the third of five 7-min epochs (*silent, sound, sound+water, sound, silent*). Once familiar, changing the water's taste reduces consumption that attenuates the next day (attenuation of taste neophobia - ATN), but not if the ambient sound also changes the next day; this ATN disruption depends on hippocampus. The cofiring hypothesis predicts that conjoint ensemble activity will distinguish the non-spatial contexts, despite indifferent place fields. The prevalence, quality and stability of place fields was unchanged across the *neutral* and *avoidance* conditions, and unchanged across the ATN experiment. CEBRA, a machine learning algorithm identified latent subspaces defined by conjoint neuronal population activity that reliably encodes position, spatial frame (stationary or rotating), and the distinct *neutral* and *avoidance* contexts. Adjacent on-manifold population activity vectors were more similar than distant vector pairs, validating the CEBRA-identified latent subspaces. Stability of the subspaces encoding the *neutral* and *avoidance* contexts increased with experience. Similarly, the subspaces defined by cofiring during the ATN experiment reliably encoded the taste and sound contexts. These findings support the cofiring hypothesis and demonstrate its utility by decoding the positional information in the conjoint discharge of CA1 neurons and by revealing extra-positional information about spatial and non-spatial context, which is undetected by analyses that rely on single-neuron tuning properties that ignore their cofiring.

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Poster

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Topic: I.08. Learning and Memory

Support: NIA K99/R00 AG049090
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R56 MH133929
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Title: Dynamic Interfacing Between Allocentric and Egocentric Frames via the Parietal-Hippocampal Network During Spatial Navigation

Authors: *Y. ZHENG[1], J. HURTADO[4], H. BAYSAL[2], S. C. MOSELEY[2], A. A. FENTON[5], A. A. WILBER[3];
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Abstract: Effective navigation and memory formation are critical for survival and depend on dynamic transformations between allocentric and egocentric reference frames. Such transformations, including the recall of a city's layout or choosing a body centered direction at a specific intersection and world centered orientation are thought to rely on interactions within a parietal cortex (PC)-hippocampal (HPC) network.Recently, we examined how this circuit supports coordination between route centered, allocentric and egocentric direction using a complex sequence task. The task induced multiple reference frames and bidirectional functional interactions between the HPC and PC, but it did not behaviorally segregate egocentric and allocentric reference frames or the transformations between them. To rectify this, we performed a paired recordings from a novel task (Map to Action Transformation Task, MATT) that does differentiate these states. Rats were trained to navigate on an eight-arm maze using distal cues, then we covered those cues so rats needed to transform allocentric location of the reward zone into egocentric direction (e.g., three zones to the right). We also performed random lights task (RLT), randomly cue navigation to targets, to identify cell tuning properties.We use population brain states to identify possible allocentric, egocentric and transformation brain states and then we interrogate them with further analyses. First, we applied a dimensionality reduction technique, FibeRed, to separate neural population activity with allocentric and egocentric base space, and assessed the residual that does not fit the base space variable well. We found that for the transformation condition of the MATT task, specific phases (when distal cues are visible vs when they are obscured) modulate residual fiber structure in HPC and PC, suggesting certain task phases differentially deviate off the base space (potentially consistent with transformation from allocentric to egocentric). Next, we decoded the choice of the rat and found that decoding accuracy was the highest during start box compared to maze traversal. In addition, we identified many cells in PC that were active in sequence during both tasks and a smaller but still large number of cell pairs active in sequence across the HPC and PC. We found very few cell pair sequences that were active across both tasks in HPC, consistent with HPC remapping. We are now looking for sequences of cell activity that represent a putative transformation cell sequence. Thus, a picture is beginning to emerge about how PC-HPC interactions supports transformations from allocentric memory to egocentric goal directions.

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Poster

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Topic: I.08. Learning and Memory

Support: NIH Grant R01MH137669

Title: Ketamine discoordinates "theta ticks" in the hippocampus

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Abstract: Ketamine is a powerful dissociative drug and recently approved rapid acting antidepressant, but we do not understand how it manipulates brain networks to induce lasting change in mood. We used Neuropixels to record local field potentials (LFPs) and single unit action potentials in the hippocampus, somatosensory cortex (sCTX), thalamus, and medial prefrontal cortex (mPFC) of awake behaving head-fixed C57BL/6J mice exploring a friction-less Neurotar environment. Ensemble-LFP data were recorded from hundreds of neurons while administering systemic, escalating (0, 3, 10, 30 mg/kg i.p.) doses of ketamine to enable within ensemble/subject comparisons. Considering LFPs, we found that 7-Hz cycles at all sites in the hippocampus form a system of coupled local theta oscillators with anatomically fixed phase offsets: a “global theta” cycle. Considering spikes, we found that neurons throughout the hippocampus (DG, CA3, CA1) and all other areas recorded (mPFC, sCTX, thalamus) possess a preference to fire spikes at one specific phase of the global theta cycle which is the same in all subjects. This creates a series of discrete, globally synchronized, theta phase-locked spiking events: “theta ticks.” These theta ticks coincide with dentate spikes and the arrival of other synchronous inputs to dentate gyrus that originate from medial entorhinal cortex. Theta ticks are also detected in archival tetrode recordings from navigating rats. The preferred spike time of place cells relative to theta ticks remains unchanged despite global remapping of their spatial firing fields between environments. In contrast, ketamine treatment decreases phase-locking of hippocampal neurons to global theta cycles, making spike times less coordinated relative to theta ticks. These findings lead to a new proposal for understanding how ketamine alters cognition: ketamine “frees the mind” from rigid, stereotyped thought patterns by freeing neurons of the brain from a rigid, stereotyped activation cycle.

Disclosures: L.A. Arend: None. **E. Park:** None. **A.A. Fenton:** None.

Poster

PSTR032: Hippocampal Circuit II

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Title: A transcriptomic axis aligns with in vivo functional dynamics in hippocampal inhibitory circuits

Authors: *H. YONG[1], S. A. HERRLINGER[2], M.-E. CONDE PAREDES[3], C. O'TOOLE[4], J. YOO[4], B. Y. RAO[5], T. S. MIHAILA[6], J. SHI[5], S. DEY[7], E. VAROL[7], A. LOSONCZY[1]; [1]UT Southwestern Med. Ctr., Dallas, TX; [2]Zuckerman Inst., [3]Neurosci., [5]Neurobio. and Behavior, [6]MD/PhD Program, [4]Columbia Univ., New York, NY; [7]New York Univ., Brooklyn, NY

Abstract: Linking molecular identity to function in vivo at single-cell resolution remains an outstanding challenge in neuroscience. Here, we bridge this gap in the mouse hippocampus with an end-to-end pipeline of cell-resolved two-photon imaging and spatial transcriptomics. CA1 interneurons exhibiting heterogeneous physiological responses during a virtual-reality navigation task were post hoc clustered by gene expression into 5 GABAergic subclasses and 14 types. Physiological responses of individual cells aligned with a transcriptomic axis, and a classifier trained on physiological features alone recovered the same ordered organization. Our approach establishes a direct, scalable framework for linking in vivo circuit dynamics to constituent cell identity, revealing a transcriptomic axis that encompasses the structural and functional diversity of hippocampal inhibitory neurons.

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Poster

PSTR033: Hippocampal: Entorhinal Cortex

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Program #/Poster #: PSTR033.01/II4

Topic: I.08. Learning and Memory

Support: NIH/NIMH 1 395 DP2 MH129958-01
NSF CAREER Award: IOS-2145814

Title: Medial entorhinal cortex integrates temporal reward statistics to guide adaptive foraging

Authors: *J. R. MORRIS[1], J. C. BOWLER[2], J. G. HEYS[2];
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Abstract: To support essential behaviors such as locating resources and estimating opportunity costs, the brain must continuously integrate spatial and temporal information. While the role of medial entorhinal cortex (MEC) in spatial coding is well characterized, growing evidence shows that this region also supports temporal processing and explicit timing behavior (Kraus et al., 2015; Heys and Dombeck, 2018). Recent work has used reductionist timing tasks to demonstrate the existence of time cells in MEC and their role in abstract decision-making (Bigus et al. 2024). Yet it remains unclear what computational role these temporal representations serve and how they contribute to adaptive behavior in natural settings. To address this, we developed a foraging paradigm in which mice alternate between two reward patches connected by a hallway. Rewards in each patch follow distinct stochastic decay functions, creating predictable, patch-specific opportunity cost profiles in which the value of staying decreases over time. The decay rate (τ) in each patch and the travel time between them define unique optimal patch residence times (PRTs). Mice reliably adjust their PRTs in response to the differing reward decay rates (τ) over the course of learning. Furthermore, by using feature-holdout analyses in generalized linear models of behavior, we show that patch-leaving decisions increasingly depended on latent temporal reward statistics rather than simpler heuristics such as time since the last reward. DREADD-mediated inactivation of MEC abolished this effect: patch-leaving behavior no longer depended significantly more on latent temporal features than on heuristic features. Using chronically implanted Neuropixels 2.0 probes, we found that time cells emerge in MEC at regular epochs during immobility at reward ports. Tuning curves of individual time cells and decoder analyses of population activity suggest that temporal dynamics are highly context dependent and linked to inference-based behavior. We also found that when patch-specific τ values change covertly between blocks, mice quickly adjusted PRTs, indicating that they updated internal models of patch value in response to the new temporal contingencies. Decoding analyses revealed that context-dependent temporal codes in MEC are preserved across distinct spatial environments when the temporal context is held constant. Together, these findings suggest that MEC temporal codes integrate task context and reward statistics to support flexible, inference-guided foraging decisions.

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Poster

PSTR033: Hippocampal: Entorhinal Cortex

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Topic: I.08. Learning and Memory

Support: NIMH DP2 MH129958
NSF Career Award: IOS-2145814

Title: Organization of spatial and temporal representations in the medial entorhinal cortex

Authors: *H.-W. LEE[1], D. MEDURI[2], J. C. BOWLER[1], B. WANG[2], J. G. HEYS[1];
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Abstract: The medial temporal lobe supports episodic memory by integrating information about what, where, and when. The medial entorhinal cortex (MEC) is best known for spatial coding (Fyhn et al., 2004), but MEC activity is also correlated with time (Kraus et al., 2015; Heys and Dombeck, 2018). Here, we asked how spatial and temporal information are organized across MEC populations by comparing tasks in which mice learned to use either spatial location or elapsed time to guide behavior. We recorded MEC activity using Neuropixels probes while mice performed spatial navigation in an open field and a head-fixed virtual reality (VR) environment, as well as a head-fixed temporal delayed nonmatching-to-sample (tDNMS) task. Grid cells were identified by distance-periodic firing during the dark condition and validated in open-field foraging sessions. Non-grid cells were classified as spatial cells or non-spatial cells based on their VR activity. Across the full population, time cells were defined by reliable tuning to trial time during tDNMS.

We first asked whether grid cells, spatial cells, and time cells arose from overlapping or distinct MEC populations. The overlap between grid cells and time cells (6.2% of total cells) was significantly lower than expected by chance. Within the non-grid population, spatial cells and time cells showed only partial overlap (9.5% of total cells), with most tuned cells preferentially encoding either spatial or temporal information.

We next asked whether grid cells also encoded temporal information when elapsed time was required to guide behavior. During tDNMS, grid cells rarely showed reliable temporal tuning and instead maintained distance-periodic firing, similar to their activity during the dark condition. Grid cells also showed weaker time tuning than non-grid cells. This separation was also evident at the population level. In low-dimensional state space, grid cell ensemble activity clustered around repeated task events during the VR task, whereas event-associated activity during tDNMS was more dispersed across trials. These results suggest that grid cells preserve a distance-based coding scheme and do not consistently encode temporal task structure, even during a timing-dependent behavior. Finally, within the non-grid population, spatial and temporal tuning strength were negatively correlated across cells, further supporting a partial separation between spatial and temporal coding in MEC.

These findings suggest that spatial and temporal information are largely segregated across MEC populations, with distinct coding schemes that may be integrated downstream, potentially within hippocampal circuits.

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Poster

PSTR033: Hippocampal: Entorhinal Cortex

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Program #/Poster #: PSTR033.03/II6

Topic: I.08. Learning and Memory

Support: NIH Grant K00AG101214

Title: Evaluating the effect of chronic social isolation in aged CA1 spatial coding

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Abstract: As the population ages, a key consideration in the care of cognitively impaired older adults, particularly those in assisted living environments or experiencing partner loss, is the role of social connectedness (Evans et al., 2019). Emerging evidence indicates that the quality and quantity of social interactions significantly affect cognitive performance and mental health in aging populations (Kang et al., 2023). Conversely, chronic social isolation has been linked to declines in learning and memory, as well as neurobiological changes in key brain areas (Zelikowsky et al., 2018). Despite this, the mechanisms by which isolation accelerates or contributes to cognitive decline remains poorly understood. To address this gap, we utilize cellular-resolution 2-photon calcium imaging in the dorsal hippocampus of young and aged mice undergoing social isolation. Given its role in both memory and social behavior—and its vulnerability to aging and chronic stress—we investigated how social isolation and aging interact to influence cognitive aging. Our central hypothesis is that social isolation in aged animals impairs context-dependent spatial learning by degrading CA1 ensemble organization. Mice underwent two weeks of social isolation or remained group-housed, then imaged in a virtual reality (VR) spatial memory task. Young control mice could discriminate environments, learn distinct reward locations, and update behavior during reward reversals, displaying reduced spatial correlations across environments and place cell reactivation within familiar environments. Isolated middle-aged (12-14 months) were able to navigate different VR environments, demonstrating reduced velocity in novel environments and anticipatory licking at reward zones, but demonstrated impaired remapping and reduced place field stability compared to group-housed controls. Ongoing analyses will compare performance across age groups, focusing on spatial map correlations, day-to-day stability, and place field emergence in novel environments. Future directions include investigating the roles of neuropeptide pathways in mediating this hippocampal dysfunction. Through this work, we aim to advance understanding of how social environment and age-related changes jointly influence memory-related circuits, ultimately informing cognitive treatments for socially vulnerable aging populations.

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Poster

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Topic: I.08. Learning and Memory

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Title: Distinct Interneuron Populations Regulate CA3 Place Field Formation and Remapping

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Abstract: Hippocampal place cells (PCs) are neurons whose activity is tuned to specific physical locations, termed place fields (PFs) (O'Keefe, 1976). A key piece of evidence supporting the hippocampus' role in spatial memory came from the discovery that place cells remap to form representations of each unique context (Muller & Kubie, 1987; Rolls, 2013). Thus, studying the mechanisms of remapping provides a critical window into the neurobiological basis of memory formation. Place fields for some CA3 neurons appear immediately following exposure to a novel environment, while others gradually develop as experience accumulates (Dong et al., 2021). PNs receive potent "detonator" synapses from dentate gyrus mossy fibers (MF) (Vyleta et al., 2016). This strong excitatory drive is balanced by feedforward inhibition from parvalbumin (PV^+) interneurons targeting stratum pyramidale (s.p) and and feedback inhibition from somatostatin (SST^+) interneurons targeting stratum lacunosum-moleculare (s.l-m). Recent work has identified kirrel3-expressing ($K3^+$) interneurons which receive input from MF axons and drive feedforward inhibition to PNs, in both stratum radiatum (s.r) and stratum oriens (s.o) (Martin et al., 2015; Tuñon-Ortiz et al., 2025). Anatomically, these interneuron populations serve to regulate the three main excitatory inputs to PNs; entorhinal inputs in s.l-m, mossy fiber inputs in stratum lucidum (s.l), and recurrent CA3 collaterals in s.r and s.o. To investigate the differential role of these interneurons we have performed a combination of biophysical circuit modeling, and in vivo electrophysiological recordings as mice navigate familiar and novel virtual environments. Our neural recordings show that PV^+ and $K3^+$ interneurons regulate the formation of PFs in familiar and novel environments. However, whether these populations control specific aspects of PFs formation remains unclear. Additionally, we built a biophysical model of the CA3 circuit that simulates PC mapping and remapping in novel and familiar environments. Multicompartment adaptive exponential integrate-and-fire (ADEX) PNs receive excitatory input from simulated MEC grid cells, mossy fibers, and from other PNs in addition to inhibitory input from $K3^+$, PV^+, and SST^+ ADEX interneuron populations. Using this computational model, we found that feedforward and feedback inhibition via $K3^+$ interneurons influence the number of active PCs and shape their spatial tuning while PV^+ and SST^+ interneurons regulate overall activity and stabilize excitatory inputs. These findings highlight the distinct regulatory roles of CA3 interneurons, including the function of a novel subtype.

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Poster

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University of Utah

Title: Prior experience shapes abstraction and neural representations across piriform cortex and lateral entorhinal cortex

Authors: *C. JENSEN, J. BOWLER, D. AZHAR, M. WACHOWIAK, J. G. HEYS;
Univ. of Utah, Salt Lake City, UT

Abstract: The ability to apply past experience to new situations is fundamental to learning, yet the neural mechanisms that enable the brain to transform sensory inputs into abstract, generalizable representations remain poorly understood (Bernardi, et al., 2020). In the olfactory system, neural populations in piriform cortex (PC) encode stimulus information (Stettler & Axel, 2009) which is relayed to downstream regions such as lateral entorhinal cortex (LEC), where representations are thought to become more aligned with associative memory and task structure (Lee, et al., 2021). Although these observations may suggest a hierarchical progression from sensory encoding to abstraction, some work has demonstrated context-dependent representations in PC (Poo, et al., 2022). Yet, how olfactory representations evolve across learning in PC and LEC—and how experience shapes these representations between tasks—remains largely unknown. To address these questions, we combined dual-site Neuropixels recordings in mice with recurrent neural network (RNN) modeling to determine how odor representations are transformed from PC to LEC during learning and how these transformations support generalization. To assess neural dynamics related to learning across contexts, we trained RNNs to model two delayed non-match to sample tasks previously utilized in mouse behavioral studies: 1. a temporal DNMS (tDNMS) task and 2. an odor identity DNMS (iDNMS) task. We then tested RNNs on novel trial types in overlapping feature space (i.e., tDNMS-trained RNNs tested on novel temporal trials using the same input) and novel task types with non-overlapping feature space (i.e., tDNMS-trained RNNs tested on the iDNMS task, and vice versa). The within-feature space RNNs were validated in vivo by presenting tDNMS-trained mice with novel probe trials. Both in silico and in vivo responses to these novel trials suggest that learning was anchored around the “Go” cue, rather than a comparison rule. Consistent with this, mice also generalized successfully within task structure, performing the tDNMS task with high accuracy independent of odor. Results from RNNs and mice tested on novel tasks with non-overlapping feature space revealed variable task performance on both novel and previously learned tasks depending on the structure of training. Ongoing behavioral experiments and analyses of dual-site recordings will further validate these findings in vivo and determine how representations of odor identity and task features are transformed across PC and LEC during learning. Together, these findings highlight how prior experience shapes the emergence of flexible, generalizable behavior.

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Poster

PSTR033: Hippocampal: Entorhinal Cortex

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Title: Entorhinal subregions encode timing-task structure through distinct stimulus- and task-aligned reference frames

Authors: J. C. BOWLER[1], C. M. JENSEN[1], D. B. AZHAR[2], J. MORRIS[2], ***J. G. HEYS**[2]; [1]Neurobio., [2]Univ. of Utah, Salt Lake City, UT

Abstract: The entorhinal cortex (EC), historically characterized as a gateway for cortical input as it propagates to and from the hippocampus, has recently proven to be a dynamic site rich in complex conjunctive coding and associative learning (Nilssen et al. 2019). The discovery of grid cells in the medial EC (MEC), which tessellate space with a lattice of context-locked repeating spatial receptive fields, positioned MEC as a candidate substrate for generating abstract allocentric maps of the environment (Hafting et al. 2005). Meanwhile, the lateral subregion of the EC (LEC), which supports cue-context-position associations (Wilson et al. 2013) and goal-location learning (Bowler et al. 2023), is thought to represent space relative to the observer through an egocentric framework (Wang et al. 2018). Prominent roles for temporal processing have been ascribed to both EC subregions. Time cells in MEC have been observed to tile elapsed time during trials. Additionally, MEC time cells are critical for interval learning and distinguishing temporal contexts (Bigus et al. 2024). It remains unclear how LEC represents temporal structure during active timing tasks, and whether the EC subregions process temporal information jointly rather than in isolation. We record from LEC during two active timing tasks: first, a head-fixed, odor timing task wherein mice identify trials with odor cues of non-matching duration; second, a freely moving foraging paradigm in which animals learn optimal patch residence times as rewards deplete at different rates. Across these experiments, we compare LEC and MEC population activity, including simultaneous recordings in the same animal. Consistent with a more egocentric reference frame, we find that LEC represents timing tasks relative to the current state and local cue changes, with high correlated responses to odor stimuli regardless of when they are presented within a trial. We find individual units with strong odor-locked tuning. In contrast, in MEC we find evidence for an abstract representation of task timing emerging across learning, consistent with learning a global task-based reference frame. Together, these results suggest that EC subregions process temporal information through distinct but coordinated reference frames during active timing.

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Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.07/II10

Topic: I.08. Learning and Memory

Support: SFB 1436

Title: In vivo reconstruction of septal-entorhinal connectivity with 7T diffusion MRI

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Abstract: The septal region is a principal source of subcortical input to the entorhinal cortex (EC). In animal models, septo-entorhinal projections are central to the circuitry supporting spatial coding and episodic memory, and this pathway may be vulnerable to early aging and Alzheimer's-related change. However, the septo-entorhinal connection has not yet been reliably reconstructed in the living human brain. Its small caliber, deep location, and course through regions of dense fiber crossing pose major challenges for conventional whole-brain tractography.To address this problem, we asked whether the connection between the septal region and EC can be reconstructed in vivo, and whether its anatomical trajectory is consistent across individuals using ultra-high-field diffusion MRI. Diffusion data were acquired at 7T (1 mm isotropic, multi-shell, high angular resolution) in a cohort including younger and older adults. Data were preprocessed with a standard pipeline, and fiber orientations were estimated with multi-tissue constrained spherical deconvolution. We reconstructed streamlines directly between anatomically defined regions: an EC mask from automated medial temporal lobe segmentation (ASHS) and a septal mask derived from automated subcortical-limbic segmentation. To assess anatomical specificity within the septal complex, we further compared reconstructions seeded from the septal nuclei with those seeded from the adjacent basal forebrain. Across initial subjects, targeted tractography recovered a coherent pathway between the septal region and EC. The core trajectory was preserved across both tightly constrained and more permissive tractographyparameter settings, suggesting that the reconstruction is not driven by one specific parameter set. Ongoing analyses assess reproducibility across the full cohort and evaluate anatomical specificity, including the pathway's relationship to neighboring fiber systems. By enabling in vivo reconstruction of entorhinal-septal connectivity, this work provides a methodological basis for studying how this circuit relates to entorhinal function, spatial coding, and memory across healthy aging and early disease.

Disclosures: G. Callau Navarro: A. Employment/Salary (full or part-time):; Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE). **V. Segen:** A. Employment/Salary (full or part-time):; German Center for Neurodegenerative Diseases (DZNE). **P. Bahrd:** A. Employment/Salary (full or part-time):; DZNE. **T. Wolbers:** A. Employment/Salary (full or part-time):; German Center for Neurodegenerative Diseases.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.08/II11

Topic: I.08. Learning and Memory

Support: DFG grant 425899996 – SFB 1436
Velux Stiftung 1809

Title: Entrohinal grid-cell-like coding stability underlies episodic memory integrity in aging

Authors: *V. SEGEN[1,2], G. CALLAU NAVARRO[3], P. BAHRD[4], S. SCHWARCK[5], A. MAAß[4], T. WOLBERS[6];
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Abstract: Episodic memory declines with advancing age, yet the neural mechanisms underlying this decline remain incompletely understood. Episodic memory is thought to depend on entorhinal-hippocampal representations that bind events to their spatial and temporal context. Grid cells in the medial entorhinal cortex, which provide a spatial metric for navigation, have been proposed to contribute to this process by supporting the spatial framework of episodic memory. However, direct evidence linking human grid cell-like representations to episodic memory performance in aging is limited.Here, we examined whether the integrity of episodic memory is associated with grid cell-like coding in 101 healthy older adults. Episodic memory integrity was quantified using a composite Memory Age Gap (MAG) score, reflecting individual differences in memory performance relative to age-based expectations. Using fMRI during a spatial navigation task, we assessed hexadirectional, or six-fold, BOLD modulation—a signature of grid-like coding—in the posterior medial entorhinal cortex (pmEC). MAG scores were strongly predicted by six-fold BOLD modulation in pmEC, whereas no comparable association was observed for other directional periodicities. Importantly, MAG was not related to structural properties of this region, including volume, gray-matter microstructural integrity (mean diffusivity), or intracortical myelination.To understand the functional mechanisms underlying reduced six-fold modulation, we examined the temporal stability of grid-like representations. Lower temporal stability of orientation coding—quantified as the correlation of grid orientation

estimates between runs in 60° space—predicted weaker six-fold modulation in pmEC. Furthermore, instability of orientation coding within pmEC predicted both reduced grid-like modulation and reduced temporal stability.Together, these results identify grid cell-like coding integrity as a key neural mechanism linking entorhinal function to episodic memory integrity in healthy aging. This mechanism may represent a promising target for interventions aimed at promoting memory resilience in later life. Ongoing longitudinal analyses will test whether declines in grid cell-like coding predict future episodic memory decline.

Disclosures: V. Segen: None. **G. Callau Navarro:** None. **P. Bahrd:** None. **S. Schwarck:** None. **A. Maaß:** None. **T. Wolbers:** None.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

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Program #/Poster #: PSTR033.09/II12

Topic: I.08. Learning and Memory

Support: Deutsche Forschungsgemeinschaft (DFG; project id: 425899996 – SFB 1436)

Title: Proximity to criticality as a marker of memory resilience in cognitive aging

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Abstract: Episodic memory depends on the brain's ability to integrate information across multiple time scales while maintaining stable representations that can later be retrieved. This dual requirement — flexibility for encoding new experiences and stability for preserving stored information — may be particularly vulnerable in aging, where memory decline is often accompanied by altered neural variability and changes in large-scale network organization. Critical brain dynamics provide a theoretical framework for understanding how neural systems balance stability and flexibility: near a critical point, activity occupies a marginally stable regime characterized by approximate temporal scale invariance, broad dynamic range, and efficient information storage and transmission. However, how proximity to criticality relates to individual differences in cognitive aging and memory resilience remains an open question.To address this important question, we applied a recently developed temporal renormalization group (tRG) framework to characterize proximity to criticality across the aging brain. We analyzed resting-state fMRI data from 226 older adults aged 60-87 years (mean age = 70.5 ± 6.8 years; 47% female), spanning a range of episodic memory performance from cognitively average to exceptional memory aging. For each participant, regional BOLD time series were extracted using a whole-brain cortical parcellation supplemented by detailed medial temporal lobe (MTL) subregion masks. Proximity to criticality was estimated by fitting autoregressive models to

regional time series and computing the information-theoretic distance to the nearest critical manifold, following the tRG toolkit (Sooter et al., 2025). To assess robustness, we used a multiverse analytical approach varying autoregressive model order, fitting method, and distance metric. Ground-truth simulations were used to evaluate the reliability of criticality estimation under our acquisition parameters.We characterized whole-brain spatial maps of proximity to criticality and conducted a detailed regional analysis of MTL subregions, structures essential for episodic memory and selectively vulnerable in aging. Group-level and cognition-related differences were evaluated using linear mixed-effects models accounting for the nested structure of regions within participants. Together, this work represents the first application of tRG-based criticality analysis to cognitive aging and may provide novel insight into how memory resilience in old age is supported by dynamical brain states that balance stability, flexibility, and information integration across time.

Disclosures: J. Chen: None. **L. Fischer:** None. **A. Maaß:** None. **T. Wolbers:** None.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

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Program #/Poster #: PSTR033.10/II13

Topic: I.08. Learning and Memory

Support: CIHR Grant MOP-133693

Title: Pathway-specific routing of reward and event boundaries from the lateral entorhinal cortex to the hippocampus

Authors: *Y. CHEN[1,2], Z. CHEN[1,2], Y. LIN[3], Q. SHA[1,4], Y. CHEN[1], A. AHMED[5], J. LIU[1], K. TAKEHARA-NISHIUCHI[1,2,3];
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Abstract: The lateral entorhinal cortex (LEC) is a major hub in the hippocampal-neocortical memory network, containing neurons that encode sensory cues, objects, rewards, and contextual information. However, how these signals are selectively routed to distinct hippocampal subregions remains unclear. To address this question, we compared the activity of LEC neurons projecting to the dentate gyrus (DG) or CA1 during goal-directed navigation in mice. Water-restricted mice navigated a square maze twice daily, consisting of a sampling epoch followed by a test epoch. Rewards were available at two of four fixed locations and remained constant within a day but changed across days, requiring encoding during sampling and retrieval during testing. Using retrograde AAVs in wild-type mice, we expressed GCaMP8f in LEC neurons projecting to dorsal DG or CA1 and recorded their activity with fiber photometry. CA1-projecting LEC neurons showed robust biphasic responses during reward sampling, characterized by a transient increase in activity initiating ~20 ms before reward-seeking actions, followed by strong

suppression during reward consumption. These neurons also exhibited transient activity increases during transitions between maze paths. The magnitude of both activity patterns was comparable between the sampling and testing epochs. DG-projecting LEC neurons displayed similar biphasic reward responses during sampling, while during test, these neurons developed ramping activity that emerged several seconds before reward-seeking actions. Unlike CA1-projecting neurons, DG-projecting neurons did not respond to path transitions. During random foraging in the same maze, reward-, anticipation-, and path-transition-related activity patterns remained detectable. However, overall activity fluctuations were reduced in both DG- and CA1-projecting neurons, suggesting that stronger recruitment of these pathways under increased memory reliance. Together, these findings support functionally segregated processing of event content and event boundaries within the LEC-hippocampal circuit, with the LEC conveying reward-related information to both DG and CA1 through distinct temporal dynamics, while selectively routing path-transition signals to CA1.

Disclosures: Y. Chen: None. **Z. Chen:** None. **Y. Lin:** None. **Q. Sha:** None. **Y. Chen:** None. **A. Ahmed:** None. **J. Liu:** None. **K. Takehara-Nishiuchi:** None.

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PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

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Program #/Poster #: PSTR033.11/II14

Topic: I.08. Learning and Memory

Support: CIHR Operating Grant MOP-133693
Ontario Graduate Scholarship

Title: The Lateral Entorhinal Cortex Supports Adaptive Switching between Memory Encoding and Retrieval

Authors: *Z. CHEN[1,2], Y. CHEN[1,2], D. CHOI[1], K. TAKEHARA-NISHIUCHI[1,2,3];
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Abstract: At any given time, the brain must determine whether to encode new information or retrieve existing memories. This decision is strongly influenced by contextual information, including spatial location, temporal structure, and ongoing behavioural demands. Here, we investigated the role of the lateral entorhinal cortex (LEC) in mediating this context-dependent switching, motivated by its robust representation of contextual information (Pilkiw et al., 2017) and its anatomical position as an interface between the hippocampus and neocortex. Water-restricted mice underwent a goal-directed navigational task, in which they collected rewards at two out of four ports in a square-shaped maze across two daily epochs. Reward locations remained constant within a day but changed across days, requiring animals to encode new reward locations during the first epoch and retrieve them during the second epoch. When the

LEC excitatory cells were chemogenetically inhibited from the first epoch onward, mice were slower to learn new reward locations and showed no evidence of memory retention one hour later. When the same manipulation was applied after learning, mice initially selected correct locations during unrewarded probe trials but rapidly switched from memory-guided navigation to exploratory search both at rewarded and unrewarded locations. Importantly, inhibiting the same neuronal population did not impair performance in a spatial reference memory task in which reward locations remained fixed across days, indicating that the deficits were not attributable to impaired spatial memory, motivation, or locomotor activity. These findings suggest that the integrity of the LEC activity is necessary for adaptive switching between memory encoding and retrieval based on the temporal context. Specifically, LEC activity promotes the maintenance of retrieval states in the face of minor expectation violations, thereby suppressing unnecessary exploration and encoding of redundant information in familiar experiences.

Disclosures: Z. Chen: None. **Y. Chen:** None. **D. Choi:** None. **K. Takehara-Nishiuchi:** None.

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PSTR033: Hippocampal: Entorhinal Cortex

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Program #/Poster #: PSTR033.12/II15

Topic: I.08. Learning and Memory

Support: LG202104-01-08

Title: Whole-brain single-neuron projectomes reveal structured output streams of the entorhinal cortex

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Abstract: The entorhinal cortex (EC) is a major interface between cortical, hippocampal, and subcortical circuits, but how individual EC neurons distribute long-range outputs remains unclear. We examined 976 whole-brain single-neuron projectomes from mouse EC to define projection phenotypes, axonal output architecture, collateral co-targeting, EC topography, and hippocampal entry routes. Projection-profile grouping separated EC neurons into 19 projection-defined classes organized along three major output axes: a telencephalic associative-limbic axis targeting isocortex, olfactory areas, striatum, pallidum, and cortical subplate; a diencephalic state-related axis targeting thalamus and hypothalamus; and a hippocampal formation axis. Projection target was associated with distinct axonal architectures after controlling for total axonal length. Hippocampal-, thalamic-, and hypothalamic-projecting neurons tended to form denser, locally elaborated arbors, whereas telencephalic targets were more often reached by longer and more direct output architectures. Collateral co-targeting was structured: target pairs were coupled, coincident, or segregated relative to null models preserving projection breadth,

and some coupled or segregated pairs persisted after accounting for anatomical proximity. Thus, EC output is not a diffuse relay; it selectively couples some downstream regions while keeping others apart. Within telencephalic outputs, recurrent projection motifs linked affective, interoceptive/value, action-selection, and motor-planning nodes, while selective boundaries limited broad mixing between context, olfactory-affective, and rule/state signals. Within the hippocampal formation, EC neurons showed distinct DG- and CA1-preferring routes with different extra-hippocampal projection patterns; strong DG projection was enriched in superficial populations. Finally, EC soma position organized projection identity and output architecture across multiple downstream targets, extending beyond the classical EC-DG topographic map. Together, these results reveal that EC single neurons distribute information through organized projection axes, target-specific axonal architectures, selective collateral co-targeting, and hippocampal entry routes. This organization may provide an anatomical basis for separating and coordinating context, value, action, and spatial-memory signals during spatial cognition.

Disclosures: S. Chen: None.

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PSTR033: Hippocampal: Entorhinal Cortex

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Program #/Poster #: PSTR033.13/II16

Topic: I.08. Learning and Memory

Support: NIH Grant AG099139

Title: Disruption of parvalbumin neurons and perineuronal nets in the entorhinal cortex induces memory deficits in adult mice

Authors: X. MA[1], Y. CHEN[1], J. AYERS[1], Y. BAI[1], X.-Y. LU[1], ***Y. LEI**[2];
[1]Neurosci. & Regenerative Med., Med. Col. of Georgia at Augusta Univ., Augusta, GA; [2]Med. Col. of Georgia At Augusta Univ., Augusta, GA

Abstract: Parvalbumin (PV)-expressing GABAergic interneurons in the entorhinal cortex (EC) are selectively vulnerable during the early stages of Alzheimer's disease (AD). However, whether EC PV neurons directly regulate cognitive behaviors and AD-related pathology remains unclear. Using a Cre-dependent viral strategy to selectively ablate PV neurons in the EC, we found that loss of EC PV neurons reduced spontaneous inhibitory postsynaptic currents onto pyramidal neurons and impaired spatial working memory and object recognition memory in adult wild-type mice. PV neurons are enwrapped by perineuronal nets (PNNs), specialized extracellular matrix structures that help maintain PV neuron function. Enzymatic degradation of PNNs in the EC using chondroitinase ABC similarly impaired memory performance, disrupting spatial working memory and long-term object recognition. These findings demonstrate that EC PV interneurons and their associated extracellular matrix structures are essential for normal cognitive function. To further test whether PV neuron dysfunction contributes to AD pathology

progression, we will use a chemogenetic approach to inhibit EC PV neurons in 3-4-month-old 5xFAD mice, a prodromal age at which these mice do not yet exhibit baseline cognitive deficits. This experiment will determine whether reducing EC PV neuron activity is sufficient to induce cognitive impairment and accelerate AD-related pathology.

Disclosures: X. Ma: None. **Y. Chen:** None. **J. Ayers:** None. **Y. Bai:** None. **X. Lu:** None. **Y. Lei:** None.

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Topic: I.08. Learning and Memory

Support: Research Center Program of the Institute for Basic Science (IBS-R002-A1; M.W.J.).

Title: Medial entorhinal D1 receptor signaling supports value-dependent anticipatory behavior

Authors: *J. KIM, M. SEO, M. W. JUNG;
Dept. of Biol. Sci. (KAIST) / Ctr. for Synaptic Brain Dysfunctions (IBS), Korea Advanced Inst. of Sci. and Technol. / Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Accumulating evidence indicates that the hippocampal formation contributes to value-based decision making. In this context, we previously showed that neurons in layer II of the medial entorhinal cortex (MEC) robustly encode value-related signals. To determine whether dopaminergic signaling contributes to MEC value processing, we examined the behavioral effects of receptor-specific pharmacological blockade during a probabilistic classical conditioning task. Blocking D1 receptors in the MEC selectively disrupted value-dependent anticipatory licking, whereas D2 receptor blockade did not produce a comparable effect. These results suggest that D1 receptor-mediated dopaminergic signaling in the MEC contributes to value-dependent behavioral responses. Complementing these behavioral findings, tdTomato-labeled cells in Drd1-Cre;Ai9 and Drd2-Cre;Ai9 mice showed distinct laminar distribution patterns within the MEC, providing anatomical context for receptor-specific dopaminergic modulation. Future studies examining dopamine dynamics and MEC neuronal activity will be needed to clarify how dopamine signals shape value-related computations in this region.

Disclosures: J. Kim: None. **M. Seo:** None. **M.W. Jung:** None.

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Program #/Poster #: PSTR033.15/II18

Topic: I.08. Learning and Memory

Support: NIMH Grant
BP-Endure

Title: Remyelination rescues object recognition memory after acute demyelination Mneyan M.[1], Maleeha N.[2,3], Sclar M.G.[4], Lifshits G.[1], Melendez-Vasquez C.[1,4], Likhtik E.[1,4]

Authors: *M. MNEYAN[1], N. MALEEHA[1], E. LIKHTIK[2], M. SCLAR[2], C. V. MELENDEZ-VASQUEZ[1], G. LIFSHITS[1];
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Abstract: Multiple sclerosis (MS) is a neurodegenerative disease characterized by demyelination of the central nervous system, with motor symptoms being the focus of most research. However, the pathophysiology of cognitive impairments suffered by patients with MS are not well understood, limiting treatment approaches. To address this, we combined behavior and local field potential (LFP) recordings in a mouse model of MS. Using the cuprizone (CPZ) model of demyelination, we previously showed that CPZ decreases object recognition memory and neural activity in two key regions, the entorhinal cortex (EC) and the dorsal hippocampus (dHPC). To gauge circuit dynamics in the EC-hippocampal circuit, we implanted male mice (C57BL/6J, n=12) with LFP wires in the EC, dHPC, and ventral hippocampus (vHPC). After two weeks of recovery, mice were placed on a CPZ diet and LFPs were recorded during the novel-object recognition task (NORT) in one group (n=6, “remyelination”) after acute demyelination (6 weeks) and again at week 12, following 6 weeks of remyelination after removal of CPZ from the diet. LFPs were also recorded during the NORT in another group (n=6, “chronic demyelination”) after acute and chronic demyelination (at 6- and 12-weeks, respectively). Following completion of all experiments, mice were perfused, brain tissue was collected and stained for myelin basic protein (MBP). Behavioral analyses show that performance on the NORT becomes significantly impaired as mice progress from the acute to the chronic demyelination timepoint, and that remyelination rescued this decline. Furthermore, we observed a positive correlation between NORT performance and total myelin basic protein content in the vHPC (p=0.06). To better understand how myelin loss and recovery affect hippocampal-entorhinal communication, we are investigating whether remyelination affects theta and gamma oscillatory dynamics in the EC-dHPC-vHPC circuit during the NORT. In summary, we find that chronic demyelination impairs object recognition memory, potentially due to dysfunctional EC-hippocampal communication, which can be rescued by remyelination.

Disclosures: M. Mneyan: None. **N. Maleeha:** None. **E. Likhtik:** None. **M. Sclar:** None. **C.V. Melendez-Vasquez:** None. **G. Lifshits:** None.

Poster

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Program #/Poster #: PSTR033.16/II19

Topic: I.08. Learning and Memory

Title: A circuit model of contextual inference in motor learning through MTL-cerebellar interaction

Authors: *C. BHATIA[1], E. A. AMEMATSRO[2], S. J. GERSHMAN[3];
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Abstract: How the brain learns context-specific motor skills and knows when to reuse them remains unknown at the circuit level. Though context inference models of motor learning have successfully explained hallmarks of motor learning such as savings and anterograde interference, these models remain algorithmic, often relying on exact Bayesian inference. Here we demonstrate that interactions between Medial Temporal Lobe (MTL) and cerebellum—long associated with structure learning and motor learning, respectively, and known to strongly interact—can serve as a biological substrate for contextual inference in motor learning enabling the reduction of interference between conflicting skills while maintaining forward transfer between structurally related ones.

We develop a circuit model in which a recurrent MTL-like module and a cerebellar-like forward model are trained to minimize next-state prediction error during movement under changing contexts: force fields, drifts, rotations. The MTL module infers the latent context using the cerebellar model's prediction errors as input. Over training, context becomes linearly decodable from MTL's representations and MTL can track the underlying context, within a single trial, even when the contexts change unexpectedly. Pairing our MTL and cerebellar modules with a Motor Cortex-like recurrent module, we show that this inferred context produces savings in a motor learning task: faster (>15x) relearning of a previously experienced perturbation. Ablating the MTL analog abolishes context inference and reproduces recently observed MTL-dependent motor learning deficits.

Beyond inferring individual contexts, the model learns a latent manifold relating contexts. This latent structure allows the model to generalize to unseen contexts and enables forward transfer across contexts. Further, we show the same context inference mechanism can be applied to reward prediction errors in a reversal learning task, bridging motor and cognitive structure learning.

Together, these results identify MTL-cerebellar interactions as a circuit-level substrate for contextual inference and the unsupervised discovery of latent structure.

Disclosures: C. Bhatia: None. **E.A. Amematsro:** None. **S.J. Gershman:** None.

Poster

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Topic: I.08. Learning and Memory

Support: NSF DGE-2036197
NIH 4R01AG080818-02
NIH 5R01MH124867-05

Title: Inhibition and behavioral timescale synaptic plasticity jointly decorrelate to increase memory capacity

Authors: *A. SHAH[1], I. VOITOV[1], A. MUSAD[1], Z. KHAN[1], D. S. PETERKA[2], S. FUSI[3], A. LOSONCZY[1];
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Abstract: In hippocampal CA1, it is thought that memory-efficient encodings are supported by 1) a decorrelated, sparse population code, generated by competitive inhibitory interactions between pyramidal cells (CA1PCs) and 2) the rapid formation of robust single-neuron tuning by behavioral timescale synaptic plasticity (BTSP) (Priestley et al. 2022, *Neuron*). While *in vitro* recordings have revealed indirect inhibitory interactions between CA1PCs, limited work has tested whether changes in single-CA1PC tuning can propagate to modify population activity. Furthermore, although BTSP is well-studied in single CA1PCs, we lack a theoretical understanding of how BTSP and inhibitory interactions coordinate to generate a high-capacity neural code. To probe inhibitory interactions at single-neuron resolution, we used two-photon calcium imaging alongside two-photon optogenetics (2P-stim) to inactivate (GtACR1-ST) or induce (rsChRmine-KV2.1) place fields (PFs) in CA1PCs as mice (R4Ag11+) navigated virtual reality (VR) environments. During PF inactivation (0.89% of CA1PCs), we observed sparse but consistent recruitment (1.99% of CA1PCs) of activity in non-targeted 'UP' neurons (N=10 mice, 87 trials). Inhibitory interactions were functionally relevant and persistent: on non-stimulation laps, UP units were unlikely to be cotuned to the inactivation zone and maintained anti-cotuning in novel VR environments. Next, we used 2P-stim to induce clusters of new PFs as mice navigated in VR (N=11 mice, 158 induction events). We found that non-stimulated neurons that were cotuned to induction locations were suppressed on laps following induction, and that the strength of suppression correlated with the number of induced fields. To understand how these network interactions could complement single-cell plasticity, we built a computational model of CA1 equipped with activity-dependent BTSP and lateral inhibition. We find that sparse projections and inhibition are sufficient to decorrelate inputs, but that BTSP can provide further decorrelation that translates to an increase in memory performance. Our work provides the first precise and causal account of competitive coding in CA1 and posits that BTSP shapes population-level coding and memory capacity beyond its role in single-cell tuning.

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Poster

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Program #/Poster #: PSTR033.18/II21

Topic: I.08. Learning and Memory

Support: National Science Foundation of China 32530042

Title: Fear memory persistence and attenuation emerge from competitive dynamics of preconfigured hippocampal engram ensembles

Authors: *Y. HAO[1], Y. NIU[1], Y. HUANG[2], B. LEI[3], Y. ZHONG[1];
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Abstract: Memory extinction is often viewed as a new inhibitory learning process that suppresses the expression of a previously formed fear memory. However, whether extinction recruits neurons *de novo* or engages a preconfigured population already present during the original learning episode remains unclear. Here we used longitudinal two-photon *in vivo* imaging of Fos-GFP expression and calcium activity to track CA1 neurons across virtual-reality-based contextual fear conditioning, recall, extinction and relapse. Fear learning recruited a Fos-upregulated CA1 ensemble with elevated calcium activity, enhanced coactivation structure and preferential reactivation during recall. By contrast, extinction recruited a distinct CA1 ensemble whose neurons were already identifiable during fear learning by suppressed activity, weak coupling to the learning ensemble and geometric segregation within the learning-state manifold. Low learning activity predicted later extinction recruitment, and artificial suppression of sparse CA1 neurons during learning biased their subsequent engagement during extinction-associated recall. Fear relapse revealed that memory expression was not governed by irreversible erasure of either ensemble, but by reversible switching between learning- and extinction-ensemble dominance. All-optical mapping further indicated that local inhibitory interactions mediate reciprocal competition between these ensembles. Together, these findings identify a preconfigured extinction-recruited CA1 population as a latent competitor of the learning ensemble, suggesting that fear attenuation and relapse reflect reversible, inhibition-mediated shifts in ensemble dominance.

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Topic: I.08. Learning and Memory

Support: DARPA INSPIRE, HR00112530333

Title: Distributed representational drift supports episodic memory formation for prospective learning.

Authors: *P. YE LI[1], N. HIRATANI[2];
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Abstract: Learning in variable environments requires animals to use past experience to guide future actions, yet how the brain forms episodic memories from information about when, where, and what occurred, and how it uses these memories for prediction, remains elusive. Here, we investigate whether and how representational drift in hippocampal CA1, gradual changes in neural activity patterns across repeated recording sessions over days to weeks, support the formation and retrieval of time-stamped episodic memories. Motivated by previous work on the distributed coding of temporal history across multiple decay rates, we developed a computational model in which representational drift with distributed drift rates binds temporal context to neural activity. This mechanism allows reward or threat episodes to be stored and later retrieved across multiple timescales for prospective prediction. We then tested a key assumption of the model: that the time constants of representational drift are distributed across neurons. Across datasets, CA1 neurons showed broadly distributed drift time constants, with weak but significant stability of these time constants across environments and over time. These results suggest that representational drift may provide temporal information to episodic memories and support prospective learning through distributed mechanisms.

Disclosures: P. Ye Li: None. **N. Hiratani:** None.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.20/II23

Topic: I.08. Learning and Memory

Support: R01 NS127123
R01 MH136274
F32 NS124752
Chicago Institute for Neuroscience start-up funds

Title: Dentate gyrus mossy cells regulate granule cell specificity to promote the stabilization and retrieval of novel representations throughout the hippocampus

Authors: *A. F. TORTOLANI[1], D. GOODSMITH[2], J. PONCE[1], M. SHEFFIELD[1];
[2]Dept. of Neurobio., [1]Univ. of Chicago, Chicago, IL

Abstract: Appropriate memory formation and retrieval is dependent on the development of stable representations in the hippocampus. The dentate gyrus is essential in memory formation;

however, how the hilar mossy cells specifically contribute to the formation, stabilization, and retrieval of hippocampal representations remains unclear. Mossy cells are a major excitatory cell type in the dentate gyrus that form an intricate circuitry with the granule cells, inhibitory interneurons in the dentate gyrus, and CA3 pyramidal cells, yet are vastly understudied in comparison to the other major excitatory cell types in the hippocampus. To determine how mossy cells influence hippocampal representations, we performed two-photon calcium imaging of neural populations in CA1 and CA3 during chemogenetic DREADD-based inhibition of the mossy cells as head-fixed mice navigated familiar and novel linear virtual reality environments. When animals enter a novel environment, they develop stable spatial representations over a period of learning and further refine these maps with experience. We find that mossy cell inhibition specifically disrupts the development of stable spatial representations, both in CA1 and CA3, over a period of initial encoding in a novel environment. Additionally, appropriate retrieval of an experience is thought to depend on the accurate recall of these representations. We find that mossy cell inhibition decreases the fidelity at which these representations are retrieved during a second experience selectively in a novel environment in both CA1 and CA3. To investigate the mechanisms in the dentate gyrus that give rise to these effects, we imaged the granule cells during this same task and find that mossy cell inhibition significantly increases overlap between context specific granule cell populations. Specifically, there was a selective decrease in the context specific population for the novel environment which may contribute to the stabilization deficits of novel representations in CA1 and CA3. Together, these results suggest that mossy cells regulate granule cell specificity which helps both the initial stabilization and subsequent retrieval of novel representations in CA1 and CA3. This work highlights the role of hilar mossy cells as a key regulator of learning and memory dynamics throughout the hippocampus.

Disclosures: A.F. Tortolani: None. **D. GoodSmith:** None. **J. Ponce:** None. **M. Sheffield:** None.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.21/II24

Topic: I.08. Learning and Memory

Support: NIH Grant F32NS124752
NIH Grant RF1NS127123
NIH Grant R01MH136274
Chicago Institute for Neuroscience start-up funds

Title: Hippocampal representational drift is an active dentate gyrus-dependent process

Authors: *D. GOODSMITH, W. CARSON, M. SHEFFIELD;
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Abstract: Representational drift, the evolution of neural activity across repeated experiences, has been widely observed in hippocampal spatial maps even in identical, highly familiar contexts. However, the functional significance and underlying mechanisms of this drift remain unclear. While drift may merely reflect biological variability within the hippocampal circuit, it may instead serve an active role in memory function. One possibility is that drift supports episodic memory segmentation, forming distinct representations of similar experiences in the same environment to support memory discrimination. Granule cells (GCs) in the dentate gyrus (DG) are thought to perform pattern separation to promote discrimination between similar experiences and are therefore well suited to encode small differences between distinct episodes to drive drift in the hippocampal circuit. We therefore evaluated how chemogenetic inhibition of GC activity affected the stability and drift of hippocampal spatial representations.
We performed two-photon calcium imaging in the dorsal CA1 of head-fixed mice navigating virtual linear environments. A Cre-dependent inhibitory DREADD was expressed in a subset of mature GCs in Dock10-Cre mice. On separate recording days, mice were injected with either the DREADD agonist DCZ (to inhibit GC activity) or saline. GC inhibition significantly increased spatial stability and reduced representational drift across repeated exposures to a familiar environment on the same day. In contrast, GC inhibition had little effect on the stability of newly formed representations in novel environments, suggesting a selective role for GCs in the updating of established spatial maps. We next tracked the same population of cells across days and found that GC inhibition during re-exposure to the familiar environment was sufficient to reduce drift, suggesting that the reinstatement of the prior CA1 spatial representation was enhanced. These results suggest that representational drift is an active, GC-driven process. Drift may be a direct result of GC pattern separation, encoding small differences between experiences in the same spatial context to segment unique episodes and promote memory discrimination.

Disclosures: D. GoodSmith: None. **W. Carson:** None. **M. Sheffield:** None.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.22/II25

Topic: I.08. Learning and Memory

Title: Investigating the role of hippocampal δ-$GABA_A$receptors in memory functions

Authors: *N. MAMISASHVILI, M. BROWN, K. NASRALLAH, O. LANFORD, E. PINTO; Fordham Univ., New York, NY

Abstract: A central goal in neuroscience is understanding the mechanisms behind complex brain functions and their breakdown in neurological disorders. Memory deficits, particularly in memory discrimination (the ability to distinguish between similar experiences), are common in autism spectrum disorder, PTSD, and panic disorders. GABA, the brain's primary inhibitory neurotransmitter, regulates neural circuits through phasic (brief) and tonic (persistent) inhibition.

Research has largely focused on phasic inhibition via synaptic GABA receptors, but tonic GABA currents — mediated by non-synaptic receptors — also powerfully regulate neuronal excitability and information processing. Despite this, little is known about how tonic inhibition in specific brain regions contributes to memory and behavior. The hippocampal formation is a promising area of investigation given its well-established role in memory. Within it, the dentate gyrus (DG) serves as a key relay station, transferring information from the entorhinal cortex into the hippocampus proper. Non-synaptic δ-containing $GABA_A$ receptors (δ-$GABA_A$Rs) are highly enriched in dentate granule cells (GCs), the DG's principal neurons, and evidence suggests their tonic inhibitory control is essential for proper hippocampal function. In this study, we investigate the functional role of δ-$GABA_A$Rs in DG granule cells using a conditional knockout mouse model with targeted deletion of the δ subunit in adult male mice. We assessed behavioral outcomes through classical tests measuring anxiety-like behavior and hippocampus-dependent memory. In parallel, electrophysiological recordings in acute hippocampal slices, along with c-Fos and N-RAM immunolabeling, were used to examine how δ-$GABA_A$R deletion affects DG circuit function. Our findings show that δ-$GABA_A$Rs are the primary drivers of tonic inhibition in the DG and are responsible for gating the recruitment of granule cells. This work addresses a critical gap in understanding how tonic inhibition shapes hippocampal processing and behavior, with implications for treating the cognitive and emotional disturbances associated with altered GABAergic signaling.

Disclosures: N. Mamisashvili: None. **M. Brown:** None. **K. Nasrallah:** None. **O. Lanford:** None. **E. Pinto:** None.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.23/II26

Topic: I.08. Learning and Memory

Support: NS064025

Title: Adult-born neurons excel at temporal pattern separation

Authors: *H. PANIKKAVEETTIL ASHRAF[1], A. D. MADAR[2], S. BASU[3], J. RYU[5], K. NATHAN[1], H. SUH[4], M. V. JONES[6], J. I. WADICHE[7], L. S. OVERSTREET-WADICHE[8]; [1]Neurobio., The Univ. of Alabama at Birmingham, Birmingham, AL, United States, Birmingham, AL; [2]Neurobio., Univ. of Chicago, Chicago, IL; [3]Dept. of Neurosci., [4]Neurosciences, Cleveland Clin., Cleveland, OH; [5]Univ. of Alabama, Birmingham, Birmingham, AL; [6]Dept Neurosci., Univ. of Wisconsin-Madison, Madison, WI; [7]Neurobio., UAB, Birmingham, AL; [8]Neurobio., Univ. Alabama Birmingham, Birmingham, AL

Abstract: The hippocampal dentate gyrus transforms similar patterns of cortical activity into distinct neural representations, a computation known as pattern separation that supports

mnemonic discrimination. The dentate gyrus undergoes continuous adult neurogenesis, and selective manipulation of young adult-born granule cells (abGCs) alters the discrimination of similar experiences. Because abGCs exhibit high intrinsic excitability, prevailing models have predicted that this physiological property impairs pattern separation, leading to the assumption that new neurons contribute only indirectly through circuit-level interactions. However, a real-time assessment of how individual abGCs transform input spike trains has been lacking, limiting our understanding of their computational capacity relative to mature granule cells (mGCs). Here, we directly tested the ability of abGCs to decorrelate cortical patterns of activity using simultaneous whole-cell recordings from abGCs and neighboring mGCs while optogenetically driving predefined cortical input patterns with systematically varied similarity. Contrary to prevailing predictions, 4-6-week-old abGCs exhibited enhanced separation of highly similar temporal input patterns, an advantage that converged to mGC levels by 8 weeks. Partially blocking GABAA receptor-mediated inhibition increased granule cell firing and reduced decorrelation, confirming that inhibition supports pattern separation. The degree of perforant path synaptic connectivity correlated with pattern separation, suggesting that low synaptic connectivity underlies the computational advantage of abGCs. Together, these results suggest that limited cortical innervation of abGCs enhances decorrelation of input spike trains, potentially contributing to the role of adult neurogenesis in memory resolution.

Disclosures: H. Panikkaveettil Ashraf: None. **A.D. Madar:** None. **S. Basu:** None. **J. Ryu:** None. **K. Nathan:** None. **H. Suh:** None. **M.V. Jones:** None. **J.I. Wadiche:** None. **L.S. Overstreet-Wadiche:** None.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.24/II27

Topic: I.08. Learning and Memory

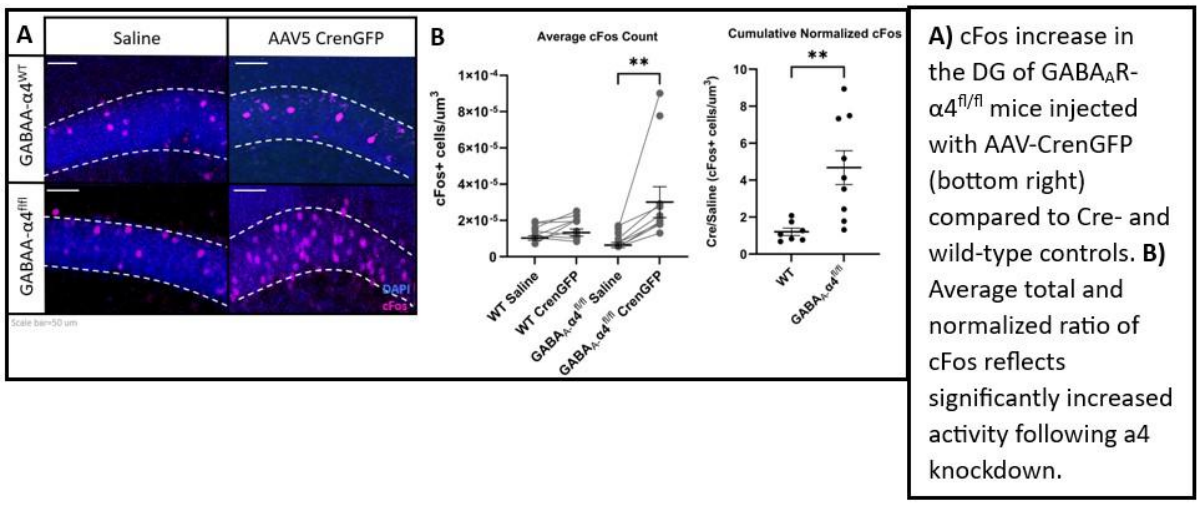
Support: R01 NS117371
OHSU Foundation

Title: Tonic Inhibition Mediated by $GABA_A$-a4 Receptors Facilitates Sparse Coding in the Dentate Gyrus

Authors: *M. KRUSH, C. CHATZI, E. SCHNELL, G. L. WESTBROOK;
Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: The dentate gyrus (DG), the information entry zone to the hippocampus, receives and integrates contextual and spatiotemporal information from the entorhinal cortex. It encodes these inputs “sparsely” with few granule cells active at any one time. This quiescence provides a high signal-to-noise ratio and is vital for proper information encoding during learning and memory formation. We hypothesize that this sparsity is partially mediated by ambient GABA binding to

high affinity α4-containing $GABA_A$ receptors ($GABA_A$-α4) resulting in tonic inhibition. The role of tonic inhibition in shaping sparse coding and circuit function is not well defined. To determine whether tonic inhibition maintains low granule cell activity, wild type mice were pharmacologically treated with the selective $GABA_A$-α4 agonist THIP and neuronal activity assessed using the immediate early gene *cFos*. Fewer Fos^+ granule cells were present in THIP-treated p55-65 mice compared to controls, suggesting that $GABA_A$-α4 receptors contribute to baseline (tonic) inhibition in the DG (n=10, $p<0.0145$, two-tailed paired t-test). To examine $GABA_A$R-α4 loss *in vivo*, we used a viral knockdown using Cre (AAV5-CMV-CrenGFP) micro-injected into DG of p30-35 $GABA_A$-α4 floxed mice. Cre mediated knockdown of α4 led to a 5-fold increase in baseline granule cell activity measured via cFos in p55-65 floxed mice compared to Cre- and WT controls (n=7 WT, 9 KO, $p<0.0055$, two-tailed t-test). Cumulatively, our experiments demonstrate disrupted tonic inhibition at baseline and implicate α4-mediated inhibition in mediating information encoding in the dentate gyrus.



A) cFos increase in the DG of $GABA_A$R-$\alpha4^{fl/fl}$ mice injected with AAV-CrenGFP (bottom right) compared to Cre- and wild-type controls. **B)** Average total and normalized ratio of cFos reflects significantly increased activity following a4 knockdown.

Disclosures: M. Krush: None. **C. Chatzi:** None. **E. Schnell:** None. **G.L. Westbrook:** None.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

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Program #/Poster #: PSTR033.25/II28

Topic: I.08. Learning and Memory

Support: NIH Award R01MH131317
The University of Texas at Austin Graduate Continuing Fellowship

Title: Dynamics of Dentate Spikes During Spatial and Nonspatial Changes in Environments

Authors: *P. G. DEMETROVICH[1], L. L. COLGIN[2];
[1]Neurosci., The Univ. of Texas at Austin, Austin, TX; [2]Ctr. for Learning and Memory, The Univ. of Texas At Austin, Austin, TX

Abstract: The dentate gyrus (DG) is thought to play a key role in the formation of dissociable memory representations for similar contexts. Neurons in the DG receive highly processed spatial and nonspatial sensory information from the medial and lateral entorhinal cortices, respectively. Spatial and nonspatial information is thought to be transmitted to the DG during discrete local field potential events called dentate spikes. Here, we tested the extent to which different spatial and nonspatial stimuli modulate dentate spike dynamics. We performed extracellular recordings of DG place cells and local field potentials in rats (4 males and 1 female) exploring a familiar spatial environment, in which social stimuli and nonsocial odors of varying ethological relevance were presented, and a novel spatial environment. Surprisingly, the occurrence of dentate spikes associated with lateral entorhinal cortex input (i.e., DS1 events) increased during exploration of ethologically relevant stimuli, and this increase was greater for social stimuli. In contrast, DS1 rates were significantly lower in a novel spatial environment compared to a familiar spatial environment. These results suggest that the DG preferentially responds to social stimuli at the network level, providing novel insights into how spatial and nonspatial information is processed in the DG.

Disclosures: P.G. Demetrovich: None. **L.L. Colgin:** None.

Poster

PSTR033: Hippocampal: Entorhinal Cortex

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

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Topic: I.08. Learning and Memory

Support: NSF Fellowship GRFP to ND
NSF Grant IOS-2438821 to EDK

Title: Neural stem cell-expressed excitatory amino acid transporter 1 supports normal hippocampal functioning

Authors: *N. DEVASTHALI[1], B. PARLAR[2], E. D. KIRBY[3,4];
[1]Neurosci. Grad. Program, [2]Undergraduate Neurosci. Major, [3]Dept. of Psychology, [4]Ctr. for Brain Injury Recovery & Discovery, The Ohio State Univ., Columbus, OH

Abstract: Glutamate is the primary excitatory neurotransmitter of the brain, and its presence in synapses is regulated to prevent excitotoxity. Most previous work on synaptic glutamate clearing has focused on astrocytic excitatory amino acid 2 (EAAT2), which transports glutamate from the extracellular space to inside the cell. In the dentate gyrus (DG) of the adult mouse hippocampus, neural stem cells (NSCs) abundantly express EAAT1 throughout their cell bodies, including in the terminals of their processes that wrap around and ensheathe glutamatergic synapses on

granule neurons. NSCs are primarily known to contribute to DG function by proliferating to give rise to new, functional neurons that integrate into existing hippocampal circuitry to support learning, memory, and affect regulation. Since NSC-EAAT1 likely has contact with synaptic glutamate, NSCs may be able to clear synaptic glutamate and regulate the activity of granule cells. We therefore hypothesized that NSC-EAAT1 modulates DG function by maintaining sparse firing of granule neurons, a property hypothesized to underpin effective pattern separation. To investigate this, we used CRISPR technology to generate a new EAAT1$^{fl/fl}$ mouse, in which a critical exon of EAAT1 is flanked by LoxP sites. Crossing EAAT1$^{fl/fl}$ mice with NestinCreER$^{T2+/-}$ mice yielded a tamoxifen sensitive NSC-specific knockout of the EAAT1 gene. Tamoxifen treated EAAT1$^{fl/fl}$;NestinCreER$^{T2+/-}$ mice (cKO) showed significant loss of EAAT1 protein in NSCs compared to Cre-negative littermates (WT). cKO mice showed increased immunolabelling for the immediate early gene cFos, a proxy measure for neuronal activity, in granule neurons at baseline and after a cognitive task compared to similarly treated WT mice. Additionally, cKO mice showed a trend for impaired hippocampus-dependent memory in a novel object location task compared to WT mice. Together, these findings suggest that NSC-EAAT1 is required to maintain sparse firing of granule neurons, and may support hippocampus-dependent memory.

Disclosures: N. Devasthali: None. **B. Parlar:** None. **E.D. Kirby:** None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.01/Web Only

Topic: I.10. Human Learning and Cognition

Title: Muscle strength and cognitive function in adults with obesity

Authors: *Z. REYES LOPEZ[1], I. I. RAMOS-RODRÍGUEZ[4], C. GUZMAN[2], I. E. JUAREZ-ROJOP, Jr.[5], G. NOLASCO-ROSALES[3];
[2]Investigación, [3]División Académica de Ciencias de la Salud, [1]Univ. Juárez Autónoma de Tabasco, Villahermosa, Mexico; [4]Lab. de Cardiometabolismo, Univ. Juárez Autónoma de Tabasco, Villahermosa, Mexico; [5]División Académica de Ciencias de la Salud, Univ. Juárez Autonoma De Tabasco, Villahermosa, Tabasco, Mexico

Abstract: Obesity represents a global public health problem with increasing prevalence among young adults. It is characterized by excessive adiposity and chronic systemic inflammation, which compromise synaptic plasticity and promote progressive brain atrophy. At the same time, reduced muscle strength (dynapenia) emerges as an early marker of neuromuscular decline with a direct impact on cognitive function. It has been demonstrated that the coexistence of dynapenia and obesity increases the risk of cognitive decline. Most studies have focused on assessing dynapenia and cognitive function in adults over 65 years of age. Given this context, we propose to determine the association between muscle strength and cognitive function in adults with

obesity. An analytical cross-sectional study will be conducted. The sample will consist of adults aged 30 to 64 years with obesity (BMI over 30 kg/m²), excluding those with prior neurological diseases. Upper limb muscle strength will be assessed using a hand dynamometer (grip strength in kg), while lower limb strength will be measured using the Sit to Stand (STS-5) test, which consists of timing exactly how long it takes the patient to complete five consecutive repetitions of standing up from a chair and sitting back down. Global cognitive function will be assessed using the Mini-Mental State Examination (MMSE). As a result, significant inverse correlation is anticipated between muscle strength values and cognitive function, such that participants with lower strength may exhibit greater cognitive decline. It has been demonstrated that the coexistence of dynapenia and obesity increases the risk of cognitive decline. Lower-limb strength may have greater predictive power than handgrip strength, given that knee extension has been identified as a significant mediator between mobility and cognition. These findings would position dynamometry as an accessible and reproducible cognitive screening tool in primary care for patients with obesity.

Disclosures: Z. Reyes Lopez: None. **I.I. Ramos-Rodríguez:** None. **C. Guzman:** None. **I.E. Juarez-Rojop:** None. **G. Nolasco-Rosales:** None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.02/II30

Topic: I.10. Human Learning and Cognition

Support: AIIMS Raebareli Intramural funding
(AIIMS/RBL/IRC/IM031, Dated: 21.09.2021).

Title: Cognitive, Physical, and Neurobiological Profiles in Early and Late Diagnosis Type 2 Diabetes Mellitus: A Cross-Sectional Comparative Study

Authors: *D. CHOUDHARY[1,2];
[2]Physiol., [1]All India Inst. of Med. science, Raebraereli, India, Rae Bareli, India

Abstract: Objective and Rationale: Type 2 diabetes mellitus (T2DM) exerts systemic effects influencing cerebral, neuromuscular, and neurotrophic systems that accumulate with disease duration. Because early and late diagnoses may represent distinct biological states, this confirmatory study characterizes and compares integrated multidomain datasets—spanning cognitive, physical, metabolic, and serum neurobiological biomarkers—in adults based on T2DM duration.**Methods:** To ensure scientific rigor, this cross-sectional study evaluated 80 human adults with confirmed T2DM, equally allocated into an early diagnosis group (, diagnosis years, serving as the comparative baseline) and a late diagnosis group (, diagnosis years). Relevant biological variables including age and sex were tracked across groups. Multi-domain assessments consisted of clinical/anthropometric measurements, glycaemic indices, battery-

based cognitive testing (ACE-III, MMSE, MoCA), and physical performance tests. Rigorous neurobiological tracking was achieved via serum enzyme-linked immunosorbent assay (ELISA) quantifying dopamine, serotonin 5-hydroxytryptamine (5-HT), insulin-like growth factor-1 (IGF-1), and S100 calcium-binding protein B (S100B). Independent-samples testing, Pearson correlations, and empirical receiver operating characteristic (ROC) analyses were executed to ensure statistical validity. **Results:** The late diagnosis group was older, exhibited higher fasting/postprandial blood glucose, and elevated glycated haemoglobin (HbA1c). Cognitively, global screening scores were uniformly lower in the late diagnosis group, presenting domain-specific deficits in attention, memory, executive function, visuospatial processing, and sensorimotor speed. Physical performance was severely reduced, displaying lower grip strength, poorer flexibility, and slower mobility. Neurobiologically, late-diagnosis subjects showed significantly lower serum dopamine, serotonin 5-HT, and IGF-1 (), while S100B did not differ (). ROC analysis demonstrated excellent discriminatory accuracy for dopamine (AUC 0.996), serotonin 5-HT (AUC 1.0), and IGF-1 (AUC 0.953). **Conclusions:** Longer-standing T2DM is strongly linked to an unfavourable multidomain profile marked by decreased cognitive capacity, diminished physical reserve, and depleted circulating neurobiological biomarkers. These insights highlight the clear value of incorporating neurobiological and functional markers alongside traditional metabolic tracking in advanced T2DM management.

Disclosures: D. Choudhary: None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.03/II31

Topic: I.10. Human Learning and Cognition

Title: Effects of a Multicomponent Cognitive Stimulation Program on Cognitive Performance and Emotional Symptoms in Older Adults with Mild Cognitive Impairment

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Abstract: Population aging represents an increasing public health challenge in Mexico, particularly regarding the prevention of cognitive decline and the preservation of queality of life in older adults. Mild cognitive impairment (MCI) has been associated not only with cognitive deterioration, but also with elevated symptoms of anxiety and depression, which may negatively impact daily functioning and autonomy. The present study evaluated the effects of multicomponent cognitive stimulation program on cognitive performance and emotional symptomatology in older adults with MCI.A total of 21 older adults (M age = 67.1 years, SD = 10.04) participated in the study. Inclusion criteria included MoCA scores between 13 and 19 and the absence of a prior dementia diagnosis. Participants attended a twice-weekly group-based neurocognitive intervention derived from the PPID program, which included reality orientation,

attention exercises, memory and language training, reminiscence therapy, and mindfulness activities. Pre- and post-intervention assessments measured global cognitive performance (MoCA), verbal fluency, depression (BDI-II), and anxiety (BAI). Paired-samples t-tests were used to evaluate intervention-related changes.Results showed significant reductions in depressive symptoms, decreasing from M=9.43, SD=10.1 to M=610, SD=6.01, t(20) = 2.12, p = .046, d = 0.463. Although cognitive measures did not reach statistical significance, moderate effect sizes suggested clinically relevant stabilization and slight improvements in cognition and verbal fluency. Overall, these findingds support the potentual utility of cognitive stimulation programs for promoting emotional well-being and cognitive stability in older adults with MCI.

Disclosures: S. Quiñones Beltran: None. **L. Llamas-Alonso:** None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.04/II32

Topic: I.06. Social Cognition

Support: NIH R01AG083628

Title: Identification of novel kinases in the pathophysiology of mild cognitive impairment to Alzheimer's

Authors: *A. G. WALLSTRUM[1], J. VERGIS[1], A. S. IMAMI[1], R. ZIDAN[1], N. DECARLO[1], N. BEARSS[1], N. HENKEL[2], R. E. MCCULLUMSMITH[1,3];
[1]Dept. of Neurosci. and Psychiatry, Univ. of Toledo Col. of Med. and Life Sci., Toledo, OH; [2]Intrnl. Med., Harvard Med. Massachusetts Gen. Hosp., Boston, MA; [3]Neurosci. Inst., ProMedica, Toledo, OH

Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disease responsible for 50-75% of all cases of dementia and affecting over 55 million individuals worldwide. Amyloid-beta (Aβ) plaque accumulation and neurofibrillary tangles of hyperphosphorylated tau are well-known pathological mechanisms underlying AD, though they are insufficient in explaining the progression of AD to dementia. Mild cognitive impairment (MCI), an intermediate phenotype, provides an opportunity to further elucidate the pathological changes that occur early in the disease course and lead to the characteristic impairments in memory and functioning experienced by AD patients.We utilized our validated Kinome Random Sampling Analyzer (KRSA) to identify over- and underrepresented kinases in pooled control (n=3), MCI (n=6), and AD (n=7) postmortem dorsolateral prefrontal cortex (dlPFC) homogenate samples run on the kinome array STK chip. KRSA analysis confirmed multiple kinases previously implicated in AD, including AKT and AMPK1; however, we identified several globally understudied STK kinases whose KRSA scores were > 1.0 in our CTL vs MCI and MCI vs AD kinome array datasets, including PAK5, PDK4, TAOK3, and RSK4.PAK5 is a kinase which functions to inhibit MARK2/Par1

activity and modulate microtubule dynamics, particularly in the survival of cancer cells, and was identified as a “hit” kinase dysregulated throughout AD progression in female (CTL vs MCI KRSA Z-score: 1.07; MCI vs AD Z-score: 1.83) and male subjects (CTL vs MCI KRSA Z-score: 0.97; MCI vs AD Z-score: 2.34). RSK4 was also implicated in both early and late AD progression in female (CTL vs MCI KRSA Z-score: 3.41; MCI vs AD Z-score: 4.14) and male subjects (CTL vs MCI KRSA Z-score: 1.33; MCI vs AD Z-score: 3.64). A member of the ribosomal S6 kinase family, RSK4 is a downstream effector of Ras/ERK signaling pathways and has not previously been studied in neurodegenerative diseases; these kinases highlight some of the many novel directions of investigation into the development and progression of AD.Current disease-modifying immunotherapies for AD, namely monoclonal antibodies that target and clear Aβ plaques, are efficacious in slowing cognitive decline only in the earliest stages of the disease and are thus limited by late diagnoses. Consequently, these patients are limited to therapies aimed at managing symptoms rather than treating and slowing the progression of the disease. Challenges in early diagnosis and the lack of disease-modifying therapies with later stage benefits emphasize the need for a deeper understanding of the pathophysiology of AD to identify new treatment strategies.

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Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.05/JJ1

Topic: I.10. Human Learning and Cognition

Support: NIH Grant F31 MH10924701A1
NIH Grant R01DA038891
Canadian Institutes of Health Research Fellowship
Paul Janssen Fellowship in Translational Neuroscience
New York State Psychiatric Institute MRI Pilot Award

Title: Neuromelanin-Sensitive MRI Explains Variability in Dopamine-Dependent Learning in Parkinson's Disease

Authors: *H. BACHMANN[1,2], R. T. GERRATY[2], M. SHARP[3], A. BUCH[4], D. SHOHAMY[2]; [1]Neurobio. And Behavior, [2]Zuckerman Inst., Columbia Univ., New York, NY; [3]Neurol., McGill Univ., Montreal, QC, Canada; [4]Biomed. Engineering, Psychiatry & Behavioral Sci., Duke Univ., Durham, NC

Abstract: Cognitive impairments are a non-motor feature of Parkinson’s disease (PD) and are thought to reflect the degeneration of dopaminergic neurons. Given dopamine’s central role in reinforcement learning and feedback-guided behavior, prior work has focused on understanding

how dopamine dysfunction contributes to learning deficits in PD. However, findings have been inconsistent, particularly regarding the effects of dopamine replacement therapy on learning. This behavioral variability may reflect differences in the integrity of dopaminergic circuits, which have not yet been accounted for. Neuromelanin-sensitive MRI (NM-MRI) is a non-invasive in vivo proxy for the structure and function of midbrain dopaminergic nuclei, providing a new opportunity to examine these individual differences. This allowed us to ask whether heterogeneity in dopaminergic circuit integrity explains variability in the effects of dopamine medication on learning in PD. To answer this question, we combined multimodal neuroimaging and computational modeling approaches. Participants with mild-to-moderate PD (n = 25) completed a probabilistic reversal learning task while being scanned with fMRI, and were separately tested while ON versus OFF medication. Reward prediction errors were estimated by fitting a hierarchical Bayesian model to participant choices, and NM-MRI was used to quantify midbrain dopaminergic integrity. Dopamine medication did not affect learning, overall, nor prediction error-related BOLD activation. However, NM-MRI revealed that the effects of medication on task accuracy varied across individuals. Higher neuromelanin signal was associated with greater ON-medication accuracy following a rule reversal. At the neural level, fMRI demonstrated that prediction errors were associated with BOLD activity in reward-related regions across both medication states. Consistent with the behavioral findings, the effect of medication on prediction error-related BOLD activation in orbitofrontal cortex was dependent on neuromelanin signal. Together, these findings suggest that the effects of dopamine medication on learning depend on the integrity of midbrain dopaminergic circuits. Specifically, relatively preserved midbrain dopaminergic nuclei (i.e., higher neuromelanin signal) are associated with greater medication-related improvements in learning following reversal. More broadly, this highlights how NM-MRI can bridge heterogeneity in PD pathology with variability in cognition and behavior.

Disclosures: H. Bachmann: None. **R.T. Gerraty:** None. **M. Sharp:** None. **A. Buch:** None. **D. Shohamy:** None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.06/JJ2

Topic: I.10. Human Learning and Cognition

Title: Investigating time perception in ADHD symptomatology: Estimation behavior in multiple time scales and subjective time pressure

Authors: *L. C. A. SCOTT[1], A. CARRASCO[1], B. W. LOCKE[1], V. I. GARCIA[1], C. VANDIVER[2], K. CARRASCO[1];
[1]Psychology, [2]California State University, Fresno, Fresno, CA

Abstract: Time perception, the subjective experience of elapsed time, has been implied as an impaired function in attention-deficit/hyperactivity disorder (ADHD). However, behavioral literature has produced inconsistent results and rarely accounts for ADHD's high comorbidity with other mental health conditions that may alter the experience of time. This study investigated the time perception of participants with varying ADHD symptomatology across multiple time scales, including trial estimations of emotionally expressive images from the Karolinska Directed Emotional Faces database (1-10 seconds), prospective and retrospective estimations of 10-item knowledge tests (approximately 3 minutes each), and episodic lecture estimation (approximately 19 minutes) within the same participants, while controlling for anxiety and depressive symptomatology. Alongside the estimation tasks, participants (N=113) completed the Adult ADHD Self-Report Scale (ASRS) v1.1, the Generalized Anxiety Disorder Scale (GAD-7), the Center for Epidemiological Studies Depression Scale (CES-D), and the Chronic Time Pressure Inventory (CTPI). ADHD symptomatology was not a predictor of estimation accuracy in any task, opposing evidence of a general deficiency in estimation ability. However, ADHD was a strong predictor of experienced time pressure after controlling for anxiety and depressive symptoms with a principal component analysis ($\beta = 0.32$, $p_{adj} = .031$), suggesting an impaired consideration to time rather than a disruption in time precision, suggesting abnormal prefrontal function instead of striatal. As a secondary finding, Pearson's r correlations, with false discovery rate corrections, revealed an estimation bias progressively drifting towards underestimation in the absence of feedback ($r = -0.59$, $p < .001$), yet in both conditions with corrective feedback, estimations closely reflected actual stimulus durations (Feedback: $t(94) = -5.74$, $p < .001$; Feedback and Motivation: $t(94) = -5.39$, $p < .001$), according to t-test analyses, indicating that temporal estimation requires external recalibration to maintain accuracy. These findings suggest a reconceptualization of time perception in ADHD as a unique functional relationship with time rather than an impairment in duration estimation.

Disclosures: L.C.A. Scott: None. **A. Carrasco:** None. **B.W. Locke:** None. **V.I. Garcia:** None. **C. Vandiver:** None. **K. Carrasco:** None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.07/JJ3

Topic: I.06. Social Cognition

Title: Assessment of ERK2 kinase activity in schizophrenia: A DLPFC postmortem analysis

Authors: *L. AHMED, A. S. IMAMI, N. DECARLO, S. HANNA, J. VERGIS, N. BEARSS, R. E. MCCULLUMSMITH;
Neurosciences and Psychiatry, Univ. of Toledo Col. of Med. and Life Sci., Toledo, OH

Abstract: Schizophrenia (SCZ) is a severe mental illness characterized by positive, negative, and cognitive symptoms. Positive symptoms include hallucinations and delusions, while negative

symptoms include diminished drive and social withdrawal. The disorder affects approximately 1% of the population and is associated with reduced life expectancy. Recent evidence suggests that mitogen-activated protein kinase (MAPK) signaling pathways play a prominent role in the multifactorial pathophysiology of SCZ. For example, extracellular signal-regulated kinase 2 (ERK2), a serine/threonine kinase, integrates neurotransmitter and growth factor signaling. ERK2 also regulates neurodevelopment and neuronal survival, processes disrupted in SCZ. Prior work has primarily examined MAPK gene expression in SCZ. However, accumulating evidence suggests that gene expression measurements may not reflect protein kinase activity. Differential ERK2 gene expression has been reported in the dorsolateral prefrontal cortex (DLPFC) of individuals with SCZ; nonetheless, ERK kinase activity has not been thoroughly examined. We specifically hypothesize that ERK2 activity is reduced in SCZ compared with control subjects. To test this hypothesis, we measured ERK2 activity in the DLPFC using a novel kinase assay platform. Postmortem DLPFC samples were obtained from the University of Maryland Brain and Tissue Bank (UMBTB) from 21 SCZ subjects, and 26 matched disease-free comparison subjects. ERK2 activity was significantly reduced in the SCZ group compared with controls ($p = 0.0049$). Our findings suggest that altered ERK2 signaling may contribute to the pathophysiology of SCZ. Future studies will examine other MAPK family members, including p38 and c-Jun N-terminal kinase (JNK), which are involved in stress responses and neuronal signaling, to determine whether dysregulation of MAPK signaling extends beyond ERK2 alone. Because the assay measured ERK2, a specific isoform of the ERK family, these findings suggest that MAPK signaling alterations may be pathway and isoform-specific.

Disclosures: L. Ahmed: None. **A.S. Imami:** None. **N. DeCarlo:** None. **S. Hanna:** None. **J. Vergis:** None. **N. Bearss:** None. **R.E. McCullumsmith:** None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.08/JJ4

Topic: I.06. Social Cognition

Title: Integrative Multi-Region Transcriptomic Analysis of Schizophrenia Identifies Distinct Molecular Signatures and Drug Repurposing Targets

Authors: *R. SIROLE[1], J. VERGIS[1], A. BUTLER[1], A. S. IMAMI[1], N. BELL[1], R. E. MCCULLUMSMITH[1,2];
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Abstract: Schizophrenia is a complex neuropsychiatric disorder affecting approximately 23 million adults worldwide, yet cross-regional transcriptomic characterization remains relatively unexplored, leaving it unclear whether molecular alterations are shared across cortical areas or region-specific. In this study we aim to identify shared and region-specific transcriptomic

signatures of schizophrenia across four cortical brain regions and to nominate candidate drug repurposing leads using an integrated bioinformatics framework. We analyzed a publicly available postmortem transcriptomic dataset from PsychENCODE comprising 40 individuals, including 19 neurotypical controls and 21 individuals diagnosed with schizophrenia. Differential gene expression signatures were generated for the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), medial temporal area (MTA), and temporal pole area (TPA). Gene Set Enrichment Analysis (GSEA) and leading-edge gene analysis were performed for each region. iLINCS-based perturbagen analysis identified perturbagens producing transcriptomic signatures discordant with each region's schizophrenia-associated expression profile. The GSEA revealed genes associated with neuroimmune suppression as the most consistent pan-cortical finding, with convergent downregulation of HLA family members, CD74, HAVCR2, and ANXA1 across ACC, MTA, and TPA, with analogous neuroimmune suppression in DLPFC. Upregulated signatures were region-divergent: glutamate receptor subunits (GRIN2A, GRIA1) in ACC; DNA mismatch repair and spindle assembly genes (NBN, MLH1, MAD2L1) in DLPFC; mitochondrial Complex I subunits (NDUFS7, NDUFS1) in MTA; and receptor tyrosine kinases (EPHA4, ERBB4, RET, KIT) in TPA. Notably, SNAP25 was upregulated in ACC but downregulated in DLPFC, illustrating region-specific dysregulation. iLINCS perturbagen analysis identified kinase inhibitors as discordant across all regions, including MEK inhibitors in ACC, CDK and PI3K inhibitors in DLPFC, and AKT and NFkB inhibitors in TPA. Together, these findings demonstrate that schizophrenia is characterized by both convergent and region-specific transcriptomic alterations across cortical brain regions. Broadly dysregulated kinase signaling emerges as a cross-regional therapeutic target, nominating candidate drug repurposing leads. These findings show the value of multi-region transcriptomic integration for identifying shared and region-specific mechanisms of schizophrenia pathophysiology.

Disclosures: R. Sirole: None. **J. Vergis:** None. **A. Butler:** None. **A.S. Imami:** None. **N. Bell:** None. **R.E. McCullumsmith:** None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.09/JJ5

Topic: I.10. Human Learning and Cognition

Support: TRDRP 2022 T32IR5211

Title: Sensory Gating and Neural Activity Variations in Schizophrenia, Schizoaffective, and Bipolar I Disorders

Authors: *A. NGUYEN[1], J. KEROLOS[2], A. NGUYEN[3], J. V. PATTERSON[4];
[1]neuropsychiatry and human behavior, [2]Univ. of California, Irvine, Orange, CA;
[3]neuropsychiatry and human behavior, UCI Hlth., Orange, CA; [4]Psychiatry, Univ. California, Irvine, Orange, CA

Abstract: Sensory gating is a neurophysiological process that enables the brain to filter redundant or irrelevant sensory information, supporting efficient cognitive and perceptual functioning. Deficits in sensory gating have been consistently observed in psychiatric disorders, particularly schizophrenia and bipolar disorder, and may reflect underlying abnormalities in inhibitory neural mechanisms and auditory temporal processing. This study investigates sensory gating differences among individuals diagnosed with schizophrenia, schizoaffective disorder, and bipolar I disorder compared to healthy controls, with the goal of examining how auditory inhibitory processing varies across diagnostic groups. Auditory sensory gating was assessed using the paired-click paradigm, in which two identical auditory stimuli are presented 500 milliseconds apart while electroencephalography (EEG) records neural responses. Event related potentials (ERPs), specifically using the P50, N100, and P200 components, was analyzed as indicators of auditory processing and inhibitory control. In addition to analysis of individual channels collected from the EEG, Independent Component Analysis (ICA) was applied to isolate neural activity. Results showed minimal group differences in P50, suggesting relatively intact early sensory registration. In contrast, N100 and P200 demonstrated significant group-related differences. Healthy controls showed stronger sensory gating responses than bipolar I and schizoaffective groups, while the schizophrenia group consistently showed the weakest suppression between the two stimuli. Controls also exhibited larger P200 amplitudes compared to clinical groups, reflecting stronger later-stage auditory processing. These findings suggest that sensory gating abnormalities are most pronounced during later stages of auditory processing and may serve as neurophysiological markers of inhibitory dysfunction across psychotic and mood disorders.

Disclosures: A. Nguyen: None. **J. Kerolos:** None. **A. Nguyen:** A. Employment/Salary (full or part-time):; Employment in Department of psychiatry and human behavior. **J.V. Patterson:** 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.; Supported by the Tobacco-Related Disease Research Program (TRDRP) (T32IR5211).

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.10/Web Only

Topic: I.10. Human Learning and Cognition

Support: TRDRP Grant T32IR5211
UCI Undergraduate Research Opportunities Program (UROP) Fellowship (2025-2026)

Title: Separable contributions of nicotine use and psychosis history to attentional allocation in bipolar I disorder

Authors: *A. NG, A. CHUN, A. T. NGUYEN, J. V. PATTERSON;
Dept. of Psychiatry and Human Behavior, UCI Hlth., Orange, CA

Abstract: Bipolar I disorder (BPI) is frequently associated with cognitive impairments, particularly in working memory and attention. Previous work has shown that nicotine may enhance cognitive performance, though findings remain inconsistent; moreover, BPI patients with psychosis demonstrate greater cognitive deficits than patients without. However, few studies have examined how psychosis and nicotine may jointly influence attentional allocation, which is the focus of the present exploratory study. Participants (n=159) completed an auditory oddball paradigm while electroencephalography (EEG) was being recorded. EEG recordings were processed using EMSE software for artifact correction, independent component analysis (ICA) decomposition, and filtering to isolate P300a and P300b event-related potentials (ERPs). Participants also completed the Auditory Verbal Learning Test (ALVT), Visuospatial Sequencing Test (VST), and Continuous Performance Test (CPT) as part of a cognitive battery, which assessed working memory and sustained attention. Two-way ANOVAs assessed smoking group and psychosis effects for each outcome. We found that smokers (mean 15.6 ± SE 1.3 μV, n=48) and vapers (16.3±1.32 μV, n=38) have significantly larger P300b amplitudes than nonsmokers (10.3±1.04 μV, n=73) in the deviant condition (p=0.009), suggesting enhanced attentional processing to salient stimuli in nicotine users. A significant smoking group by psychosis interaction was observed for P300a latency in the deviant condition (p=0.02): nonsmokers without psychosis history showed delayed early attentional responses compared to nonsmokers with psychosis history, indicating that psychosis may be associated with excessive orienting towards salient stimuli independent of nicotine. Behavioral results revealed a significant smoking group effect for CPT performance with vapers having the highest sustained attention (p=0.005), as well as a significant psychosis main effect for CPT performance with patients with psychosis outperforming those without (p=0.03). These findings suggest that rather than a simple interaction, nicotine exposure and psychosis history may be contributing to distinct but co-occurring alterations in attentional processing in BPI: nicotine enhances the amplitude of attentional ERPs, reflecting degree of salience detection, while a history of psychosis enhances attentional timing. These results may advance understanding of the separable neural mechanisms by which nicotine and psychosis shape impairments in attention in BPI.

Disclosures: A. Ng: None. **A. Chun:** None. **A.T. Nguyen:** A. Employment/Salary (full or part-time):; Department of Psychiatry and Human Behavior, UCI Health. **J.V. Patterson:** 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.; Supported by the Tobacco-Related Disease Research Program (TRDRP) (T32IR5211).

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.11/JJ7

Topic: I.10. Human Learning and Cognition

Support: TRDRP Grant T32IR5211

Title: Influence of Nicotine Use on Neural Processing of Auditory Target Detection in Bipolar I Disorder

Authors: *M. KHAN[1], N. SARGISYAN[2], A. NGUYEN[3], J. V. PATTERSON[4];
[1]Univ. of California, Irvine, Chino, CA; [2]Univ. of California, Irvine, Orange, CA; [3]UCI, Fountain Valley, CA; [4]Psychiatry, Univ. California, Irvine, Orange, CA

Abstract: Patients with bipolar I disorder often show abnormalities in brain responses linked to attention and stimulus evaluation, but it remains unclear how nicotine use may influence these processes. This study examined whether acute nicotine use was associated with differences in auditory target detection and event related potential markers during an auditory oddball task in patients with bipolar I disorder. Participants were grouped as non smokers, cigarette smokers, or vapers, and EEG data were recorded while they responded to target tones presented among frequent and deviant tones. ERP components of interest included N200, P300a, and P300b, and group differences were analyzed using independent component and individual channel approaches. Behavioral performance did not differ significantly across groups, as accuracy and reaction time were similar for non-smokers, smokers, and vapers. In contrast, EEG results showed significant differences in neural activity. Smokers and vapers generally displayed enhanced P300b responses than non smokers in the deviant condition, and smokers showed stronger N200, P300a, and P300b responses in the frequent condition. These findings suggest that nicotine use is associated with enhanced neural markers of auditory attention in bipolar I disorder. Overall, the results point to a measurable relationship between nicotine use and cortical processing of auditory stimuli in this population and support the need for future work separating acute nicotine effects from the longer term effects of smoking and vaping.

Disclosures: M. Khan: None. **N. Sargisyan:** None. **A. Nguyen:** A. Employment/Salary (full or part-time):; Department of Psychiatry and Human Behavior, UCI Health. **J.V. Patterson:** 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.; Supported by the Tobacco-Related Disease Research Program (TRDRP).

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.12/JJ8

Topic: I.10. Human Learning and Cognition

Support: TRDRP 2022 T32IR5211

Title: Differences in Modulation of Cortical Inhibition and Memory Between Smokers, Nonsmokers, and Vapers with Bipolar I Disorder

Authors: *L. KUGAN[1], J. FONG[2];
[1]Univ. of California, Irvine, Irvine, CA; [2]Univ. of California, Irvine, Alhambra, CA

Abstract: Nicotine usage through smoking and vaping has been known to be prevalent in patients with bipolar disorder I (BP-I), which brings up the question of whether nicotine is used as a form of self medication that contributes to desensitization of common BP-I symptoms. Although smoking cigarettes and vaping both deliver nicotine, there may be distinctions in beneficial effects on brain function and varying health risks. This study investigates how these different modes of nicotine intake may affect cortical inhibition and cognitive performance in individuals with BP-I. Sensory gating was used as our key indicator of cortical inhibition measured through electroencephalography (EEG) during a paired-click paradigm. Event-related potential (ERP) components which include P50, N100, and P200 were the main focus when identifying changes in sensory gating. We hypothesized that patients with BP-I who consumed nicotine would have improved sensory gating and cognition, due to nicotines' psychoactive effects. There was a significant correlation between nicotine administration and cognitive performance, with smokers showing stronger ERP responses and significant correlations between sensory gating (P50 amplitude difference) and cognitive tasks, while vapers exhibited the least preservation errors and fastest reaction times. We also found that psychosis had an impact on amplitude differences: smokers without psychosis showing increased amplitudes and non-psychosis patients exhibiting larger S2 mean amplitudes, suggesting that psychosis, a common comorbidity in BP-I, may also influence sensory gating and neural responsiveness.

Disclosures: L. Kugan: None. **J. Fong:** None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.13/JJ9

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

Title: Integrated protein-RNA spatial multiomics enables subcellular mapping of brain cell types and Alzheimer's disease pathology

Authors: *A. L. HECK, K. YOUNG, Y. CUI, R. LIU, B. FILANOSKI, **M. NAVARRO**, L. HAMANISHI, L. WU, A. WARDHANI, M. HOANG, E. HOBBS, J. BEECHEM;
Bruker Spatial Biol., Seattle, WA

Abstract: High-plex spatial imaging of brain cells remains a major challenge due to the extreme complexity and scale of neuronal and glial morphology. Neurons extend axons and dendrites far beyond the cell body, forming highly branched networks that require tight spatial coordination of RNA and protein localization. These spatially organized processes are essential for normal brain

function and are disrupted in neurodegenerative diseases such as Alzheimer's disease (AD), highlighting the need for approaches that can capture neural protrusions and resolve molecular biology with subcellular context. To address this challenge, we developed a Human Neuroscience Protein Panel for the CosMx® Spatial Molecular Imager (SMI) platform, which was optimized for spatial multiomic profiling of brain tissue. The panel is designed to enable identification of major brain cell types and subtypes and more complete segmentation of neural projections and fine processes. It targets key markers spanning neurons (e.g. MAP2), glia (e.g. IBA1), and vascular populations (e.g. CD31), along with proteins central to major neuroscience research areas. Notably, it includes markers of Alzheimer's disease (AD) pathology such as amyloid plaques and neurofibrillary tangles, facilitating direct spatial interrogation of hallmark disease features alongside cell-type-resolved molecular profiling. Implemented on the SMI platform, this assay allows for simultaneous detection of 64 proteins and 18,935 protein-coding transcripts within the same tissue section. By integrating protein and RNA measurements, this multiomic approach improves segmentation of neural cell types and their processes, supporting more accurate transcript assignment and richer characterization of cellular states. We demonstrate the power of this approach in human AD brain tissue. Using the HieraType algorithm for integrated cell typing, we combine protein and RNA signatures to define neuronal, glial, and vascular subtypes with increased confidence. In addition, we examine pathway-level changes identified through whole transcriptome RNA profiling in relation to Alzheimer's pathology, including regions enriched for plaques and neurofibrillary tangles. These analyses reveal spatially resolved alterations in disease-associated pathways across distinct cell types and microenvironments. Ultimately, this work highlights the Human Neuroscience Protein Panel as a key advance for spatial neuroscience, enabling comprehensive, high-resolution spatial mapping of brain cell types, states, and disease-associated biology.

Disclosures: A.L. Heck: A. Employment/Salary (full or part-time):; Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **K. Young:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **Y. Cui:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **R. Liu:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **B. Filanoski:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **M. Navarro:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **L. Hamanishi:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **L. Wu:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **A. Wardhani:** A. Employment/Salary (full or part-

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Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.15/JJ10

Topic: I.01. Attention

Title: Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SUVN-I6107, a Pure M1 Positive Allosteric Modulator: Results from a First-in-Human Study in Healthy Subjects

Authors: *A. K. SHINDE, V. GOYAL, P. JAYARAJAN, V. PALACHARLA, S. JETTA, S. PANDEY, R. SUBRAMANIAN, R. BADANGE, P. CHOUDAKARI, R. NIROGI, V. JASTI; Suven Life Sci. Ltd, HYDERABAD, India

Abstract: Targeting the muscarinic M1 receptor remains a promising strategy for treating cognitive dysfunction associated with dementia. SUVN-I6107 is a novel, selective muscarinic M1 positive allosteric modulator (M1 PAM) with minimal intrinsic agonist activity that demonstrated memory-enhancing effects and a favorable safety profile in preclinical models. A first-in-human Phase 1 study (NCT06705088) evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamic effects of SUVN-I6107 following single and multiple oral-dose administration in healthy subjects. This randomized, double-blind, placebo-controlled, single-center study comprised a single ascending dose (SAD) segment in healthy adults (5 cohorts) and a multiple ascending dose (MAD) segment in healthy elderly subjects (3 cohorts). Primary objectives were to assess safety and tolerability, while secondary objectives characterized PK following single and multiple dosing. Exploratory assessments included pharmacodynamic measures and evaluation of food effects. SUVN-I6107 was safe and well tolerated across all dose levels evaluated. In the SAD segment, plasma concentration-time profiles were generally consistent across doses, with median Tmax ranging from approximately 2-6 h postdose. Absorption was delayed at higher doses. Exposure (AUC) increased dose proportionally, whereas Cmax increased slightly less than dose proportionally. Administration with food resulted in modest but statistically significant increases in Cmax and AUC. Renal excretion of unchanged drug was minimal (<1% of dose), and no clinically meaningful sex-

related differences in PK parameters were observed. In the MAD segment, SUVN-I6107 was safe and well tolerated following twice-daily dosing in healthy elderly subjects. Steady-state concentrations were achieved between Days 3 and 9. By Day 14, median Tmax ranged from 2.5-3.5 h postdose. The mean terminal half-life ranged from 7.43-8.95 h, and accumulation following repeated dosing was modest (<2-fold). Both AUC and Cmax increased approximately dose proportionally across the evaluated dose range, with no meaningful sex-related differences in PK parameters. Results from the current study demonstrate that SUVN-I6107 is safe and well tolerated and exhibits favorable PK properties, including dose-proportional exposure, limited accumulation, and minimal renal excretion. The results support further clinical development of SUVN-I6107 as a potential treatment for cognitive impairment associated with dementia.

Disclosures: A.K. Shinde: A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Palacharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Jetta:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Badange:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **P. Choudakari:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Jasti:** A. Employment/Salary (full or part-time):; Suven Life Sciences.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.16/JJ11

Topic: I.01. Attention

Title: SUVN-L1101142, a Novel Muscarinic M4 Positive Allosteric Modulator, for the Treatment of Alzheimer’s Disease and Schizophrenia

Authors: *K. BITRA, N. GUDURU, A. DAS, K. BOJJA, A. SHAIKH, S. THOKE, S. GAYAKVAD, L. GOTLA, A. JANA, M. KUMBHARE, G. MOHARIYA, M. NISSANKARARAO, R. NIROGI;
Suven Life Sci. Ltd, Hyderabad, India

Abstract: Targeting muscarinic M4 acetylcholine receptors (M4) with positive allosteric modulators (PAMs) represents a promising approach for treating neuropsychiatric disorders. PAMs offer a potentially safer strategy by enhancing the response to endogenous acetylcholine. SUVN-L1101142 is a novel M4 PAM being developed for the treatment of neuropsychiatric symptoms associated with Alzheimer’s disease (AD), other dementias, and schizophrenia. The present studies characterized the pharmacokinetics, pharmacological profile, efficacy, receptor occupancy, and safety of SUVN-L1101142 in preclinical models. The activity of SUVN-

L1101142 at the allosteric site of muscarinic M4 and M2 receptors was evaluated using GloSensor cAMP assays, while activity at M1, M3, and M5 receptors was assessed using CRE-luciferase reporter assays. Receptor occupancy at the M4 allosteric site was determined in rats. Antipsychotic-like activity was evaluated in amphetamine-induced hyperlocomotion and DOI-induced head-twitch models. M4 receptor involvement was confirmed using a selective M4 antagonist. Procognitive effects were assessed using the object recognition task in rats. Potential motor adverse effects and preliminary toxicity were also evaluated. SUVN-L1101142 demonstrated high selectivity for M4 receptors, exhibiting greater than 500-fold selectivity over other muscarinic receptor subtypes. The compound has good plasma exposures in rodent and non-rodent species with adequate brain penetration. The compound significantly attenuated amphetamine-induced hyperlocomotion and DOI-induced head-twitch responses in rats. These effects were blocked by an M4 receptor antagonist, confirming M4-mediated pharmacological activity. SUVN-L1101142 also reversed delay-induced memory deficits in the object recognition task, indicating procognitive potential. No motor side effects were observed at pharmacologically active doses. Receptor occupancy studies demonstrated a clear relationship between M4 allosteric-site occupancy and efficacy in the amphetamine-induced hyperlocomotion model. In preliminary toxicity studies, SUVN-L1101142 was well tolerated and showed no findings that would preclude further development. These results demonstrate that SUVN-L1101142 is a highly selective M4 PAM with antipsychotic-like and procognitive activity, favorable tolerability, and a receptor occupancy-efficacy relationship consistent with target engagement. Collectively, the findings support the continued development of SUVN-L1101142 as a potential treatment for neuropsychiatric symptoms associated with AD, other dementias, and schizophrenia.

Disclosures: K. Bitra: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Guduru:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Das:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Bojja:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Shaikh:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Thoke:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Gayakvad:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **L. Gotla:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Jana:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **M. Kumbhare:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **G. Mohariya:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **M. Nissankararao:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.17/JJ12

Topic: I.04. Executive Functions

Support: R01MH112584
R01MH115026
R01MH137090

Title: Temporal stability and dynamic reconfiguration of functional networks from rest-to-task switch in schizophrenia

Authors: *K. M. PRASAD;
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Abstract: Understanding how brain networks dynamically reorganize during cognitive performance relative to resting state is critical to uncover mechanisms underlying network dysconnectivity in schizophrenia (SZ). We examined the default mode network (DMN) since it shows well-documented task-related suppression deficits in SZ using energy landscape analysis (ELA), a statistical physics framework, since it directly models brain state organization and transitions at each fMRI time point. Traditional connectivity methods cannot capture moment-to-moment brain state dynamics. We applied ELA to 2 datasets: 7 Tesla fMRI data from 23 adolescent-onset schizophrenia (AOS) patients and 44 healthy controls (HC), acquired during resting state and an executive function task (Penn Conditional Exclusion Test; PCET); resting fMRI data from Human Connectome Project-Early Psychosis (HCP-EP) consisting of young adults with early psychoses. BOLD signals from 10 DMN left-hemisphere regions were binarized and modeled using a pairwise maximum entropy model (pMEM) to characterize stable states, basin occupancy, and state transition dynamics. Permutation testing (500 iterations) confirmed group differences were not due to region selection bias.
The pMEM achieved excellent fit across all conditions ($r = 0.94$-0.99). In AOS-HC contrast, HC showed 13 stable states (energy: -8 to -14) vs 7 in AOS (-6 to -10) at rest with reversal during PCET: AOS states doubled to 15 (114% increase) while HC consolidated to 4 (69% decrease). HC task engagement produced a dominant all-off DMN suppression state (~47%) with structured high-probability transition pathways. AOS showed selective anterior cingulate/medial prefrontal activation as the dominant state (~39%), with ~42% of task time diffusely distributed across 13 low-occupancy states (all $p < .05$). In the HCP-EP data, EP/SZ showed similar pattern in DMN with higher basin transitions and reduced dwell time. Number of basin transitions and total energy negatively correlated with cognitive performance in EP/SZ but not in AOS. MEM metrics did not correlate with psychopathology severity.
AOS and HC exhibit opposite patterns of task-induced DMN reorganization where controls consolidate into a stable suppression attractor under cognitive demand while AOS landscape disintegrates with loss of structured transitions analogous to a stress test unmasking latent network disorganization. EP/SZ with similar pattern suggest that task-state landscape consolidation during the younger ages and early stages of illness may be a potential biomarker and treatment target for cognitive impairment in schizophrenia, specifically using neuromodulation.

Disclosures: K.M. Prasad: None.

Poster

PSTR034: Cross-Disorder Variations in Cognition and Brain Architecture

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.18/JJ13

Topic: I.06. Social Cognition

Support: NIH Grant 5R01MH121102

Title: Differential SGK1 activity among primary cortex cells following in vitro stress conditions

Authors: ***S. HANNA**[1], N. BEARSS[1], N. DECARLO[1], L. AHMED[1], L. M. ROWLAND[2], R. E. MCCULLUMSMITH[1,3];
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Abstract: Schizophrenia is a neuropsychiatric disorder associated with a constellation of positive and negative symptoms, cognitive impairment, and mood dysregulation. The etiology of schizophrenia remains unclear; however, a growing number of studies have suggested the role of canonical insulin signaling pathways (CISPs) in its pathophysiology. Serum/glucocorticoid-regulated kinase 1 (SGK1) is a serine-threonine kinase within the MTOR/PI3K signaling pathway and is associated with modulation of various ion channels and transports as well as inhibition of glycogen synthase kinase 3β (GSK3β). Previous studies have suggested the role of SGK1 in microtubule depolymerization of neurons, driving neurite formation; thus, we studied the activity of SGK1 and its functional neighbors in a stress model of rat primary cortex cells. E18 Sprague-Dawley rat dissociated cortex cells were plated onto 10cm poly-D-lysine-coated plates and grown until observable neurites and axons were noted. Plates of dissociated primary cortical cells were then treated with one of two options: 100μM hydrocortisone (HC) dissolved in DMSO or DMSO alone as a vehicle (Veh) treatment. Following a 24-hour incubation, cells were lysed and assayed for SGK1 and Akt serine/threonine kinase (AKT) activity through phospho-immunoblot analysis. Expression levels of phospho-SGK1 and phospho-AKT were captured using the Licor Odyssey 9120 Imaging System and quantified using Imaging Studio.Expression levels were normalized to valosin-containing protein (VCP) levels and differences between HC and Veh groups were analyzed through GraphPad Welch's t-test. We found increased ($p < 0.05$) pSGK1, but not AKT, in HC-treated cells compared to our control Veh group. Our findings suggest that modulation of SGK1 activity during cellular stress occursthrough PI3K-independent signaling pathways, adding a different perspective into the role of CISP for periods of cortical stress in the etiology of SCZ. Next steps include measuring activity of other functional neighbors to SGK1 in postmortem SCZ brain tissue.

Disclosures: S. Hanna: None. **N. Bearss:** None. **N. DeCarlo:** None. **L. Ahmed:** None. **L.M. Rowland:** None. **R.E. McCullumsmith:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.01/JJ14

Topic: I.08. Learning and Memory

Title: Discovery of Novel Oxindole Derivatives as Potential Anti-Alzheimer Agents Through Structure-Based Drug Design

Authors: C. JHAGTA[1], ***M. SINGH**[2];
[1]Chitkara Col. of Pharmacy, Chitkara University, Punjab, India, Rajpura, India; [2]Chitkara Col. of Pharmacy, Chitkara University, Punjab, Rajpura, India

Abstract: Discovery of Novel Oxindole Derivatives as Potential Anti-Alzheimer Agents Through Structure-Based Drug Design
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Background: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder and the most prevalent form of dementia, accounting for approximately 70% of dementia cases in the elderly population. The disease is characterized by multiple interconnected pathological mechanisms, including cholinergic dysfunction, toxic amyloid-β (Aβ) plaque accumulation and aggregation, tau hyperphosphorylation mediated by enzymes glycogen synthase kinase-3β (GSK-3β), and oxidative stress induced by reactive oxygen species. In the present study, we aimed to identify novel oxindole-based small-molecule inhibitors targeting acetylcholinesterase (AChE), a key therapeutic target in AD, using a structure-based drug design approach.**Methods:** A library of oxindole analogues was rationally designed and screened based on synthetic feasibility. The selected compounds were evaluated for their pharmacokinetic and toxicity profiles through ADME-T analysis. Compounds demonstrating favorable properties were further subjected to molecular docking studies against AChE. The top three hit compounds were subsequently investigated using molecular dynamics simulations, followed by MM/GBSA binding free energy calculations to assess their binding stability and interaction characteristics.**Results:** Among the screened compounds, MS-8, MS-7, and MS-10 emerged as the most promising candidates based on their docking performance. MS-10 exhibited the strongest binding affinity toward AChE (7E3H), with an average binding free energy (ΔG_bind) of −76.8 kcal/mol. Detailed interaction analysis revealed the formation of two stable and persistent hydrogen bonds with key active-site residues, GLY122 and SER203, exhibiting hydrogen bond occupancies of 89.3% and 83.73%, respectively. These interactions involved residues associated with the catalytic active site (CAS) and catalytic triad of the enzyme.**Conclusion:** The findings highlight SER203 as a critical catalytic residue located deep within the active binding pocket of AChE and essential for ligand stabilization. Van der Waals, hydrophobic, and electrostatic interactions were identified as the major contributors to the overall binding

energy. This study provides valuable insights for the rational design and optimization of selective oxindole-based AChE inhibitors as potential therapeutic agents for AD.

Disclosures: C. Jhagta: None. **M. Singh:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.02/JJ15

Topic: I.08. Learning and Memory

Support: FACULTAD DE MEDICINA UNAM-IN207025

Title: Role of the NMDA receptor in cisplatin-induced conditioned odor aversion in rats: A model of anticipatory nausea

Authors: *T. D. AREMU[1], K. MEZA-SOSA[2], W. GONZALEZ ALFONSO[3], G. I. VÁZQUEZ CERVANTES[4], I. FLORES MORENO[5], B. PINEDA OLVERA[6], G. PEREZ DE LA CRUZ[7], J.-P. MORIN[9], G. R. ROLDAN[8], V. PEREZ DE LA CRUZ[10];
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Abstract: Anticipatory nausea is an acquired response in patients undergoing chemotherapy, in which the smell and the clinical environment, can trigger discomfort even before the anticancer drug is administered. This phenomenon can be experimentally studied using cisplatin (CIS)-induced conditioned odor aversion (COA). NMDA receptors have been involved in learning and consolidation of aversive memories. In this context, MK-801, a non-competitive antagonist of these receptors, could interfere with the acquisition of the memory associated with the discomfort induced by CIS. This study aimed to evaluate the evaluate the dissociative ability of MK-801, a non-competitive antagonist of NMDA receptors, in attenuating CIS- induced COA. Forty male Wistar rats were divided into four groups: Control, Cisplatin (CIS), MK-801, CIS+MK-801. During acquisition, animals had access to drink water in the presence of almond odor (benzaldehyde), used as a conditioned stimulus. Ten min before odor exposure rats were

given MK-801 (0.1 mg/kg) or vehicle, and immediately after drinking they were ip. injected 6 mg/kg CIS or vehicle depending on the group. During memory retrieval, rats were allowed to choose between tap water and almond scented water, thus assessing conditioned aversion. Subsequently, c-Fos transcript and protein were determined in the medial prefrontal cortex. CIS induced conditioned odor aversion, while MK-801 significantly attenuated this response (>50%), suggesting the involvement of NMDA receptors in the acquisition of CIS-induced aversive memory. At the molecular level, c-Fos expression showed an upward trend after CIS administration, while the CIS+MK-801 group showed significant increase compared to the control group. Furthermore, c-Fos protein levels showed no increase in the CIS group, while the groups treated with MK-801+CIS showed a significant decrease as compared to CIS group. These results suggest that NMDA receptor-mediated glutamatergic activation is involved in the formation of anticipatory nausea memory and may modulate changes in proteins involved in neuronal activity and brain plasticity.

Disclosures: T.D. Aremu: None. **K. Meza-Sosa:** None. **W. Gonzalez Alfonso:** None. **G.I. Vázquez Cervantes:** None. **I. Flores Moreno:** None. **B. Pineda olvera:** None. **G. Perez de la Cruz:** None. **J. Morin:** None. **G.R. Roldan:** None. **V. Perez De La Cruz:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.03/JJ16

Topic: I.08. Learning and Memory

Support: INPRF NC25236.0

Title: Memory alterations in rats associated with epileptogenesis induced by kindling with pentylenetetrazol

Authors: *S. GUZMÁN HERNÁNDEZ[1], J. VALDES-RANGEL[3], A. DE GYVES-HERNANDEZ[2], A. VALDÉS-CRUZ[4], G. JIMÉNEZ RUBIO[5];
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Abstract: Epilepsy involves a predisposition to seizures and is preceded by epileptogenesis, the process that leads to its development. Memory impairment is highly prevalent in epilepsy, negatively affects quality of life, and is associated with the etiology, frequency, and duration of

seizures. The pentylenetetrazol (PTZ)-induced epileptogenesis model reproduces the progressive development of seizures until the kindling state is established, allowing the analysis of cognitive alterations associated with repeated seizure activity. The aim of this study was to evaluate changes in spatial, recognition, and working memory during PTZ-induced epileptogenesis and to determine differences in memory performance between rats that reached the kindling state and those that did not. Young male Wistar rats were assigned to a Sham group receiving saline solution and an experimental group treated with PTZ (35 mg/kg, i.p.) every third day. PTZ-treated animals were further divided into PTZ-kindling, consisting of animals that reached the kindling state, and PTZ-15, consisting of animals that received fifteen PTZ administrations without developing kindling. Behavioral testing began one day after the final treatment. Recognition memory was assessed with the Novel Object Recognition (NOR) task, whereas spatial and working memory were evaluated with the Novel Placement Recognition (NPR) task and the T-maze task. The results showed that both the PTZ-15 and PTZ-kindling groups failed to discriminate between novel and familiar objects in the NOR task, unlike the Sham group. Regarding the discrimination index, only the PTZ-15 group showed a reduction compared with the Sham and PTZ-kindling groups. In the NPR task, only the PTZ-kindling group showed a lower discrimination index than the Sham group, suggesting spatial memory impairment after kindling. In the T-maze task, Sham animals progressively reduced testing time, indicating learning, whereas PTZ-15 and PTZ-kindling animals failed to improve performance, suggesting deficits in task acquisition and consolidation. These findings indicate that PTZ treatment induces impairments in recognition memory, spatial memory, and learning processes. The cognitive impact of PTZ appears to depend on the progression of epileptogenesis, as the establishment of the kindling state is associated with a distinct pattern of impairment. Specifically, spatial memory deficits predominated in the PTZ-kindling group, whereas recognition memory impairment was more evident in the PTZ-15 group. Collectively, these data support a relationship between repeated seizure activity and cognitive dysfunction.

Disclosures: S. Guzmán Hernández: None. **J. Valdes-Rangel:** None. **A. De Gyves-Hernandez:** None. **A. Valdés-Cruz:** None. **G. Jiménez Rubio:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.04/JJ17

Topic: I.08. Learning and Memory

Title: BDNF-Dependent Disruption of Methamphetamine-Seeking Behavior by Memantine Following Memory Reactivation

Authors: *M. HANNA;
Biol., Vanguard Univ., Costa Mesa, CA

Abstract: A major contributor to drug relapse is exposure to environmental stimuli previously associated with drug administration. Such cues evoke memories of the effects of the drug and induce drug-seeking behavior. (Anastasio et al., 2018). Drug-associated memories undergo consolidation, during which initially unstable memories are placed in a permanent state (Milekic & Alberini, 2002). When these memories are later triggered and reactivated, they become labile and susceptible to disruption before re-stabilizing (Haubrich & Nader, 2017). Previous studies have shown that administering memantine, an NMDA receptor antagonist, immediately after a drug-associated memory is reactivated disrupts drug-seeking behavior (Goltseker et al., 2017). Memantine is believed to act by blocking memory reconsolidation by inhibiting the pathways that lead to synaptic potentiation, especially by blocking calcium influx through the NMDA receptor, which is necessary to induce AMPA receptor expression at the postsynapse (McDougall et al., 2024). Several studies have shown that memantine can improve cognitive function and enhance memory consolidation in animal models of Alzheimer's disease (Samartgis et al., 2012) and in neurotoxin-induced models (Borre et al., 2012). Memantine has also been shown to increase BDNF expression, a major molecular factor essential for memory consolidation and reconsolidation (Marvanova et al., 2001). Thus, memantine may enhance the consolidation of an extinction memory. In this study, we examined the effects of the NMDA antagonist memantine and ANA-12, a non-competitive TrkB antagonist that blocks the action of BDNF. Using the conditioned place preference paradigm, we found that administration of memantine (10 mg/kg) after exposure to the methamphetamine-paired compartment disrupted drug-seeking behavior compared to rats injected with saline. Unlike rats injected with memantine, rats injected with ANA-12 (10mg/kg) alone and rats injected with memantine + ANA-12 did not show reduced drug-seeking behavior. Our data suggest that memantine's ability to reduce methamphetamine-seeking behavior after memory reactivation is BDNF-dependent. Future studies will examine whether memantine facilitates the consolidation of extinction memories or blocks reconsolidation by testing for spontaneous recovery and the ability to form new memories immediately after memantine administration.

Disclosures: M. Hanna: None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.05/JJ18

Topic: I.08. Learning and Memory

Title: Semecarpus anacardium Decreases Oxidative Stress and Improves Memory Through Inhibiting Acetylcholinesterase and Reducing Glutamate-Induced Calcium Influx

Authors: *R. NAWAZ[1], F. KHAN[2], F. M. AL-MUGHAIRBI[3], A. HAMID[4];
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Abstract: Aim of the Study Semecarpus anacardium (SA) is traditionally used in Arabian and Indian folkloric medicine for enhancing learning and memory. However, the underlying mechanisms contributing to these therapeutic and neuroprotective effects have yet to be explored scientifically. We aimed to investigate SA's memory-enhancing, neuroprotective, and antioxidant effects in a battery of in-vitro and in vivo tests against glutamate-induced cell death in rats' adrenal pheochromocytoma cell line (PC12 cells). Materials and Methods A modified open-field apparatus carried out delayed matching to sample (DMS) and delayed non-matching to sample (DNMS) tests. Spontaneous alternation and spatial memory tests were carried out in the elevated plus maze. 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) proliferation assay kit was used to see the effect of compounds on cell viability. The concentration of intracellular Ca+2 was measured with Fluo-3 AM. The effects of SA on acetylcholine esterase (AChE) enzyme inhibition were measured by Ellman's method. The superoxide dismutase (SOD) activity of the SA extract was measured using a biochemical assay. Results When DMS and DNMS task tests were conducted in an open-field apparatus, it was found that animals treated with SA improved declarative memory. SA treatment also resulted in the enhancement of spatial memory when animals were subjected to spontaneous alternation tests. Histopathological analysis revealed that neuronal structure was intact, and cell viability increased by SA after glutamate-induced neuronal injury. The calcium imaging experiments found that SA treatment reduced excessive calcium influx, which seems to be the primary mechanism of neuroprotection offered by SA. AChE was inhibited by SA treatment, which might explain the memory-enhancing abilities of the plant. The SA extract was also found to provide antioxidant benefits, as indicated by the enhanced activity of SOD after SA treatment. Conclusions Our study suggests that several different drug targets and pathways are affected by SA extract, which, either separately or in combination, might be responsible for this plant's traditional memory-enhancing and neuroprotective properties. These drug targets and pathways include increased cell viability, enhanced SOD activity, Inhibition of AChE, and reducing excessive calcium entry in the neuronal cells

Disclosures: R. Nawaz: None. **F. Khan:** None. **F.M. Al-Mughairbi:** None. **A. Hamid:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.06/JJ19

Topic: I.08. Learning and Memory

Support: NSTC 113-2410-H-468-021-MY2

Title: Training History Determines the Effects of Memantine on Temporal Prediction and Inhibitory Control: Involvement of Striatal ERK Signaling

Authors: *R.-M. LIAO;
Asia Univ., Taichung, Taiwan

Abstract: Although memantine (MEM), a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, is clinically used for dementia and relapse prevention, its neurobehavioral mechanisms remain unclear. This study examined the effects of MEM on two forms of temporally controlled operant behavior maintained by fixed-interval at 30 seconds (FI 30s) and differential reinforcement of low-rate response at 10 seconds (DRL 10s) schedules in rats. While FI schedules primarily foster temporal prediction, DRL schedules emphasize temporally organized inhibitory control. To extend the framework about current operant performance being dictated by historical cognitive systems, we further determined whether the effects of MEM were modulated by prior training history. In this study, male Wistar rats were trained under each schedule, receiving either continuous or intermittent training regimens (n = 6 per group). The continuous regimen consisted of 15 consecutive daily sessions, whereas the intermittent regimen included non-training days distributed across the 15-session acquisition phase. Rats acquired both FI and DRL behaviors but showed distinct profiles depending on the training regimen. Compared with continuous training, intermittent training reduced FI response output and attenuated the bimodal inter-response time (IRT) distribution in DRL performance. Following MEM administration (0, 1.25, 2.5, 5, and 10 mg/kg), DRL behavior showed greater sensitivity than FI behavior. MEM at 10 mg/kg decreased DRL responses regardless of training history, whereas low-dose MEM (1.25 mg/kg) selectively increased DRL responding after intermittent training. MEM effects on FI response microstructure were also dependent on dose and training history. Importantly, MEM at 5 mg/kg increased responses within the 9-11-s bins of the DRL IRT distribution, suggesting enhanced temporal precision. Biochemical analyses showed that MEM enhanced ERK1 phosphorylation in the dorsal striatum, implicating striatal ERK signaling. Together, these findings demonstrate that MEM differentially modulates schedule-controlled behaviors depending on training history, possibly enhancing temporal prediction and inhibitory control through striatal ERK-mediated mechanisms.

Disclosures: R. Liao: None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.07/JJ20

Topic: I.08. Learning and Memory

Support: NSTC 113-2410-H-468-021-MY2

Title: Task-dependent effects of mGluR2/3 agonist and antagonist on timing-based operant behaviors in male rats

Authors: ***Y.-C. LIN**[1], S.-F. CHEN[2], R.-M. LIAO[1], Z.-L. LI[1], C. LI[1], Y.-J. WANG[1], T. YEH[1], H.-W. HUNG[1];
[1]Dept. of Psychology, Asia Univ., Taichung, Taiwan; [2]Natl. Cheng-Chi Univ., Taipei, Taiwan

Abstract: Group II metabotropic glutamate receptors (mGluR2/3) modulate glutamatergic neurotransmission, and their dysregulation is strongly implicated in neuropsychiatric disorders. However, their roles in timing-based operant behaviors involving distinct cognitive demands remain unclear. This study examined the effects of the mGluR2/3 agonist LY354740 (0, 4, 8, 12 mg/kg) and antagonist LY341495 (0, 1.5, 3, 6 mg/kg) on two temporally controlled operant tasks: a differential reinforcement of low-rate responding at 10 seconds (DRL 10s) and a fixed-interval at 30 seconds (FI 30s) in independent cohorts of male Wistar rats. The FI 30s schedule reinforces the first response emitted after a 30-second interval has elapsed and typically produces a scalloped response pattern, reflecting temporal regulation of response output. In contrast, the DRL 10s task requires rats to withhold responding for at least 10 seconds to obtain a reinforcer, whereas non-reinforced responses reset the interval timer. Thus, although both schedules involve temporal control, DRL performance additionally requires inhibitory control to suppress premature responding. After stable baseline performance was established, rats were challenged to determine the contribution of mGluR2/3 signaling to DRL and FI performance. In the DRL 10s task, LY354740 only increased burst responses without significantly altering other behavioral measures. By contrast, LY341495 produced broader effects on DRL performance by decreasing total responses, non-reinforced responses, and peak response rate, thereby increasing modified response efficiency. In the FI 30s task, LY354740 significantly reduced total responses and area under the curve, whereas LY341495 produced no significant effect. These findings demonstrate task-dependent dissociation in mGluR2/3 modulation of timing-based operant behaviors: LY341495 preferentially altered DRL performance requiring greater temporal inhibition, whereas LY354740 exerted stronger effects on FI performance primarily involving temporal regulation of response output. These reciprocal patterns suggest that mGluR2/3 signaling differentially regulates operant behaviors according to timing-based cognitive demands, providing a framework for targeting impulsive dysfunctions in neuropsychiatric disorders.

Disclosures: Y. Lin: None. **S. Chen:** None. **R. Liao:** None. **Z. Li:** None. **C. Li:** None. **Y. Wang:** None. **T. Yeh:** None. **H. Hung:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.08/JJ21

Topic: I.08. Learning and Memory

Support: Wellcome Trust, UK

Title: Preclinical characterisation of a selective α5 $GABA_A$receptor negative allosteric modulator with cognitive restorative activity

Authors: *M. POPA[1], O. F. MONTEIRO[2], D. BELELLI[2], J. J. LAMBERT[2], R. M. ANGELL[1], S. E. WARD[1], J. R. ATACK[1];
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Abstract: α5-containing GABAA receptors (α5 GABAARs) are enriched in the prefrontal cortex and hippocampus, where they mediate tonic and slow phasic inhibition and contribute to cognitive and affective processes. Negative allosteric modulation of α5 GABAARs has been associated with procognitive and antidepressant-like effects in preclinical models and has shown translational potential in human studies. We sought to identify a selective α5 GABAAR negative allosteric modulator (NAM) with favorable pharmacological properties and efficacy in models of cognitive dysfunction. Compound A was identified through iterative medicinal chemistry optimization combined with human recombinant receptor binding and electrophysiological assays. In vitro microsomal stability and membrane permeability studies informed progression to pharmacokinetic and α5 GABAA receptor occupancy studies in rat hippocampi. Functional effects were also assessed at native receptors using electrophysiological recordings in rodent hippocampal slices, including measurements of inhibitory postsynaptic currents (IPSCs) and long-term potentiation (LTP). Cognitive efficacy was evaluated using spontaneous alternation in a T-maze following pharmacologically or inflammation-induced cognitive impairment. At recombinant receptors, Compound A displayed high selectivity for α5-containing GABAARs relative to other receptor subtypes. In hippocampal CA1 neurons, Compound A significantly reduced α5-mediated stratum lacunosum-moleculare evoked IPSCs without affecting α1-3-mediated miniature or spontaneous IPSCs. Following oral administration in rats, 50% hippocampal receptor occupancy was achieved at 0.6 mg/kg, corresponding to a plasma EC50 of 40 ng/mL. Compound A restored impaired LTP in a mouse model of Huntington's disease and reversed etomidate-induced LTP deficits. In behavioral studies, oral administration of Compound A reversed deficits in spontaneous alternation induced by either scopolamine or lipopolysaccharide.These findings demonstrate that Compound A, a novel selective inhibitor of α5 GABAAR function enhances hippocampal plasticity and reverses cognitive impairments across multiple preclinical models, supporting further evaluation of α5 GABAAR NAMs for disorders characterized by cognitive dysfunction.

Disclosures: M. Popa: A. Employment/Salary (full or part-time):; Draig Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Draig Therapeutics. **O.F. Monteiro:** None. **D. Belelli:** None. **J.J. Lambert:** F. Consulting Fees (e.g., advisory boards); Draig Therapeutics. **R.M. Angell:** A. Employment/Salary (full or part-time):; Draig Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Draig Therapeutics. **S.E. Ward:** A. Employment/Salary (full or part-time):; Draig Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Draig Therapeutics. **J.R. Atack:** A. Employment/Salary (full or part-time):; Draig Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Draig Therapeutics.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.09/JJ22

Topic: I.08. Learning and Memory

Support: PAPIIT-UNAM (IN221025)
CONAHCYT (Support for AF-I, CVU 697921)

Title: Glucocorticoid receptor activation and histone acetylation enhance extinction memory of contextual fear conditioning

Authors: *A. FUENTES IBAÑEZ[1], M. M. MONROY[2], O. A. GUTIERREZ[3], N. SERAFÍN[3], G. L. QUIRARTE[4], G. R. ROLDAN[5];
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Abstract: Extinction is a form of cognitive and behavioral flexibility that allows animals to adapt tonew circumstances. Glucocorticoids are stress hormones that modulate the acquisitionand extinction of contextual fear conditioning. Glucocorticoids, such as corticosterone(CORT), facilitate extinction, but the associated cellular mechanisms remain poorlyexplored. Chromatin modifications represent a key molecular pathway in the regulation ofgene expression required for long-term synaptic plasticity and memory. Studiesdemonstrate that systemic administration of a histone deacetylase inhibitor, such assodium butyrate (NaB), facilitates gene transcription and enhances memory consolidation.However, it remains unclear whether histone deacetylases are involved in theglucocorticoid-mediated facilitation of extinction. To evaluate this, we trained rats in acontextual fear conditioning task and 48 hours later subjected them to an extinctionsession. Immediately after extinction, CORT (10 or 30 ng), NaB (0.3 or 1 µg), or vehiclewas administered into the infralimbic cortex. Extinction retention was assessed 48 hourslater. In a separate group, the glucocorticoid antagonist RU486 (10 ng) was administered5 minutes before extinction, followed immediately by NaB (1 µg). Our results showed thatboth the CORT 10 ng and 30 ng groups exhibited more efficient extinction compared tothe control group. Additionally, this effect was specific to the infralimbic cortex and not theprelimbic cortex. The NaB 1 µg group also showed enhanced extinction relative to theNaB 0.3 µg and vehicle groups. However, this effect was not observed when NaB 1 µgwas infused 120 minutes after extinction training. Finally, the vehicle-NaB 1 µg groupshowed more efficient extinction than the vehicle-vehicle, RU486-vehicle, and RU486-NaB 1 µg groups. These findings suggest that glucocorticoids facilitate memory extinction,in part, by increasing histone

acetylation and promoting gene expression viaglucocorticoid receptor activation in the infralimbic cortex.

Disclosures: A. Fuentes Ibañez: None. **M.M. Monroy:** None. **O.A. Gutierrez:** None. **N. Serafín:** None. **G.L. Quirarte:** None. **G.R. Roldan:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.10/JJ23

Topic: I.08. Learning and Memory

Support: SECIHTY-CBF2023-2024-1641
P3C2025-UDG

Title: RAGE inhibition restores recognition memory in middle-aged CD-1 mice with diet-induced type 2 diabetes

Authors: *D. E. SILVA SILVERIO[1], S. J. LOPEZ-PEREZ[2];
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Abstract: Type 2 diabetes mellitus (T2DM) is a major risk factor for cognitive decline and Alzheimer's disease. Although advanced glycation end product receptor (RAGE) signaling has been implicated in diabetes-associated neurodegeneration, its contribution to cognitive dysfunction in physiologically relevant models remains poorly understood. We evaluated whether pharmacological inhibition of RAGE attenuates cognitive deficits in middle-aged male and female CD-1 mice with hypercaloric diet-induced T2DM. Mice (n=10/group) were maintained on a control or hypercaloric diet and treated with the RAGE antagonist FPS-ZM1. T2DM development was confirmed by glucose intolerance and insulin resistance assessed by the area under the curve (AUC) of glucose and insulin tolerance tests. Cognitive assessments were performed before euthanasia at 9 months of age. Recognition memory was evaluated using the Novel Object Recognition task and spatial memory using the Barnes maze. Data were analyzed by two-way ANOVA followed by Tukey's post hoc tests. Recognition memory was significantly affected by treatment ($F_{(3,30)}$=10.22, p <0.0001), whereas sex and the sex-by-treatment interaction were not significant. T2DM mice showed a reduced discrimination index compared with controls (p =0.0001). FPS-ZM1 improved performance in diabetic animals (p =0.0158), restoring discrimination indices to control levels. No differences were observed between control and control+FPS-ZM1 groups. Spatial memory was largely preserved, with no differences in target quadrant occupancy, escape latency, or primary errors. A treatment-by-sex interaction was detected only for escape-hole visit frequency, with reduced visits in female T2DM mice. These

findings indicate that hypercaloric diet-induced T2DM selectively impairs recognition memory during middle age and that RAGE inhibition attenuates this deficit in both sexes. The preservation of most spatial memory measures suggests that recognition memory may be particularly vulnerable during early diabetes-associated cognitive dysfunction. Collectively, these results support a role for RAGE signaling in T2DM-associated cognitive impairment and identify RAGE inhibition as a potential therapeutic strategy.

Disclosures: D.E. Silva Silverio: None. **S.J. Lopez-Perez:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.11/JJ24

Topic: I.08. Learning and Memory

Title: The Novel NMDA Receptor Inhibitor ZA-II-05 Attenuates Vanadium Neurotoxicity in Caenorhabditis elegans, Rat Hippocampal Slices and Mice

Authors: *A. LADAGU[1], F. OLOPADE[2], P. CHAZOT[3], A. OYAGBEMI[2], S. OHIOMOKHARE[3], T. ELUFIOYE[2], O. FOLARIN[2], T. GILBERT[2], M. FULLER[4], T. LUONG[5], E. HALPRIN[6], J. MCKAY[7], Z. ATES-ALAGOZ[8], J. OLOPADE[2], J. OLOPADE[1], A. ADEJARE[9];
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Abstract: Neurodegenerative diseases impose a substantial global health burden, affecting millions of people worldwide. Many of these conditions are associated with hyperactivation of the N-methyl-D-aspartate (NMDA) receptor. This study evaluated the neuroprotective efficacy of ZA-II-05, a novel NMDA receptor inhibitor, using vanadium-induced neurotoxicity models in *Caenorhabditis elegans* (*C. elegans*), rat hippocampal slices, and mice. For the *C. elegans* experiment, 150,000 synchronized worms were divided into three groups (n = 50,000 per group): control, vanadium (100 mM), and vanadium (100 mM) co-treated with ZA-II-05 (1 mg/mL) for 24 hours. Rat hippocampal slices were similarly divided into three groups (n = 15 per group): control, vanadium (300 μM), and vanadium (300 μM) co-treated with ZA-II-05 (100 μM) for 24 hours. In the mouse experiment, 24 pups from different dams (n = 3 dams) were randomly assigned into three groups (n = 8 per group): control (sterile water), vanadium (3 mg/kg), and vanadium (3 mg/kg) co-treated with ZA-II-05 (100 mg/kg). Mice pups received intraperitoneal injections every 72 hours for six months, were sacrificed 24 hours after the final injection, and their brains were excised for analysis. Targeted *in vivo* fluorescence imaging was performed on

the ventral nerve cord of *C. elegans* and on organotypic rat hippocampal slices. Histopathological examination of mouse hippocampus was conducted using myelin basic protein (MBP) immunohistochemical staining. Data were analyzed using descriptive statistics and one-way ANOVA, with significance set at $\alpha = 0.05$. Vanadium exposure in *C. elegans* resulted in decreased nuclear presence compared to controls; however, co-treatment with ZA-II-05 significantly restored nuclear presence relative to vanadium alone. In rat hippocampal slices, co-treatment with ZA-II-05 significantly reduced vanadium-induced apoptosis, as evidenced by decreased fluorescence intensity. Vanadium-exposed mice exhibited reduced myelin basic protein expression, but co-administration of ZA-II-05 significantly increased myelin expression across the examined brain regions compared to vanadium-only treated mice. Collectively, ZA-II-05 alleviated vanadium-induced neurodegeneration in *C. elegans*, rat hippocampal slices, and mice. These findings position ZA-II-05 as a promising candidate for further development in the management of neurodegenerative diseases.

Disclosures: A. Ladagu: None. **F. Olopade:** None. **P. Chazot:** None. **A. Oyagbemi:** None. **S. Ohiomokhare:** None. **T. Elufioye:** None. **O. Folarin:** None. **T. Gilbert:** None. **M. Fuller:** None. **T. Luong:** None. **E. Halprin:** None. **J. McKay:** None. **Z. Ates-Alagoz:** None. **J. Olopade:** None. **J. Olopade:** None. **A. Adejare:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.12/KK1

Topic: I.08. Learning and Memory

Title: The importance of habituation in scopolamine induced cognitive impairment assessed in the novel object recognition task

Authors: A. CHAND[1], M. CONWAY[1], C. SIMMONS[1], J. S. DAVIES[1], M. BURNETT[1], N. MIRZA[2], S. BÄCK[1], ***D. RIAL**[3];
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Abstract: The novel object recognition (NOR) task is a widely used behavioural test for assessing learning and memory. Like many basic behavioural tests, the methodology is highly adaptable for investigating different aspects of learning and memory. Methodological variables such as habituation to arenas may influence sensitivity and pharmacological responsiveness. This study evaluated arena habituation on the cognitive impairment of scopolamine assessed in the NOR task. Forty-eight male C57BL/6J mice aged 9 weeks were assigned to habituated or non-habituated cohorts. Within both cohorts, mice were assigned to vehicle or scopolamine based on body weight and cage (n=12/group/cohort). Mice in the habituated cohort underwent 10 mins exposure to empty arenas on Day 1. On Day 2, all mice were administered vehicle (5 ml/kg) or scopolamine (0.3 mg/kg) intraperitoneally 30 mins prior to a 5 mins training session, in which

the arena contained two identical objects. On Day 3, all mice were given a 5 mins test session, in which one object had been replaced with a novel object. EthoVision was used to calculate all behavioural data. Training object exploration time was highest for vehicle treated habituated and non-habituated mice (23.0 & 23.2 secs) followed by scopolamine treated non-habituated mice (19.4 secs) and lowest for scopolamine treated habituated mice (14.8 secs). In habituated mice, the discrimination index (DI) significantly improved for vehicle treated mice between training and test (-0.02 vs 0.26, p=0.002). The DI did not improve for scopolamine treated mice (-0.039 vs 0.121), indicating impaired memory formation. In contrast, the DI significantly improved for vehicle and scopolamine treated unhabituated mice between training and test (0.04 vs 0.38, p=0.007; -0.04 vs 0.33, p=0.004) indicating memory was not impaired. During the training session scopolamine significantly increased total distance travelled and average velocity irrespective of habituation (all $p<0.001$). Habituated scopolamine treated mice also had a significant reduction in total distance travelled (p=0.012) and average velocity (p=0.019) compared to vehicle in the test session. This effect was not observed in non-habituated mice. This study demonstrates scopolamine memory impairment is dependent on arena habituation. However, scopolamine induced changes to locomotor activity are independent of habituation. Training object exploration in scopolamine treated mice appears to be affected by habituation, perhaps explaining the lack of memory impairment.

Disclosures: A. Chand: A. Employment/Salary (full or part-time):; Sygnature Discovery. **M. Conway:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **C. Simmons:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **J.S. Davies:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **M. Burnett:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **N. Mirza:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **S. Bäck:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **D. Rial:** A. Employment/Salary (full or part-time):; Sygnature Discovery.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.13/KK2

Topic: I.08. Learning and Memory

Title: Region-Specific Modulation of Fear Extinction by 5-HT2A Receptor Antagonists in the Infralimbic Cortex and Basolateral Amygdala

Authors: *A. TYULMENKOVA[1], R. W. STACKMAN, Jr.[2];
[1]Dept. of Biol. Sci., [2]Dept. of Psychology, Florida Atlantic Univ., Jupiter, FL

Abstract: Serotonergic signaling contributes to fear extinction, but the neural circuits through which 5-HT2A receptor signaling modulates extinction-related behavior remain unclear. Previous work from our laboratory demonstrated that repeated administration of the mixed 5-

HT2A/2C antagonist MDL 11,939 impaired fear extinction in mice, whereas the selective 5-HT2A antagonist MDL 100,907 produced no detectable behavioral effects. The present study examined whether these effects are mediated within the infralimbic cortex (IL) or basolateral amygdala (BLA). Adult C57BL/6J mice underwent delay fear conditioning followed by three days of extinction training. Prior to extinction days 1 and 2, mice received bilateral microinfusions of vehicle, MDL 11,939, or MDL 100,907 (1 µg/µL; 0.2 µL/side; 0.2 µg per hemisphere) into either the IL or BLA. Freezing behavior was assessed during extinction training, retrieval, and extinction retention. Intra-BLA administration of either antagonist did not alter conditioned freezing, extinction performance, retrieval, or the number of trials to reach extinction criterion. In contrast, intra-IL administration produced a significant treatment effect during extinction day 2 and altered freezing during the first conditioned stimulus presentation of extinction day 1. MDL 11,939 increased freezing relative to vehicle, whereas MDL 100,907 produced no detectable effect. Additional analyses of extinction rate, binned extinction performance, and trials to extinction revealed no treatment-related differences in within-session extinction learning. These findings support a role for the IL, but not the BLA, as a site through which serotonergic antagonism modulates extinction-related behavior. The dissociation between MDL 11,939 and MDL 100,907 further suggests that these behavioral effects may depend on ligand-specific pharmacological mechanisms rather than general 5-HT2A receptor blockade. Ongoing studies are using chemogenetic inhibition of the IL cortex to determine whether reduced IL activity recapitulates the behavioral effects observed following intra-IL administration of MDL 11,939.

Disclosures: A. Tyulmenkova: None. **R.W. Stackman:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.14/Web Only

Topic: I.08. Learning and Memory

Support: R01AG075998
R01AG056478
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AG056478-04S1
AARG-NTF-21-846586

Title: Retinal Chlamydia pneumoniae-driven NLRP3 inflammasome activation in Alzheimer's disease and exacerbated visuocognitive deficits in murine model

Authors: *B. GAIRE, Y. KORONYO, J.-P. VIT, A. HUTTON, L. SUBEDI, D.-T. FUCHS, A. RENTSENDORJ, S. SHAHIN, N. SWERDLOW, K. BLACK, J. G. MEYER, M. ARDITI, T.

CROTHER, M. KORONYO-HAMAOUI;
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Abstract: Motivation: Recent advances in Alzheimer's disease (AD) research highlight the retina as an emerging CNS target for noninvasive AD diagnosis and monitoring, with parallels between retinal and brain AD biomarkers. An emerging theory links AD to microbial infection as a plausible contributor to disease progression. We investigated the presence and distribution of *Chlamydia pneumoniae* (Cpn) in postmortem retina and brain from AD and mild cognitive impairment (MCI) versus subjects with normal cognition (NC) and examined associated NLRP3 inflammasome activation. We further assessed whether Cpn contributes to AD pathology and cognitive decline by integrating evidence from neuronal cell cultures and AD-transgenic mice. **Approach**: We analyzed tissues from 104 human donors to quantify Cpn immunoreactivity (IR) and validated its presence in AD retina using qPCR, Giemsa staining, and FISH. Retinal and brain proteomics were performed to identify dysregulated pathways related to bacterial infection and NLRP3 inflammasome signaling. Machine-learning models were used to test whether retinal Cpn load predicted AD diagnosis and stage. Human neuronal cells and AD-transgenic mice were infected with Cpn to assess Aβ formation, NLRP3 activation, AD pathology, and cognitive function. **Results**: Cpn load was 2.9-4.1-fold higher in AD retinas and brains, but not in MCI, versus NC. Giemsa staining, qPCR, and FISH confirmed Cpn in the retina. Proteomics revealed dysregulated infection- and NLRP3-related pathways in AD retinas and brains. NLRP3 was early elevated in MCI and AD retinas, with activation evidenced by increased caspase-1, N-terminal gasdermin D, and cleaved interleukin-1β. Retinal Cpn burden was higher in APOEε4 carriers and correlated with retinal $A\beta_{42}$, NLRP3 inflammasome components, gliosis, and apoptotic/pyroptotic markers, as well as brain AD pathology and cognitive decline. IBA1-positive microglia increased in AD retinas, but Cpn-associated microglia ($TMEM119^{+}$) were 61% fewer than expected, suggesting impaired Cpn phagocytosis. Machine learning identified retinal Cpn or NLRP3, combined with $A\beta_{42}$, as predictors of AD diagnosis and stage. In human neuroblastoma cells and AD-model mice, Cpn infection induced Aβ formation, NLRP3 activation, neuroinflammation, and cytotoxicity; chronic infection further exacerbated visuocognitive decline. **Conclusions**: These findings demonstrate elevated retinal Cpn in AD, coupled with NLRP3 activation, Aβ accumulation, neuroinflammation, neurodegeneration, and cognitive decline, implicating Cpn as a disease amplifier and supporting development of NLRP3- or antibiotic-based interventions.

Disclosures: B. Gaire: None. **Y. Koronyo:** None. **J. Vit:** None. **A. Hutton:** None. **L. Subedi:** None. **D. Fuchs:** None. **A. Rentsendorj:** None. **S. Shahin:** None. **N. Swerdlow:** None. **K. Black:** None. **J.G. Meyer:** None. **M. Arditi:** None. **T. Crother:** None. **M. Koronyo-Hamaoui:** None.

Poster

PSTR035: Pharmacological Modulation of Learning and Memory: Receptor Mechanisms, Disease Models, and Therapeutic Candidates

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.15/KK3

Topic: I.08. Learning and Memory

Title: Injury Induced Osteoarthritis Drives Cardiogenic Dementia

Authors: *A. R. MEYYAPPAN[1], P. PRASOON[2], D. S. MENDELOWITZ[4], J. R. BETHEA[3]; [1]George Washington Univ. (GWU), Washington, DC; [2]Dept. of anesthesiology perioperative and pain medicine university of Pittsburgh, The George Washington Univ., Washington DC, DC; [3]Anat. and Cell Biol., The George Washington Univ., Washington, DC; [4]George Washington Univ., Washington, DC

Abstract: Purpose:
Osteoarthritis (OA) is a systemic inflammatory disease associated with an increased incidence of cognitive impairment and heightened cardiovascular risk, particularly heart failure (HF). Women more commonly develop HF with preserved ejection fraction (HFpEF), while men exhibit mid-range EF (HFmrEF) that can progress to reduced EF (HFrEF). Here, we investigate whether selective TNFR2 agonism mitigates OA-driven inflammation and whether treating cardiovascular dysfunction prevents cognitive decline. **Methods:**
OA was induced in male and female C57BL/6J mice by destabilization of the medial meniscus (DMM) surgery. Beginning four weeks post-injury, at allodynia onset, mice received TNFR2 agonist treatment twice. Pain sensitivity was quantified using Von Frey testing. Cognition was measured after pain onset using novel object recognition (NOR). Cardiac function was monitored biweekly by echocardiography starting six weeks post-injury. At sixteen weeks, hippocampal tissue was collected for bulk RNA sequencing. **Results:**
Selective TNFR2 agonism reduced joint pain and cartilage degeneration in both sexes at a low dose. However, cognitive deficits still emerged unless cardiac dysfunction was corrected. Cognitive decline appeared only after HF onset: females developed HFpEF around 8 weeks with concurrent cognitive impairment, while males showed progressive systolic dysfunction consistent with HFmrEF-to-HFrEF transition at 10-11 weeks, followed by cognitive decline at 12 weeks. Low-dose TNFR2 agonist prevented HFpEF and cognitive impairment in females but failed to protect males from HFmrEF or related cognitive decline. Bulk RNA sequencing revealed elevated hippocampal GABA receptor A subunit expression with OA-induced HF, suggesting enhanced inhibitory tone that may impair synaptic plasticity and memory formation. Interestingly we found that administration of the TNFR2 agonist returned GABA receptor A subunits expression outlining a novel neuro-immunomodulatory mechanism that may facilitate cognitive resilience. **Conclusions:**
We show that OA induced inflammation induces heart failure and heart failure dependent cognitive decline. We further show that TNFR2 agonism is effective in preventing cognitive decline secondary to the alleviation of heart failure in our model. Specifically, Selective TNFR2 activation mitigates joint pathology and prevents HFpEF in females and HFmrEF-to-HFrEF transition in males, preserving memory in a dose- and sex-dependent manner. Hippocampal transcriptomic These results establish injury induced osteoarthritis as a model of heart failure driven cardiogenic dementia.

Disclosures: A.R. Meyyappan: None. **P. Prasoon:** None. **D.S. Mendelowitz:** None. **J.R. Bethea:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.01/KK4

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

Title: AAV-ChP: A Novel Capsid with Specific Tropism for Choroid Plexus Epithelial Cells Following ICV delivery in Mice

Authors: *J. XU[1], Q. WANG[2], S. WEI[3], B. WANG[4], D. M. LOVINGER[5], L. ZHANG[6]; [1]NIH/NIAAA/LIN, Rockville, MD; [2]Wang, Rockville, MD; [3]LIN, NIAAA/NIH, Rockville, MD; [4]AAVnerGene Inc., Rockville, MD; [5]Chief, Lab. Integrative Neurosci, Natl. Inst. on Alcohol Abuse and Alcoholism, Rockville, MD; [6]NIAAA, NIH, Rockville, MD

Abstract: Choroid plexus epithelial cells (ChPE) are the primary source of cerebrospinal fluid (CSF) production. Emerging evidence suggests that the choroid plexus (ChP) plays a much broader role than previously appreciated. Beyond CSF production, the ChP functions as a detoxification interface that removes harmful circulating substances and as an immunological surveillance hub that regulates immune-cell access to the central nervous system. Clinical studies have linked ChP dysfunction to several major neurological disorders. However, ChP research has been substantially limited by the lack of effective cell-type-specific gene-delivery tools. Although AAV5 is widely used to target the choroid plexus (ChP), ICV administration in rodents produces broader CNS transduction rather than expression restricted to the ventricular system. This lack of specificity limits the utility of AAV-based approaches for precise molecular dissection of choroid plexus epithelial (ChPE) cell function. To address this challenge, we administered the ATHENA-I AAV capsid barcode library, which includes hundreds of common AAV serotypes and engineered variants, into the mouse ventricular system by ICV injection. We then performed next-generation sequencing (NGS) to quantify the abundance and expression of individual capsid variants in ChP tissue. Through this screen, we identified a novel capsid, designated **AAV-ChP**, with preferential tropism for ChPE cells. AAV-ChP transduced more than 90% of ChPE cells, and 92% of all AAV-ChP-transduced ChP cells were ChPE cells, as demonstrated by both single-cell RNA sequencing and RNAscope analysis. Unlike AAV5, AAV-ChP-mediated expression was largely confined to the ventricular compartment, with no detectable signal outside the ventricles following ICV administration. Thus, AAV-ChP provides a valuable tool for investigating ChPE function under both physiological and pathological conditions.

Disclosures: J. Xu: None. **Q. Wang:** None. **S. Wei:** None. **B. Wang:** None. **D.M. Lovinger:** None. **L. Zhang:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.02/KK5

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

Title: sdAb-Based DNA Immunostaining for High-Throughput Multiplexed Imaging

Authors: *M. RODRIGUEZ[1], M. PEREZ[1], M. WARD[2];
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Abstract: Immunofluorescence is widely used to visualize protein localization and cellular morphology; however, conventional antibody-based methods are limited by low target abundance, background fluorescence, and restricted multiplexing capacity. To address these limitations, we developed a single-domain antibody (sdAb)-based DNA immunostaining platform for high-throughput, multiplexed imaging. sdAbs, derived from a single variable domain rather than full-length IgGs, provide improved tissue penetration and enable precise, site-specific conjugation. In this approach, sdAb-based detection is combined with DNA branch amplification, in which oligonucleotide scaffolds recruit multiple fluorescent probes to generate tunable signal amplification while preserving spatial localization.Using mitochondrial targets as proof-of-concept markers, amplified samples demonstrated increased fluorescence intensity relative to positive controls while maintaining consistent subcellular localization patterns. Negative controls exhibited minimal background fluorescence, supporting the specificity of the oligo-based amplification strategy. Although amplified signals displayed some increased diffusivity, targeting specificity and colocalization were preserved despite modest sdAb conjugation recovery of approximately 10%.This platform enables quantitative, single-cell analysis of protein localization and supports scalable, high-dimensional imaging workflows through iterative readouts and computational normalization pipelines. By integrating multiplexed imaging with systems-level analysis, this approach may reveal coordinated cellular organization patterns and support the construction of a high-dimensional cell state atlas for studying cellular responses to perturbations.

Disclosures: M. Rodriguez: None. **M. Perez:** None. **M. Ward:** A. Employment/Salary (full or part-time):; NINDS/Berkeley.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.03/KK6

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

Title: Microscopy-Guided Proteomic Profiling of Neurodegenerative Aggregates Reveals Novel Aggregate-Associated Proteins and Molecular Signatures

Authors: *J.-C. LIAO[1], C.-C. HUANG[1], Y.-C. PAN[1], B.-Y. CHEN[1], T. CHONG[1], C.-K. HUANG[1], E. CHUNG[1], H.-J. CHANG[1], M. FARIA DE OLIVEIRA[2], **D. DLUGOLENSKI**[2]; [1]Syncell Inc., Taipei City, Taiwan; [2]Syncell Inc., Livermore, CA

Abstract: Misfolded protein aggregation is a pathological hallmark of many neurodegenerative disorders, including Alzheimer's disease and synucleinopathies such as Parkinson's Disease, where the accumulation of misfolded proteins contributes to proteostatic stress, synaptic dysfunction, and progressive neuronal degeneration. Despite their central role in disease biology, the local protein composition and the interactors of pathological aggregates remains incompletely understood due to limitations of conventional proteomics approaches, which often lack the spatial precision, sensitivity, and sample type compatibility required for unbiased interrogation of heterogeneous brain pathology. Here, we employed Microscoop, an optoproteomics platform combining microscopy-guided photo-biotinylation with LC-MS/MS to enable unbiased, region specific profiling of aggregate-associated proteomes directly from fixed cells and human tissue. Fluorescence-defined regions of interest corresponding to amyloid-β (Aβ1-42) aggregates in differentiated SH-SY5Y cells and Lewy bodies in formalin-fixed paraffin-embedded human brain tissue were photolabeled using the Synlight-Rich workflow. Two-photon illumination induced localized photo-biotinylation of proteins within targeted aggregate microdomains, enabling streptavidin enrichment of photolabeled (PL) samples alongside unlabeled (UL) controls. Differential enrichment between PL and UL samples was determined using statistical significance and fold-change thresholds, followed by functional Gene Ontology analysis. Across both systems, disease-relevant molecular signatures were resolved with high spatial specificity. In the Aβ cellular model, multiple previously unreported aggregate-associated proteins were identified, including unknown candidates validated by immunofluorescence colocalization studies, demonstrating the platform's ability to enable de novo proteomic discovery at subcellular resolution. In Lewy bodies from human tissue, we observed enrichment of pathways associated with proteostasis, oxidative stress, clearance mechanisms and neuronal circuit dysfunction, providing insight into the molecular landscape surrounding α-synuclein aggregates Together, these findings demonstrate the power of spatially resolved optoproteomics to characterize pathological protein aggregates, providing new insights into aggregate-associated protein composition, deciphering pathological mechanisms, and unlocking potential therapeutic targets in neurodegenerative disease.

Disclosures: J. Liao: A. Employment/Salary (full or part-time):; Syncell Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **C. Huang:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **Y. Pan:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **B. Chen:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **T. Chong:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **C. Huang:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **E. Chung:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **H. Chang:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **M. Faria de Oliveira:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **D. Dlugolenski:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc..

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.04/KK7

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

Support: RS- 2024–00338422
RS-2022-NR075598
KGM5362521
KK2653-10

Title: Maternal exposure to polypropylene nanoplastics disrupts sex- and region-specific lipid metabolism in the brains of C57BL/6N mouse offspring

Authors: *S. PARK[1], D.-Y. LEE[2];
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Abstract: Polypropylene nanoplastics (PPNPs), produced through the degradation of widely used plastic products, are increasingly recognized as emerging environmental contaminants with potential neurodevelopmental toxicity. However, the long-term biochemical consequences of prenatal PPNP exposure on brain development remain poorly understood. In this study, we performed a region- and sex-specific targeted lipidomic analysis to examine how maternal oral exposure to PPNPs during pregnancy and lactation alters brain lipid composition in offspring at postnatal day 21. Using liquid chromatography-tandem mass spectrometry (LC-MS/MS), we profiled lipid classes in the hippocampus (HP), cortex (CTX), cerebellum (CB), and dorsal raphe nucleus (DR) of both male and female mice. Our findings revealed distinct, region-specific lipid remodeling patterns in response to PPNP exposure. Females exhibited consistent reductions in neuroprotective lipids, including lysophosphatidyletha nolamines (LPEs) and plasmalogens,

most prominently in the hippocampus. Males, in contrast, displayed elevated triglyceride levels and region-specific alterations in phospholipid composition, such as reduced phos phatidylcholines in the hippocampus and dorsal raphe. These results indicate that maternal nanoplastic expo sure, even without postnatal contact, can cause persistent, sex-specific disturbances in brain lipid metabolism. To our knowledge, this study provides the first targeted lipidomic characterization of offspring brains following maternal PPNP exposure and highlights the importance of brain region-specific lipid analysis for identifying localized disruptions in neurodevelopment caused by environmental pollutants.

Disclosures: S. park: None. **D. Lee:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.05/KK8

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

Support: the STI2030-Major project 2021ZD0202200, subject 2021ZD0202203 (M.J.)

Title: Multiplexed molecular recorders for tracking single cell state transitions

Authors: *H. ZHOU[1,2], Y. WANG[1], M. JING[1];
[1]Chinese Inst. for Brain Research, Beijing(CIBR), Beijing, China; [2]Acad. for Advanced Interdisciplinary Studies, Peking Univ., Beijing, China

Abstract: Cell-state transitions underlie development, disease progression, and tissue repair, yet current single-cell approaches largely capture static snapshots of molecular states and offer limited access to the temporal history of individual cells. Here we developed a multiplexed molecular recorder that simultaneously captures both the magnitude and timing of endogenous RNA activities in living cells during state transition. The system combines a circular RNA-based sensing module that converts target RNA abundance into programmable ADAR-based editing events, with an orthogonal temporal recording module that leverages progressive APOBEC-based editing to encode the timing of molecular activities. Following systematic optimization, we identified a circular RNA architecture that achieved robust editing efficiency and high stability, which can enable multiplexed recording of different endogenous transcripts associated with distinct cellular states. By jointly decoding A-to-I and C-to-U editing signatures, we quantitatively inferred both the intensity and relative timing of transcriptional activities in cultured cells subjected to sequential NF-κB and Wnt pathway activation, accurately recovered the transcriptional histories of cells. Furthermore, application of the system in vivo enabled the recording of dynamic molecular state histories in resident microglia, and revealed heterogeneous transcriptional histories following pathological perturbation. Together, we establish an editing-based framework for longitudinal recording of both the timing and magnitude endogenous RNA,

providing a foundation for studying cell-state transition and regulatory mechanisms in living organism.

Disclosures: H. Zhou: None. **Y. Wang:** None. **M. Jing:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

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Program #/Poster #: PSTR036.06/KK9

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

Support: NRF RS-2024-00439379
NRF RS-2023-00263628
NRF RS-2023-00213512
NRF 2022R1C1C2003822

Title: Red light-activatable STIM1 for optical control of calcium signaling

Authors: *Y. JEONG[1], J. LEE[2], Y. KOOK[3], S. LEE[4], W. HEO[1];
[1]Korea Advanced Inst. in Sci. and Technol., Deajeon, Korea, Republic of; [2]Neurol., Brigham and Women's Hospital/Harvard Med. Sch., Boston, MA; [3]Inst. for Basic Sci. (IBS), Yuseong-gu, Daejeon, Korea, Republic of; [4]Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Calcium (Ca^{2+}) signaling plays a fundamental role in gene transcription, synaptic plasticity, and cellular adaptation. Optogenetic toolkits that selectively permit Ca^{2+} entry still face limitations due to their dependence on blue light. Here, we present R-OptoSTIM1, a red-light-responsive optogenetic tool that enables control of intracellular Ca^{2+} influx via activation of CRAC (Calcium release-activated channel) channels. This system is based on the bacterial phytochrome fused to a cytosolic STIM1(Stromal interaction molecule 1) domain. R-OptoSTIM1 reliably induces robust cytosolic Ca^{2+} elevation in response to red light in diverse cell types, including neurons, astrocytes, and hepatocytes. This Ca^{2+} influx activates key transcription factors . Furthermore, activation of R-OptoSTIM1 in the mouse hippocampus enhances cFos expression and facilitates contextual fear memory formation. We also demonstrate that R-OptoSTIM1 enables non-invasive activation of cells within deep tissue such as the deep brain and liver in mice that are poorly accessible to blue light,. Collectively, R-OptoSTIM1 represents as a red light-controllable optogenetic platform for non-invasive modulation of calcium signaling and downstream cellular processes in both excitable and non-excitable tissues.

Disclosures: Y. Jeong: None. **J. Lee:** None. **Y. Kook:** None. **S. Lee:** None. **W. Heo:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.07/KK10

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

Title: Building structure activity relationships (SAR) to avoid unwanted CNS ion channel activity

Authors: *R. A. ROBERTS, M. MORTON, L. ZOLKIEWSKI;
Apconix, Macclesfield, United Kingdom

Abstract: We previously described the integrated *in vitro* liability assay for seizure ($iLA^{Seizure}$), a new approach methodology (NAM) to reduce unwanted central nervous system (CNS) ion channel activity in drug discovery and development. Here we report the development of SAR (structure activity relationships) to guide drug design away from this liability. SAR test compounds were selected from the Enamine REadily AccesibLe (REAL) database using pharmacophore features and similarity to previous test compounds (amoxapine, diphenhydramine, quetiapine, 4-AP, linopirdine) or to ion channel positive reference compounds (bepridil, NS1619, quinidine, verapamil, XE991). These 88 compounds (10 parent compounds and 78 structurally related derivatives) were screened by automated electrophysiology in cell lines expressing human $K_V2.1$, $Na_V1.2$, the $\alpha_1\beta_2\gamma_2$ $GABA_A$ or $\alpha_4\beta_2$ nicotinic receptors to generate IC_{50} values. Across all four ion channels, the derivative compounds exhibited increased, equivalent or reduced potency compared with the parent compounds, providing a complex and rich data set for SAR. Regarding individual pharmacophoric features, statistical analysis identified 12 features significantly associated with activity at the $\alpha_4\beta_2$ nicotinic receptor; 4 of these were also significantly associated with activity at $K_V2.1$. Selected parent compounds (amoxapine, diphenhydramine, quetiapine) and structural analogues were screened for seizure-like activity in human induced pluripotent stem cell neurons using microelectrode array. The seizure-like phenotype was altered with the derivatives, as expected from the respective ion channel IC_{50} values. These data provide insight into SAR for ion channels, allowing desirable sub-structures to be included while avoiding specific sub-structures associated with seizure-like drug toxicity. This offers the opportunity to avoid CNS liability in the development of novel compounds, saving time, money and resources.

Disclosures: R.A. Roberts: A. Employment/Salary (full or part-time):; ApconiX. **M. Morton:** A. Employment/Salary (full or part-time):; ApconiX. **L. Zolkiewski:** A. Employment/Salary (full or part-time):; ApconiX.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.08/KK11

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

Support: CRC 1690
CRC 1286
ERC

Title: Atomic brain imaging by Ex-SIMS

Authors: *A. NTOLKERAS[1], D. KRAH[1], K. GREWE[2], N. DAVE[2], A. SHAIB[2], S. RIZZOLI[3]; [1]Dept. of Neuro- and Sensory Physiol., Univ. Med. Ctr. Goettingen, Goettingen, Germany; [2]Dept. of Neuro- and Sensory Physiol., Univ. Med. Ctr. Goettingen, Göttingen, Germany; [3]Univ. of Goettingen Sch. of Med., Goettingen, Germany

Abstract: The study of brain physiology and its diverse pathological states remains one of the most challenging areas of research. Among the major research directions in neuroscience is the investigation of protein ageing, also known as protein turnover. The synthesis, degradation and long-term stability of proteins essential for neuronal function play critical roles in both normal brain physiology and neurological diseases. In secondary ion mass spectrometry (SIMS), biological specimens are analyzed under high-vacuum conditions and scanned with a focused ion beam, releasing secondary ions from the sample surface that are measured by mass spectrometry. Although SIMS is powerful for visualizing protein turnover, its achievable resolution of ~100 nm constrains the study of subcellular structures, such as organelles, synapses and protein complexes. In this study, we propose a correlative and expansion-enabled framework that enhances the spatial resolution of SIMS, and bridges optical and non-optical imaging modalities within a unified coordinate system. We leverage the concept of physical enlargement of the specimen under investigation, provided by the field of expansion microscopy (ExM), as our central enabling strategy. A key technical step is the adaptation of expanded hydrogel-embedded biological specimens to the vacuum environment required for SIMS, while preserving the expanded structural information for correlative analysis. Through the integration of ExM with SIMS, we aim to visualize the atomic organization and molecular localization of subcellular structures and protein complexes in direct relation to their production and degradation dynamics. Ex-SIMS allows the investigation of synaptic protein turnover at the sub-compartment level, revealing mechanisms of synaptic plasticity and remodeling. By advancing the spatial resolution of SIMS, and through correlation with existing super-resolution optical techniques, we seek to access deeper layers of information, revealing how nanoscale protein organization and turnover reflect physiological states. Ex-SIMS introduces expansion microscopy into non-optical, vacuum-based molecular imaging, opening a new avenue of ExM applications beyond fluorescence microscopy.

Disclosures: A. Ntolkeras: None. **D. Krah:** None. **K. Grewe:** None. **N. Dave:** None. **A. Shaib:** None. **S. Rizzoli:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.09/KK12

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

Support: NIH R01MH085159

Title: Multiplexed measurements of synaptic and extrasynaptic serotonin dynamics in Drosophila melanogaster

Authors: *E. SEXTON[1], J. VENTON[2];
[1]Univ. of Virginia, Charlottesville, VA; [2]Univ. of Virginia, Charlottesvle, VA

Abstract: 5-Hydroxytryptamine (5-HT), or serotonin, is an important neuromodulator in physiological processes, such as mood regulation, sleep, and learning. However, the mechanistic and spatial dynamics of serotonin release remain poorly understood. The use of the fruit fly, Drosophila melanogaster, as a model organism offers many advantages as it has a simplified, analogous neurochemistry to human systems with a wide variety of genetic tools available to researchers for manipulation. Fast-scan cyclic voltammetry (FSCV) allows for real-time neurotransmitter detection on a sub-second timescale and has been used in Drosophila larvae systems. This method, however, lacks spatial resolution as it can only measure bulk extrasynaptic serotonin release. Recent advances in genetically encoded fluorescent sensors, specifically the GRAB5-HT, enables highly selective detection of extracellular 5-HT with subcellular resolution. The central goal of this project is to characterize serotonin release dynamics in Drosophila by comparing FSCSV and GRAB5-HT measurements, enabling investigation of extrasynaptic and synaptic serotonin pools and how reuptake shapes each. To do so, we express the GRAB5-HT sensor in larval serotonergic neurons and evoke 5-HT release via optogenetic stimulation parameters. The ventral nerve cord (VNC) has been well characterized, and the location of the serotonergic neurons are well established, making Drosophila larvae a suitable, simplified, model for initial method testing. Comparison of GRAB5-HT to FSCV measurements with similar stimulation parameters is expected to show fluorescent detection of a more synaptic serotonin versus electrochemical detection of extrasynaptic serotonin in Drosophila larvae. By combining this novel method with established electrochemical methods, this work will establish a fluorescence-based imaging platform for measuring serotonin dynamics in Drosophila, laying the foundation for mechanistic studies of the spatial distribution of serotonin signaling.

Disclosures: E. Sexton: None. **J. Venton:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

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Program #/Poster #: PSTR036.10/KK13

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

Support: Intramural awards from NICHD to MS and BS

Title: A genetic detection system for CRISPR/Cas9-mediated gene disruption in Drosophila melanogaster

Authors: *K. AKALAONU, B.-M. SONG, M. STOPFER;
NICHD, NIH, Bethesda, MD

Abstract: Genome editing can reveal with great specificity how a gene functions within a defined cell population, and CRISPR/Cas9 offers the ability to knock out genes in a tissue-specific manner. However, a potential shortcoming of this approach is the heterogeneity of editing outcomes: mosaicism that can range from out-of-frame mutations to an absence of detectable sequence changes, making it difficult to reach definitive conclusions about gene function. Thus, we are generating a genetic detection system for gene disruption to identify cells bearing homozygous “null” mutations. To accomplish this, we generate knock-in lines that express an in-frame transcriptional activator. When the target gene is translated, it triggers a reporter to label the cells expressing it. When directed to this target gene via guide RNA, Cas9 cleaves at a specified sequence. A genetic binary switch restricts Cas9 expression to select cells and simultaneously triggers a second reporter to label cells undergoing editing. Co-expression of both reporters can signal an in-frame mutation, while loss of the first signals a null mutation. We then confirm deletions in defined cells through in situ hybridization, probing for signal at regions upstream from the target gene site of transcription and at the CRISPR target sequence. We are applying our system to better understand the roles of neurotransmitter receptors expressed in gustatory receptor neurons (GRNs) in the fruit fly’s primary taste organ, the labellum. These GRNs can be identified across animals by their innervation of well-mapped sensilla, hair-like structures along the surface of the organ, and their neurotransmitter profiles can be determined by reliable techniques. Our system allows us to manipulate specific subsets of GRNs, to confirm expression patterns of specific neurotransmitter receptors in the labellum, and to observe successful CRISPR action within target cells at a rate of 92 ± 3% (mean ± SEM). We observed activity in some non-target cells, likely because the genetic driver triggers Cas9 expression in additional cells at earlier life phases. To improve specificity to target cells, we refine our system by further restricting Cas9 expression to controlled times during development. Our system will allow us to identify cells bearing complete knockouts of a target gene. Our specific goal is to better understand the impact of early-stage synaptic interactions on taste-driven behavior, but, owing to its versatility, our system can be applied broadly in the nervous system to investigate synaptic interactions in any cell population with the appropriate drivers.

Disclosures: K. Akalaonu: None. **B. Song:** None. **M. Stopfer:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

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Program #/Poster #: PSTR036.11/KK14

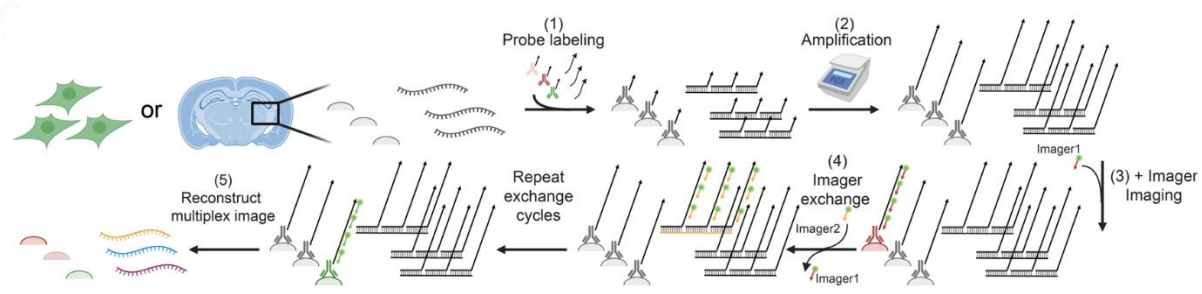
Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH BICAN MH13481201
NIMH MH134803-01A1
NIMH 1R01MH132599-01
NCI 5R01CA283202-02

Title: Synchronized in situ amplification enables high-plex protein imaging from cells to deep brain tissues

Authors: *K. SHENG[1,2], H. SU[1];
[1]Wyss Inst. at Harvard Univ., Boston, MA; [2]Systems Biol. Dept., Harvard Med. Sch., Boston, MA

Abstract: High-plex protein imaging is essential for decoding complex tissue organization, yet it remains largely confined to thin sections. Current approaches in millimeter-thick samples suffer from poor signal penetration and depth-dependent, uneven signal amplification. Even with specialized instrumentation to facilitate probe diffusion, iterative millimeter-thick tissue workflows can take more than four days per staining round, and reported eleven-marker experiments extend beyond a month. We introduce Amplification by Cyclic Extension (ACE), a DNA barcoded, synchronized *in situ* amplification strategy that uses thermally controlled cyclic extension to coordinate DNA concatemer growth across tissue depths. By synchronously activating and coordinating reaction progression throughout the sample, ACE balances local diffusion from reaction progression and enables controlled, uniform signal amplification across tissue depths. Using ACE, we demonstrate 63-plex protein and RNA imaging in thin sections, 22-plex protein imaging in 200 µm mouse brain sections, and 16-plex protein imaging in 1 mm-thick brain tissue encompassing over three million cells. For millimeter-thick tissues, ACE reduces per-round target-switching time from multiple days to less than eight hours, shifting volumetric high-plex protein imaging from months to days. Together, these results establish ACE as a synchronized amplification strategy that enables scalable high-plex protein imaging in thick tissues.



Disclosures: K. Sheng: None. **H. Su:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

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

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NIH Grant 1R01CA283202
NIH Grant 1RF1MH132599

Title: Amplified thermal-plex enables rapid fluidic-free multiplexed protein imaging in brain tissue

Authors: *H. SU[1], K. SHENG[2];
[1]Wyss Institute, Harvard Univ., Boston, MA; [2]Wyss Inst. at Harvard Univ., Boston, MA

Abstract: Multiplexed protein imaging is essential for mapping molecularly defined cell populations across brain tissue, but current workflows often depend on iterative fluidic exchange, which limits speed, scalability, and compatibility with larger or more delicate samples. We developed amplified thermal-plex, a temperature-programmed imaging strategy that enables multiplexed protein readout without fluid exchange between imaging rounds. The approach combines DNA-barcoded antibody labeling, in situ signal amplification, and thermally controlled channel switching to preserve sensitivity while accelerating sequential readout. We applied amplified thermal-plex to cultured cells and mouse brain tissue, demonstrating multiplexed protein imaging across combined thermal and fluorescence channels using standard fluorescence microscopy. In brain sections, the method resolved major neural, glial, vascular, and structural features with spatial patterns consistent with expected neuroanatomy. The resulting images supported single-cell segmentation, marker-based clustering, anatomical mapping, and neighborhood analysis, revealing coherent spatial organization of neuronal and glial populations. Thermal channel activation occurred on the order of minutes rather than hours, while preserving tissue morphology and marker localization. These results establish amplified thermal-plex as a rapid, fluidic-free framework for scalable multiplexed protein imaging in neural tissue. By reducing the dependence on repeated reagent exchange, this method will enable faster spatial proteomic analysis of brain samples across multiple spatial scales.

Disclosures: H. Su: None. **K. Sheng:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.13/KK16

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

Title: Spatial multiplexed imaging reveals tumor-neuro-immune interactions in human glioma

Authors: *D. PAUL[1], V. AGRAWAL[1], S. STRUBLE[1], M. SMITH[1], J.-E. HOFFMANN[2], A. ZILLES[2], S. DR. ALSHEIMER[2], L. TURNBULL[1];
[1]Spatial Biol., Leica Microsystems, Waltham, MA; [2]Leica Microsystems, Siegen, Germany

Abstract: Diffuse gliomas represent a spectrum of infiltrative primary brain tumors marked by profound cellular heterogeneity. Across grades, these tumors are increasingly understood as complex ecosystems composed of neoplastic, neural, and immune cell populations that dynamically interact within a spatially organized tumor-neuro-immune microenvironment. In contrast to many epithelial malignancies, gliomas arise within the central nervous system, where these interactions contribute to tumor progression, immune evasion, therapy resistance, and recurrence, and are associated with remodeling of the neuronal and glial architecture.
Spatial imaging enables interrogation of these ecosystems by supporting multiplexed, *in situ* protein profiling at single-cell resolution while preserving the tissue structure, including neurons, astrocytes, oligodendrocytes, and their processes. This is particularly important in brain tissue, where cells exhibit irregular morphology and extend or branched processes, which are not captured in dissociative approaches.
To investigate these features *in situ*, we performed high-plex spatial profiling on human FFPE glioma tissue sections using the Cell DIVE multiplexed imaging platform, enabling iterative, highcontent imaging and a novel and flexible ecosystem of **ATTOAuriga** reagents. Antibody panels were designed to identify neuronal, glial, immune, and tumor cell populations and included a mix of pre-validated **ATTOApollo** antibody panels, custom antibodies labeled with **ATTOConexa** reagents, and antibodies directly conjugated to fluorophores. These were incorporated within a single staining and imaging workflow, enabling inclusion of additional markers without redesigning the assay, alongside AI-guided analysis in Aivia for segmentation, spatial mapping, and cell phenotype classification.
Spatially resolved analysis enables interrogation of heterogeneous tumor regions and comparison of normal brain tissue and glioma. These data highlight disruption of neuronal and glial cell architecture, including loss of cellular processes, together with increased immune cell localization at tumor margins and changes in tissue organization.
Collectively, this end-to-end spatial imaging workflow provides a scalable approach for resolving cell-cell interactions across tumor, neural, and immune compartments in glioma, while preserving the structural context of brain tissue. Such an approach facilitates the identification of spatially encoded disease mechanisms.

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Poster

PSTR036: Biochemical and Molecular Techniques

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Program #/Poster #: PSTR036.14/KK17

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

Title: Oligo-Ready FlexAble and CleanAb: Scalable Antibody Labeling for Spatial and Screening/Discovery

Authors: *L. JURLAU[1], L. WU[2], P. BECKER[1], X. WANG[3], C. LINKE-WINNEBECK[1], A. BUCHFELLNER[1], D. CALLAHAN[4], L. LIAN[3], D. SHANKAR[2];
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Abstract: Single-cell and spatially resolved multi-omics have become central to neuroscience, and these workflows increasingly depend on oligonucleotide-conjugated antibodies, which are often a bottleneck. Here, we present two tailored solutions for generating oligonucleotide-labeled antibodies: FlexAble for sub-microgram antibody inputs, and CleanAb for higher-microgram-scale conjugates.FlexAble enables low-input labeling (possible for <1 µg primary antibody) using engineered peptide-based FlexLinkers that specifically bind human, rabbit, mouse, or rat IgG with high affinity. Functionalized with reactive groups (e.g., azide), FlexLinkers can be efficiently conjugated to modified oligonucleotides (e.g., DBCO). A His6-tag serves for the effortless removal of excess oligonucleotides. The resulting Oligo-FlexLinker stocks can be precisely dosed to label as little as 0.5 µg antibody per reaction within minutes.Naturally, FlexLinkers with reactive groups can be conjugated to other molecules (e.g., payloads) carrying corresponding reactive groups. For example, FlexAble-MMAE provides a low-input, fast way to explore these concepts with clinically meaningful human IgGs. By removing the need for direct chemical conjugation for each candidate, this approach can accelerate screening of therapeutic IgG formats, including those addressing neurodegeneration, neurooncology, and neuroinflammation.Additionally, FlexLinkers are available in fluorescent formats (405-750 nm) for multimodal applications. They can be used for multiplexed staining, even when the primary antibodies originate from the same species. For example, rabbit anti-Ki67, anti-MAP2, and anti-DAT co-staining of human hESC-derived midbrain organoids, capturing proliferation, neuronal differentiation, and dopaminergic lineage specification.When larger amounts of primary antibody need to be chemically (covalently) labeled with oligonucleotides or other molecules, the resulting conjugates can be effortlessly purified with CleanAb Beads. CleanAb is a novel purification strategy based on selective Fab binding of mouse or rabbit IgG. We show that CleanAb Beads enable one-step removal of excess oligonucleotides under gentle pH-neutral elution conditions, preserving antibody functionality and ensuring high yield.Together, these two technologies provide a scalable platform for preparing labeled antibodies and can support spatial omics of brain tissue, discovery in neuro-oncology, in vitro/organoid screening, etc.

Disclosures: L. Jurlau: A. Employment/Salary (full or part-time):; Proteintech. **L. Wu:** A. Employment/Salary (full or part-time):; Proteintech. **P. Becker:** A. Employment/Salary (full or part-time):; Proteintech. **X. Wang:** A. Employment/Salary (full or part-time):; Proteintech. **C. Linke-Winnebeck:** A. Employment/Salary (full or part-time):; Proteintech. **A. Buchfellner:** A. Employment/Salary (full or part-time):; Proteintech. **D. Callahan:** A. Employment/Salary (full or part-time):; Proteintech. **L. Lian:** A. Employment/Salary (full or part-time):; Proteintech. **D. Shankar:** A. Employment/Salary (full or part-time):; Proteintech.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.15/KK18

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

Support: NIH/NINDS Grant R56/R01NS136464
Brains & Behavior Seed Grant
Support from The Arnold and Mabel Beckman Foundation through The Beckman Scholars Program

Title: Comparative OUT-based substrate mapping of E3 ligases RNF216 and CHIP to identify substrates relevant to Gordon Holmes syndrome

Authors: *K. GHENT, W. WEI, A. M. MABB;
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Abstract: Protein ubiquitination regulates protein degradation and neuronal signaling through E1-E2-E3 enzymatic cascades. E3 ubiquitin ligases confer substrate specificity, yet the substrate networks regulated by many disease-associated E3 ligases remain poorly defined. Mutations in *RNF216* and *STUB1/CHIP* have been identified in Gordon Holmes syndrome (GHS), a rare neurodegenerative disorder associated with cerebellar ataxia, cognitive dysfunction, neuroendocrine disruption, and reproductive impairment. Because RNF216 and CHIP are both implicated in ubiquitin-dependent protein quality control, we investigated whether these ligases regulate convergent substrate networks relevant to GHS pathology. Here, we used Orthogonal Ubiquitin Transfer (OUT), an engineered ubiquitin-labeling platform, to identify and compare E3 ligase substrates in living cells. RNF216 OUT analysis identified 174 substrates in GT1-7 neuronal cells and 65 substrates in HEK293 cells. Comparison across cell types revealed only 3 shared RNF216 substrates, supporting cell-type-specific substrate selection. Despite limited substrate overlap, functional annotation of RNF216 substrate networks identified enrichment for pathways related to protein synthesis. In HEK293 cells, comparison of RNF216 and CHIP OUT substrate datasets identified 7 shared substrates. Functional annotation of RNF216 and CHIP substrate profiles also revealed convergence on biological processes related to protein synthesis regulation. These findings suggest that RNF216 and CHIP regulate largely distinct substrate pools while converging on shared functions. Ongoing work will extend this comparison into GT1-7 neuronal cells to determine whether RNF216 and CHIP substrate networks converge in a neural proteome. Together, these studies support OUT-based substrate mapping as a strategy to define E3 ligase signaling networks and identify pathways relevant to GHS and related neurodegenerative disorders.

Disclosures: K. Ghent: None. **W. Wei:** None. **A.M. Mabb:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.16/KK19

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

Support: WNH

Title: Cell-type specific proteomics in mouse brain using enhancer-driven viral delivery and TurboID proximity labeling

Authors: *M. PARNIAN, K. JIN, J. XIE, C. VAN VELTHOVEN;
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Abstract: The functional diversity of neuronal and glial cells in the mammalian brain is driven in part by distinct protein compositions that shape cellular identity, yet cell-type specific proteomes remain poorly defined. To address this, we developed a scalable platform combining enhancer-driven viral targeting, complementary transgenic strategies, and proximity labeling for cell-type specific proteomics in mouse brain using the TurboID enzyme. TurboID is an engineered biotin ligase that catalyzes proximity-dependent biotinylation of lysine residues, enabling labeled proteins from targeted cells to be isolated from intact tissue using streptavidin enrichment. Here, TurboID was directed to astrocytes, pan-neuronal populations, excitatory neurons, and inhibitory neuron subclasses using both promoter and enhancer-driven approaches to evaluate cell-type specific protein labeling in vivo. These populations were selected because they represent morphologically and functionally diverse brain cell classes, allowing us to test whether targeted proximity labeling can resolve proteomic differences across distinct cellular identities in vivo. Labeling specificity was confirmed by immunohistochemistry, and biochemical recovery of biotinylated proteins was assessed by western blot and streptavidin pulldown followed by liquid chromatography-mass spectrometry analysis. Imaging and biochemical results supported cell-type enriched protein biotinylation. Differential proteomic analyses comparing biotin and no-biotin conditions identified biotin-enriched proteins for each targeted population, supporting recovery of cell-type associated protein candidates from intact brain tissue. This approach provides a scalable framework for resolving proteomic identities across genetically targeted neuronal subtypes and non-neuronal cell classes.

Disclosures: M. Parnian: None. **K. Jin:** None. **J. Xie:** None. **C. van Velthoven:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.17/KK20

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

Support: Gordon and Betty Moore Foundation

Title: ZETA: A HaloTag-based platform for multi-timepoint recording of synaptic activity histories

Authors: *D. KIM[1,2], C. LEUNG[1], C. K. KIM[1], A. E. COHEN[2];
[1]Omenn-Darling Bioengineering Inst. & Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Chem. and Chem. Biol., Harvard Univ., Cambridge, MA

Abstract: Synaptic transmission is the fundamental mechanism of neuronal communication but identifying when and where synapses are active across distributed circuits remains challenging. Here, we present ZETA (veZicle Exocytosis Tracking Assay), a HaloTag-based labeling strategy for capturing active presynaptic terminals at multiple time points in the living mammalian brain. Our approach uses a HaloTag-based reporter engineered from a synaptic vesicle protein, in which HaloTag becomes accessible to synthetic HaloTag-ligands during synaptic vesicle exocytosis. By delivering spectrally distinct ligands at different time points, this strategy enables multi-timepoint labeling of synaptic activity, converting transient presynaptic release events into stable fluorescent labels that can be read out after fixation. By separating *in vivo* activity recording from *ex vivo* readout, this platform enables reconstruction of synaptic activity histories across large brain areas, including regions that are difficult to access with real time *in vivo* imaging. In cultured hippocampal neurons, KCl depolarization increased dye labeling (P = 0.0016; n = 40 neurons from 5 dishes for the stimulated group and n = 68 neurons from 8 dishes for the control group; two-sided Wilcoxon rank-sum test). In the mouse barrel cortex, optogenetic stimulation increased dye labeling in axons projecting from layer 2/3 pyramidal neurons (P = 0.05; n = 4 animals for the stimulated group and n = 3 animals for the control group; two-sided Wilcoxon rank-sum test). We then applied sequential multicolor labeling to compare synaptic recruitment across behavioral conditions. In mice expressing the reporter in medial prefrontal cortical projections, a rewarding experience following an aversive experience produced higher corresponding dye labeling in the nucleus accumbens than in the basolateral amygdala (P = 0.0078, n = 7 animals, Wilcoxon signed-rank test). This difference in dye labeling ratio between the nucleus accumbens and basolateral amygdala was no longer observed when the second stimulus was replaced with another aversive stimulus (P = 0.0625, n = 6 animals, Wilcoxon signed-rank test). We also generated cell type specific variants for multiplexed labeling of excitatory and inhibitory projections, extending the platform toward cell type specific analysis of synaptic dynamics. Together, ZETA offers a scalable approach for mapping synaptic communication across brain regions and cell types, providing insight into how the brain processes information through widely distributed circuits.

Disclosures: D. Kim: None. **C. Leung:** None. **C.K. Kim:** None. **A.E. Cohen:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.18/KK21

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

Support: NIH Grant R01 NS147385

Title: Viral Pseudotyping to target Cerebellar Interneurons

Authors: *M. R. WILLIAMS[1], T. ZAMAN[2];
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Abstract: The targeted delivery of genetically encoded tools to specific cell types is required to map and manipulate neuronal circuits. While modifying the host organism genome to express exogenous recombinases, in conjunction with recombinase dependent tools, is a popular method, it is not a method that is feasible across species. Independent from host genome modification, cell type specific gene expression is also pursued through developing capsids and non-coding DNA regulatory elements for adeno associated virus derived vectors. However, lentiviral vectors such as those derived from human immunodeficiency virus offer complementary strengths such as stable integration and large transfer vector capacity. Unlike AAVs, lentiviruses are enveloped. This difference in the biogenesis of lentiviral vectors can be leveraged experimentally to incorporate plasma membrane embedded proteins. We trialed the incorporation of membrane tethered ligands into lentiviral particles to pursue biased viral transduction towards cerebellar interneurons natively expressing the ligands receptor. We find that in adult mice infected with lentiviral particles displaying the receptor ligand along with the fusogenic stem domain of VSV-G, that highly biased infection of cerebellar interneurons was achieved, as compared to the absence of the ligand and the presence of the full VSV-G sequence. It thus may be feasible to utilize ligand display in conjunction with fusogenic domains as an independent or complementary strategy to achieve delivery of genetically encoded cargo to specific cell types across species.

Disclosures: M.R. Williams: None. **T. Zaman:** None.

Poster

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Support: NSF GRFP (L.B.)
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NIH R01 AG074004
NIH R01 AG072599
NIH R56 AG072599
NIH RF1 AG071805
NIH P30 CA008748
NSF MRI 2320241

Title: Structural epichaperomics resolves native HSP90/HSC70 chaperone scaffold states

Authors: *L. A. BOTTICELLI[1,2], S. WANG[2], C. DIGWAL[2], D. SEREDIUK[1], M. FEENER[1], A. RODINA[2], F. CHU[1], G. CHIOSIS[3];
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Abstract: Aging-associated proteostasis decline contributes to protein aggregation, synaptic dysfunction, and maladaptive remodeling of neuronal protein networks in Alzheimer's disease (AD). Chaperone proteins, including HSP90 and HSC70, normally maintain proteostasis through dynamic interactions with co-chaperones and client proteins. Under stress-associated conditions, however, subsets of these chaperones can reorganize into epichaperomes: stable scaffolds marked by distinct post-translational modification (PTM) patterns and remodeled proteome connectivity. Epichaperomes are functionally implicated in AD-related synaptic dysfunction, yet the native assembly states, PTM patterns, and structural features that define AD-relevant epichaperome remodeling remain incompletely resolved.
To address this gap, we developed Structural Epichaperomics, a complex-resolved workflow that combines native enrichment of drug-engaged epichaperome assemblies, native gel separation, LC-MS/MS proteomics, PTM mapping, and structure-informed computational analysis. As proof of principle, we applied this approach across stress- and cell-state models to determine whether epichaperomes share a conserved chaperone core while investigating context-specific composition, PTM patterns, and interaction topology.
Native epichaperome profiling revealed recurrent HSP90/HSC70/co-chaperone assemblies whose relative abundance and associated protein networks differed across cellular states. Assembly-resolved proteomics further showed that PTMs partition with specific native epichaperome subsets, supporting a model in which PTM patterns are associated with altered chaperone scaffold organization, partner recruitment, and HSP90 allostery. Computational structural analysis incorporating protein abundance ratios and PTM patterns generated predictions of state-dependent assembly features and candidate protein interfaces reconfigured in epichaperomes.
Together, these pilot data establish Structural Epichaperomics as a complex-resolved strategy for mapping native epichaperome assembly composition, PTM patterns, and structural features in AD-relevant contexts. This framework enables disease-relevant hypotheses about how HSP90/HSC70-centered epichaperome assemblies reorganize under neuronal stress and nominates candidate epichaperome interfaces and PTM states for future mechanistic testing in more direct AD models and clinically staged human brain tissue.

Disclosures: L.A. Botticelli: None. **S. Wang:** None. **C. Digwal:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C.D. is an inventor on patents related to epichaperome-targeting chemical probes

and therapeutics. **D. Serediuk:** None. **M. Feener:** None. **A. Rodina:** None. **F. Chu:** None. **G. Chiosis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); G.C. is an inventor on patents related to epichaperome-targeting chemical probes and therapeutics.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.20/KK23

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

Support: AEI grant PID2022-138105OB-C22
Project PID2022-138105OB-C22, "Role of Human Reelin in the Mechanisms of Beta-Amyloid Propagation", funded by MCIN/AEI/10.13039/501100011033 and FEDER, EU.

Title: Molecular architecture of Reelin: N-glycosilation sites

Authors: *L. PUJADAS[1,2,3,4], D. ROSSI[6], J. FORT[7,8,5], N. CARULLA[8], E. SORIANO[3,4];
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Abstract: Reelin is a glycosylated extracellular matrix protein involved in synaptic plasticity and adult neurogenesis, and exerts protective effects in Alzheimer's disease (AD) by modulating APP processing, reducing Aβ toxicity and interfering with tau phosphorylation pathways. Although altered Reelin glycosylation has been reported in AD, specific glycosylation sites remain undefined. Here, we performed an in silico analysis of the Reelin sequence, which predicted multiple potential N-glycosylation motifs distributed along the protein. To experimentally validate these predictions, we applied a proteomic approach combining enzymatic deglycosylation with PNGase F and LC-MS/MS analysis of purified Reelin following tryptic digestion. Glycosylation sites were identified based on the detection of deamidated asparagine residues specifically after deglycosylation. This approach confirmed the presence of N-glycosylation in different domains of Reelin. These results provide experimental validation of Reelin N-glycosylation and support a role for altered glycosylation in AD-related dysfunction.

Further studies will investigate the functional impact of structure of the protein in the neuroprotective roles of Reelin.

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Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.21/KK24

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

Title: Activation of GPER-1 by G1 and Bisphenol A: Preliminary Evidence of Changes in Calcium Signaling in C2C12 Cells

Authors: *S. A. SANCHEZ MENESES[1], J. SPIES MALDONADO[2], R. TORRES ANDRADE[2], D. L. CORONA QUINTANILLA[3], A. FLORES HERNANDEZ[4], F. CASTELÁN[5], L. MOLINA CALISTRO[2];
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Abstract: The G protein-coupled estrogen receptor 1 (GPER-1) is involved in non-genomic cellular responses associated with intracellular calcium mobilization and activation of signaling pathways. Its activation by estradiol can also be modulated by the endocrine disruptor bisphenol A (BPA); however, the underlying mechanisms are not yet well characterized. This study aimed to evaluate GPER-1 activation induced by the selective G1 agonist and BPA by monitoring changes in intracellular calcium using FRET-based fluorescent biosensors in C2C12 cells. The cells were transfected with calcium-sensitive biosensors and subsequently exposed to either G1 or BPA. Changes in the FRET signal were recorded in real time. Preliminary results from this study showed a trend toward alterations in calcium signaling following exposure to both compounds, suggesting a possible role for GPER-1 in regulating intracellular calcium dynamics. However, the variability observed between experiments limits the ability to draw definitive conclusions. Overall, these findings suggest that G1 and BPA may modulate calcium signaling in C2C12 cells, although further studies are needed to confirm these effects and elucidate the underlying mechanisms.

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Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.22/KK25

Topic:

Title: Novel regulation of cell surface membrane proteins through selective autophagy

Authors: *D. SIDIBE[1], A. BUSTOS[2], B. VEDAK[1];
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Abstract: Cell surface membrane proteins (SMPs) mediate cell interaction with the environment and constitute most diagnostic markers and therapeutic targets; 66% of approved human medications target an SMP. Unraveling how SMP levels are regulated is critical for understanding cell surface remodeling and signal transduction mechanisms and have immense clinical implications. While decades of research implicate the endo-lysosomal system in SMP turnover, how SMPs are selectively targeted for internalization and degradation is still being determined. Autophagy recycles cytoplasmic cargo such as organelles and proteins via different pathways, including chaperone-mediated autophagy (CMA), which selectively targets cytosolic proteins harboring a pentapeptide KFERQ-related motif for degradation. The chaperone heat shock cognate71 kDa protein (Hsc70) recognizes target cytosolic proteins through their KFERQ-related motifs and escorts them to the lysosome. We used a bioinformatic approach to uncover that 55% of SMPs harbor KFERQ-related motifs in their cytoplasmic domains, making them potential selective targets for degradation through CMA. Within that 55%, there is a striking enrichment of SMPs associated with psychiatric disorders, including depression and substance use disorder. Examples include the dopamine transporter, dopamine receptors, 5-hydroxytryptamine receptors, AMPA receptor, NMDA receptor, GABA receptor, cannabinoid receptor, and opioid receptor kappa.To experimentally assess the CMA targeting of SMPs in cultured cells, we biotinylated SMPs and monitored their colocalization with pH-dependent labeled lysosomes. When subjected to environmental stressors such as acute heat shock (40°C), we observed an increased internalization of SMPs and their colocalization with lysosomes in a CMA-dependent manner. Notably, when we introduced a KFERQ-like but not a control peptide into the cells, the colocalization was reduced, indicating KFERQ-dependent targeting of SMPs to lysosomes. Furthermore, immunoprecipitation and western blot analysis of biotinylated SMPs show their interaction with the CMA chaperone protein Hsc70. These findings suggest that CMA activation is sufficient to target SMPs to lysosomes. This paves the way for exploring chaperone-mediated autophagy of surface membrane proteins (CHAMP) as a novel selective autophagy pathway that controls cell surface proteome homeostasis.

Disclosures: D. Sidibe: None. **A. Bustos:** None. **B. Vedak:** None.

Poster

PSTR036: Biochemical and Molecular Techniques

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.23/KK26

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

Support: Clayton Foundation for Research

Title: VESPA: An integrase-based multi-AAV genome assembly platform for delivery of oversized genetic payloads in vivo

Authors: *R. NEWTON[1], S. BRADBURY[2], Y. JU[3], I. HOWELL[3], A. CRISWELL[3], E. BABAIAN[3], V. BALOG[7], C. DUNN[4], S. GUPTA[3], H. AMARAM[5], L. E. FENNO[6];
[1]Dell Medical, Univ. of Texas at Austin, Austin, TX; [2]Dell Med. Sch., Austin, TX; [3]Univ. of Texas at Austin, Austin, TX; [4]Univ. of Texas at Austin, Buda, TX; [5]Univ. of Texas at Austin, Plano, TX; [6]Psychiatry & Neurosci., Univ. of Texas at Austin, Austin, TX; [7]MIT, Cambridge, MA

Abstract: Adeno-associated virus (AAV) is the leading vector for in vivo gene delivery in both basic research and clinical gene therapy, owing to its favorable safety profile, broad tropism, and durable episomal persistence. However, its ~4.8 kb packaging limit remains a fundamental constraint, restricting both therapeutic development and the design space available for next-generation viral tools. Several split-AAV strategies have been developed to extend payload capacity by distributing oversized sequences across multiple vectors. While effective in select contexts, existing approaches commonly rely on concatemerization, homologous recombination, RNA trans-splicing, protein-level reconstitution, or Cre recombinase-driven rearrangements that are probabilistic, reversible, or dependent on protein fragment assembly. These strategies can generate background expression from unassembled fragments, impose strict constraints on split-site selection, consume viral cargo space with repetitive non-codingelements, or introduce incompatibilities with widely used genetic and viral toolsets. Together, these limitations have hindered scalability, predictability, and general adoption of split-AAV delivery approaches. Accordingly, there remains a need for a scalable, predictable, and vector-intrinsic strategy to expand the effective payload capacity of AAV while maintaining low background expression, architectural flexibility, and in vivo tolerability. Here, we present Virally Engineered Split-Payload Assembly (VESPA), a DNA-based, integrase-driven AAV genome assembly platform that overcomes key limitations of existing split-AAV approaches.

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Poster

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

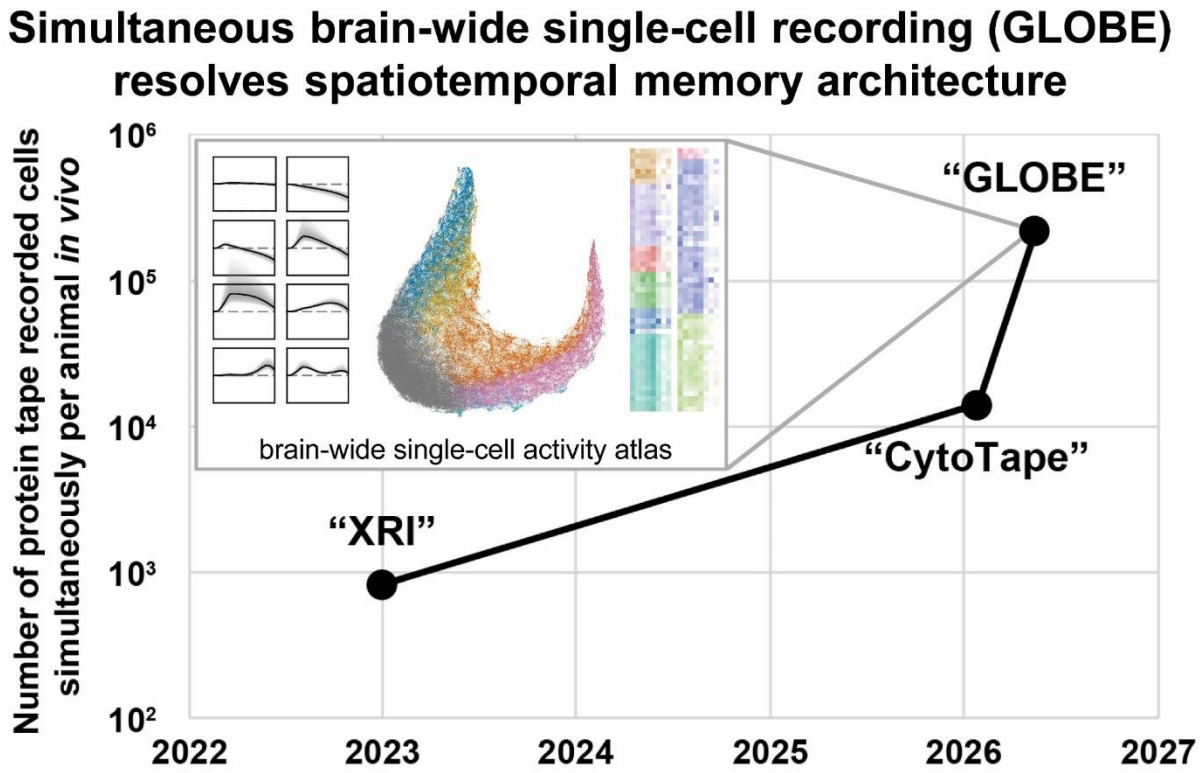
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Title: Simultaneous brain-wide single-cell recording resolves spatiotemporal memory architecture

Authors: *D. SHI[1], Y. HOU[6], Y. YAN[1], L. ZHENG[1], J. GOULD[2], B. KO[7], X. NIU[8], M.-C. CHENG[3], J.-C. HSIEH[4], D. CAI[9], A. DRAELOS[5], D. J. CAI[10], D. WEI[11], C. LINGHU[12]; [2]Neurosci. Grad. Program, [3]CDB, [4]Neurosci. graduate program, [5]Biomed. Engin., [1]Univ. of Michigan, Ann Arbor, MI; [6]UMICH, Ann arbor, MI; [7]Life science, Mount Sinai Sch. of Med., New York, NY; [8]UNIVERSITY OF MICHIGAN, Ann Arbor, MI; [9]Cell and Developmental Biol., Michigan Neurosci. Institute, Univ. of Michigan, Ann Arbor, MI; [10]Mount Sinai, New York, NY; [11]Boston Col., Boston, MA; [12]Dept. of Cell and Developmental Biology; Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Many fundamental mammalian brain functions emerge from the coordinated activity of cells distributed across large, brain-wide networks. To understand these processes in healthy and diseased states, ideally one would simultaneously measure and analyze single-cell activity at the brain-wide scale, an enduring challenge for live-measurement approaches that often face an inherent tradeoff between spatial resolution and scale. Here, we present GLOBE (sinGle-cell spatiotemporaL recOrding Brain-widE), a technology for brain-wide single-cell recording of cellular activity in vivo with spatiotemporal resolution, physiological sensitivity, and parallelization-accelerated readout. GLOBE leverages genetically encoded intracellular protein tape recorders and a high-throughput computational platform for integrated image and signal analysis. GLOBE records analog signal amplitudes across a continuous time axis, requires only standard light microscopy for in situ readout, and is compatible with expansion microscopy and RNA readouts. We applied GLOBE to record transcriptional activity of the immediate early gene Fos in 219,703 neurons simultaneously across a single mouse brain over 5.5 continuous days, with a timestamp precision of 3.1-6.7 hours (median absolute error), a local recording density of 69-90% of neurons per imaging field of view, and a post-mortem imaging readout speed of 2.9 seconds per neuron on average. GLOBE resolves the brain-wide spatiotemporal structure of single-cell activity, revealing that Fos transcriptional dynamics associated with fear learning and memory retrieval are distributed across the brain with region-specific temporal heterogeneity, and that the variance of this structure scales down as the number of sampled cells increases. We

envision GLOBE to have broad applications for dissecting and decoding physiological and pathological processes at the brain-wide scale.



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Poster

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Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.25/KK28

Topic: H.05. Mood Disorders

Support: IBS-R001-D2 to C.J.L.
IBS-R001-D2 to B.L.

Title: Stress-Induced Disruption of O- and N-Glycan Sialylation in the Medial Prefrontal Cortex Promotes Depressive-like Behaviors

Authors: *B. LEE;
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Abstract: Chronic stress is known to reshape the extracellular environment of the brain, including extracellular matrix components that are heavily modified by glycans. Despite growing evidence linking glycosylation to psychiatric disorders, the mechanistic contribution of glycan remodeling to stress-induced brain dysfunction remains largely unexplored. To address this question, we performed glycomic and molecular analyses in a mouse model of chronic stress. We identified a marked reduction in sialylated O-glycans within the medial prefrontal cortex, accompanied by decreased expression of St3gal1, a sialyltransferase involved in the terminal modification of core 1 O-glycans. Functional studies demonstrated that suppression of St3gal1 expression was sufficient to induce depression-related behavioral abnormalities, whereas restoring St3gal1 expression alleviated stress-associated behavioral deficits. Mechanistically, ST3GAL1 regulated the glycosylation state of neurexin-2 and contributed to the normalization of GABAergic synaptic transmission in the mPFC. These findings identify glycosylation as an active regulator of neural circuit function in stress-induced depression. In addition, our ongoing studies reveal broader alterations in prefrontal sialylation, including changes in the N-glycome, suggesting that multiple sialylation-dependent pathways may cooperate to influence emotional and cognitive states. Collectively, our work supports the idea that glycan remodeling represents a previously underappreciated mechanism linking chronic stress to neural circuit dysfunction and behavioral pathology.

Disclosures: B. Lee: None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.01/KK29

Topic: J.03. Anatomical Methods

Support: Austrian Science Fund (FWF) P 31263
Austrain Science Fund (FWF) P 35614

Title: Tissue clearing of large brains

Authors: *H.-U. DODT, M. PICKART, S. GUTMANN, K. BERGER;
Fac. of Life Sci., Univ. of Vienna, Vienna, Austria

Abstract: After the publication of the first cleared mouse brain (Dodt et al., 2007), brain clearing across species has become widely used to address diverse neurobiological questions, and the size of investigated specimens has progressively increased. In recent years, our lab developed a technology to clear large pieces of human brain up to the size of a half cerebellum (Oakes-Klein et al., 2026).We have now cleared whole pig brains with high transparency. The key technology was the application of a chemical dehydration reaction instead of the usual stepwise substitution of water with organic solutions. We previously applied this reaction using dimethoxypropane to clear centimeter-scale breast cancer specimens, which are notoriously hard to clear due to their

high cell density (Sabdyusheva-Litschauer et al., 2020). High transparency in organic tissue clearing requires complete elimination of water from the sample before submersion in a clearing solution such as BABB. Complete delipidation must also be performed to achieve good transparency in lipid-rich brain regions such as white matter and basal ganglia. Equally important is the removal of the brown discoloration that forms during the final clearing step with the high-RI matching solution.Imaging such extremely large samples requires objectives with a wide field of view, enabling an overview before zooming in on regions of interest. Zoom macroscopes proved most suitable, but their lenses were not designed for immersion: standard plane-window dipping caps cause strong spherical aberrations, limiting usable NAs to approximately 0.3. By developing dipping cones with a specially curved window, we effectively eliminated spherical aberration, achieving substantially improved resolution on a Zeiss Axiozoom with fully preserved working distance. NA and magnification scale with the refractive index of the clearing medium, and the zoom function provides both a sample overview and a relatively high NA without the need to change the objective. As this solution relies on general optical principles, it can be applied to any air objective and should assist researchers performing microscopy in liquids when high-end corrected immersion objectives are not available.

References:

1. Dodt HU et al., Ultramicroscopy: three-dimensional visualization of neuronal networks in the whole mouse brain. *Nat Methods.* 2007, 4: 331-6.

2. Sabdyusheva Litschauer I et al., 3D histopathology of human tumours by fast clearing and ultramicroscopy. *Sci Rep.* 2020, 10: 17619.

3. Oakes-Klein J et al., activeDISCO enables large-scale exploration of human brain anatomy by light sheet microscopy. *Commun Biol.* 2026, doi: 10.1038/s42003-026-09935.

Disclosures: H. Dodt: None. **M. Pickart:** None. **S. Gutmann:** None. **K. Berger:** None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.02/KK30

Topic: J.03. Anatomical Methods

Support: NSFC Grant 62375096
NSFC Grant 82372012
NSFC Grant 82361138569
NSFC Grant 82402341
Innovation Project of Optics Valley Laboratory Grant OVL2025BB008

Title: Fast Clearing and Immunolabeling via Alternating Electromagnetic Fields

Authors: *X. ZHONG, J. WANG, Y. ZHENG, J. WANG, J. XU, T. YU, D. ZHU;
Huazhong Univ. of Sci. and Technol. (HUST), Wuhan, China

Abstract: Efficient tissue clearing and molecular labeling have paved the way for organ-scale optical imaging, however, slow molecular exchange within biological tissues remains a major bottleneck. This limitation is particularly pronounced in large-volume, dense, or mineralized tissues, where key processes such as delipidation, decalcification, and probe penetration often require prolonged processing times. Subsequent refractive-index matching further extends the overall tissue-processing workflow, thereby limiting rapid three-dimensional imaging of intact tissues.To overcome this diffusion-limited bottleneck, we exploited the field-responsive mobility of charged or ionic species involved in tissue clearing and labeling. Specifically, we propose using an alternating electromagnetic field to enhance molecular exchange during delipidation, decalcification, and whole-mount labeling. Under specific alternating electromagnetic field conditions, charged or ionic species including delipidation detergents, calcium ions, decalcifying chelators, and labeling probes, exhibit enhanced transport behavior, promoting their migration and exchange within tissues. Compared with approaches relying solely on passive diffusion or static electric fields, this strategy improves deep-tissue penetration, reduces surface accumulation, and markedly accelerates processing speed and spatial uniformity in large-volume and dense tissues. In parallel, we screened an efficient gel system compatible with subsequent organic solvent based refractive-index matching, further supporting rapid tissue clearing and simplifies handling during three-dimensional imaging across multiple tissue types, serving as an auxiliary technique to the electromagnetic field platform.This alternating electromagnetic field-assisted platform enables ultrafast whole-mount clearing and labeling. Remarkably, it efficiently decalcified mineralized mouse femoral tissue—a notoriously challenging tissue type— can be cleared within 18 h and immunolabeled within 24 h, showing greatly accelerated processing. This platform was further applicable to clearing and labeling of multiple organs such as the mouse brain, spinal cord and kidney, demonstrating broad tissue applicability and labeling versatility. Collectively, this alternating electromagnetic field-assisted tissue-processing strategy provides an efficient and versatile platform for rapid clearing, whole-mount labeling, and three-dimensional structural analysis of complex biological tissues.

Disclosures: X. Zhong: None. **J. Wang:** None. **Y. Zheng:** None. **J. Wang:** None. **J. Xu:** None. **T. Yu:** None. **D. Zhu:** None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.03/KK31

Topic: J.03. Anatomical Methods

Support: R01MH112739
R01MH112739-05S1

Title: Optimization of a multi-brain re-embedding strategy for histological and spatial transcriptomic applications

Authors: F. C. DRIVER, K. S. SPRINGER, *A. C. JACKSON;
Physiol. and Neurobio., Univ. of Connecticut, Storrs Mansfield, CT

Abstract: High-throughput histological and spatial transcriptomic studies require the processing of large numbers of brain samples while maintaining tissue quality and anatomical consistency. In many spatial transcriptomic workflows, the use of proprietary slides represents a significant cost and can limit experimental scale. Maximizing the number of anatomically matched samples that can be collected on a single slide would improve efficiency and reduce costs. To address this challenge, we developed a multi-brain re-embedding workflow that enables the simultaneous sectioning of multiple brain samples within a single OCT-embedded block. Mouse brains were initially embedded and sectioned to a common bregma coordinate, microdissected into standardized tissue blocks, removed and re-embedded into a shared matrix for final cryosectioning. Using mouse hypothalamic tissue as a test case, we evaluated 6-brain and 12-brain re-embedding configurations under multiple assembly conditions to optimize reproducibility, tissue integrity, and anatomical alignment. Although the 12-brain configuration increased potential throughput, it proved difficult to assemble and align consistently, resulting in greater anatomical variability and more frequent sectioning artifacts. In contrast, 6-brain blocks provided a more reliable balance between throughput and section quality, yielding closely matched anatomical sections with improved structural stability. Sections collected from re-embedded blocks were compatible with downstream immunohistochemical analyses, including robust labeling of neuronal nuclear antigen (NeuN), hypocretin/orexin (OX), and melanin-concentrating hormone (MCH) and other markers in the lateral hypothalamic area (LHA). The workflow is readily adaptable with respect to sample number, orientation, and section thickness, allowing customization for specific experimental applications. Collectively, these findings demonstrate that 6-brain sample re-embedding enables simultaneous processing of closely anatomically matched samples while preserving tissue integrity and expected neuroanatomical staining patterns. This approach provides a practical and scalable strategy for high-throughput histological studies and may be particularly valuable for future spatial transcriptomic applications.

Disclosures: F.C. Driver: None. **K.S. Springer:** None. **A.C. Jackson:** None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.04/KK32

Topic: J.03. Anatomical Methods

Title: TB.Clear^{TM}: A New Pipeline for Light Sheet Imaging and Brain-Wide Quantification of Genetically-Encoded Fluorescent Proteins

Authors: E. BLAES[1], N. GUANZON[1], C. REDD[1], Y. GALLEGOS[1], J. ZEITOUN[1], A. REKSOATMODJO[1], P. CHEUNG[1], S. P. GANDHI[2], *D. G. WHEELER[1,3];
[1]Translucence Biosystems, Irvine, CA; [2]Neurobio. and Behavior, Univ. of California, Irvine, CA; [3]Activity Signaling, LLC, San Diego, CA

Abstract: Traditional histological workflows rely on thin tissue sections to visualize cellular and molecular features of the brain. While effective, sectioning disrupts 3D anatomical context and limits analysis to sampled regions. Tissue clearing and light-sheet microscopy overcome these limitations by enabling intact-brain imaging and brain-wide analysis. These approaches are valuable for studies that depend on preserved endogenous fluorescence, including experiments using FosTRAP mice to label activity-dependent neuronal populations. However, commonly used organic solvent-based clearing methods, including iDISCO+, can quench endogenous fluorescent protein signals, limiting studies that rely on genetically encoded fluorophores to label cell bodies, projections, or activity-dependent reporters. Here, we present TB.Clear, a workflow for imaging and quantifying endogenous fluorescence in intact mouse brain using a new aqueous tissue-clearing protocol designed to preserve fluorescent proteins while providing optical transparency for light-sheet imaging. Cleared samples were imaged on a ZEISS Lightsheet Z.1 equipped with the Translucence Mesoscale Imaging System, enabling acquisition of whole-brain volumetric datasets at micron-scale resolution. Images were analyzed using Voxels™, the Translucence Biosystems analysis ecosystem, which incorporates machine learning-based object segmentation and atlas-aligned regional quantification. As a proof of principle, we applied TB.Clear to a Thy1-GFP mouse brain and generated a brain-wide 3D map of endogenous GFP fluorescence. Using Voxels, we segmented GFP-positive cells throughout the intact brain and quantified regional signal patterns across hundreds of anatomically defined brain regions. This workflow produces spatially registered measurements of cellular and structural features while preserving native 3D context. Outputs include 3D visualization, automated segmentation, atlas-aligned regional quantification, and statistical summaries of signal distribution. Together, these results demonstrate that TB.Clear, combined with mesoscale light-sheet imaging and Voxels-based analysis, provides a robust platform for researchers using endogenous fluorophores and supports scalable 3D histology for intact-brain biological discovery.

Disclosures: E. Blaes: None. **N. Guanzon:** None. **C. Redd:** None. **Y. Gallegos:** None. **J. Zeitoun:** None. **A. Reksoatmodjo:** None. **P. Cheung:** None. **S.P. Gandhi:** None. **D.G. Wheeler:** None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

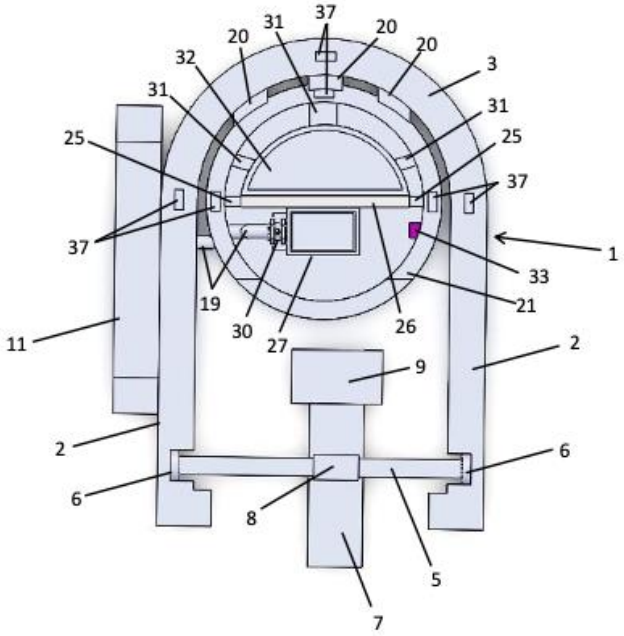
Program #/Poster #: PSTR037.05/KK33

Topic: J.03. Anatomical Methods

Title: Automated Neural Tissue Processing and Sectioning System for Experimental Neuroscience Research

Authors: *R. BELTRAN-RAMIREZ[1], X. M. BECERRA-GONZÁLEZ[2], J. MARTINEZ-MENDOZA[4], C. ROMÁN[1], J. A. DOMINGUEZ-RAMIREZ[3];
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Abstract: Histological analysis remains a fundamental tool in neuroscience research for studying neural architecture, neurodegeneration, neural injury, and the effects of experimental interventions. However, conventional tissue processing and sectioning procedures are labor-intensive, time-consuming, and susceptible to operator-dependent variability. The objective of this study was to develop and evaluate an automated modular platform capable of performing paraffin embedding, sectioning, and collection of neural tissue samples in a reproducible and scalable manner.The system integrates automated paraffin delivery, thermal regulation, tissue embedding, microcontroller-based positioning, motorized sectioning, and wireless communication for remote monitoring and control. The platform incorporates electromechanical actuators, precision-guided cutting mechanisms, temperature-control modules, and sensors that coordinate tissue processing and sectioning. Multiple units can operate simultaneously through a centralized control interface, enabling high-throughput tissue preparation.Prototype validation was performed using biological tissue specimens processed under controlled laboratory conditions. The automated workflow successfully completed paraffin infiltration, solidification, sectioning, and sample collection with minimal operator intervention. The modular architecture enabled parallel operation of multiple devices while maintaining consistent processing parameters. Automated control reduced manual handling and improved reproducibility during tissue preparation and section generation.These results demonstrate the feasibility of an automated histological processing platform for neuroscience applications. The system may improve standardization and throughput in studies requiring large numbers of neural tissue sections, including neuroanatomical mapping, neurodegenerative disease research, brain injury studies, and preclinical neuroscience investigations.



Disclosures: R. Beltran-Ramirez: None. **X.M. Becerra-González:** None. **J. Martinez-Mendoza:** None. **C. Román:** None. **J.A. Dominguez-Ramirez:** None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.06/KK34

Topic: J.03. Anatomical Methods

Support: National Natural Science Foundation of China (62522510)

Title: Optical Coherence Tomography (OCT)- and Acoustic-Guided Rapid and Precise Automated Cranial Microsurgeries in Mice

Authors: Z. SUN[1], ***H. JIANG**[2,1,3], J. QIU[1], Y. ZHANG[2,1,3];
[1]IDG/McGovern Inst. for Brain Res., Tsinghua Univ., Beijing, China; [2]Sch. of Life Sciences, Tsinghua Univ., Beijing, China; [3]Tsinghua-Peking Ctr. for Life Scis., Tsinghua Univ., Beijing, China

Abstract: Cranial microsurgery, including craniotomies for optically clear windows, viral vector delivery, or neural interface implantation, is foundational for *in vivo* imaging, neural circuit tracing, and neuromodulation. However, manual craniotomies rely heavily on operator expertise, suffer from time-to-time variability, and are highly time-consuming. To overcome these limitations and achieve beyond-human-level accuracy and operation speed, we developed a high-precision, automated robotic platform that enables accurate 3D craniotomies at high speed. The system first performs continuous tomographic scanning across the skull to precisely reconstruct its 3D anatomy with spectral-domain optical coherence tomography (SD-OCT), and the integrated real-time acoustic feedback calibrates the precise contact timing of the drill to the skull surface. A 6-degree-of-freedom robotic-arm-controlled drill adaptively enables rapid craniotomies of arbitrary geometries in 3D, achieving a hundred-fold time saving compared to human experts. Post-operative evaluations confirmed dural integrity without visible thermal damage or cortical hemorrhage. Experimentally, the platform successfully performed high-precision craniotomies across diverse cranial topologies at beyond-human speeds: large-scale craniotomies exposing the entire dorsal cortex (>50 mm²) were executed in just 10 minutes (1 minute for scanning and 9 minutes for continuous drilling); more technically demanding bilateral craniotomies over the vertical temporal cortices—an accomplishment significantly exceeding manual capabilities—were successfully completed within 30 minutes. The versatile platform supports various modular end-effectors like micro-injection pumps, thereby promising a fully automated pipeline from craniotomy to virus injection, and beyond. In conclusion, this embodied robotic platform surpasses human limits in both procedural speed and accessible surgical area, aiming to facilitate *in vivo* brain investigations.

Disclosures: Z. Sun: None. **H. Jiang:** None. **J. Qiu:** None. **Y. Zhang:** None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.07/KK35

Topic: J.03. Anatomical Methods

Title: Spatially resolved pharmacodynamics in intact neural tissue: single-section, protease-free co-detection of an oligonucleotide therapeutic, its target transcript, and target protein

Authors: *A. ACHARYA;
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Abstract: Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) act at the transcript level, so spatial measurement of target RNA modulation within drug-exposed cell types is a central pharmacodynamic readout for oligonucleotide development in the nervous system. Complete interpretation of target engagement requires four analytes on a single tissue section: the administered oligonucleotide, its target transcript, the corresponding target protein, and cell-type context. Intrathecally delivered oligonucleotides distribute across neurons and glia through free uptake, whereas receptor-mediated strategies, including antibody-oligonucleotide conjugates and transferrin receptor 1 (TfR1/CD71)-shuttled designs, route delivery through defined cellular compartments, so spatially resolved, cell-type-resolved measurement is required in both regimes.Conventional workflows distribute these analytes across serial sections and incompatible chemistries and depend on protease-mediated permeabilization for RNA in situ hybridization (RNA-ISH) that degrades protein epitopes and morphology, limiting co-detection. The short therapeutic oligonucleotide, the most direct measure of drug delivery, is also the most difficult analyte to detect in situ and is often omitted.We established a single-section, protease-free, automated workflow that resolves all four analyte classes on one preserved tissue section by combining HCR RNA-FISH and immunofluorescence (IF). HCR HiFi Probes, designed against the therapeutic siRNA (antisense strand) and target mRNA sequences, provide background-suppressed, high-fidelity detection of both the administered oligonucleotide and its target transcript. In the same section, off-the-shelf validated primary antibodies are encoded with HCR HiFi Encoders to detect the target protein alongside a cell-type marker, without secondary antibodies. All RNA and protein analytes are read out together by isothermal, enzyme-free, single-step HCR signal amplification.The workflow yields co-localized, quantitative measurement of drug distribution, target-transcript modulation, target-protein response, and cellular identity in the anatomical context of a single preserved section, resolving the pharmacodynamic relationship from delivery to molecular effect within the same cells. Because HCR HiFi Probes can be designed to any target sequence of interest and HCR amplification is isothermal and enzyme-free, the workflow is target-agnostic and compatible across automated staining platforms, providing a portable framework spanning free-uptake and receptor-mediated oligonucleotide programs.

Disclosures: A. Acharya: A. Employment/Salary (full or part-time):; Molecular Instruments. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Molecular Instruments.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.08/KK36

Topic: J.03. Anatomical Methods

Support: Lieber Institute for Brain Development

Title: Identifying Molecular Markers for the Mediodorsal (MD) Nucleus of the Human Thalamus.

Authors: *F. SIEWE[1], S. V. BACH[2,3], S. E. MAGUIRE[2], V. MALLEPALLI[2], H. A. ALGRAIN[2], S. V. MAURER[2], R. A. MILLER[2], R. BHARADWAJ[2], J. E. KLEINMAN[2,3], T. M. HYDE[2,3,4], S. C. PAGE[2,3], G. PERGOLA[2,3,8,5], K. MARTINOWICH[2,3,6,9,7], K. R. MAYNARD[2,3,7];
[1]Mol. Neuroanatomy, [2]Lieber Inst. for Brain Develop., Baltimore, MD; [3]Psychiatry and Behavioral Sci., [4]Neurol., [5]Genet. Med., [6]Neurosci., [7]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD; [8]Translational Biomedicine and Neurosci. (DiBraiN), Univ. of Bari Aldo Moro, Bari, Italy; [9]Kavli Neurosci. Discovery Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: The thalamus is a major forebrain hub for relaying and integrating information across the brain and is composed of ~30 anatomically and functionally distinct nuclei. Accurate identification of these nuclei across anatomical planes is essential for large-scale human brain spatial transcriptomics studies but remains challenging since available molecular frameworks are largely derived from rodent and non-human primate models. The mediodorsal nucleus (MD), one of the largest thalamic nuclei, spans the anterior-posterior axis of the thalamus and forms extensive connections with the prefrontal and olfactory cortex, amygdala, basal ganglia, hippocampus, and hypothalamus. To establish a molecular framework for identifying the human MD and neighboring thalamic nuclei, we leveraged rodent and nonhuman primate studies to develop a 4-plex single molecule fluorescence In-situ Hybridization (smFISH; ACDbio RNAscope) panel consisting of ETV1/NPY2R, GAD1, CCK, and MBP. RNAscope was performed on 7 adult neurotypical control human brain donors (n=3 tissue sections per donor spanning the anterior-posterior axis). Our marker panel successfully delineated the MD and neighboring thalamic nuclei, including anteroventral, ventral lateral, and lateral dorsal nuclei, across the anterior-posterior axis. While these markers robustly resolved human thalamic structures, several expression patterns differed substantially from those reported in rodents and non-human primates. For example, CCK exhibited a ring-like structure around the human MD, whereas it is more broadly expressed in rodents and enriched within the medial MD in non-

human primates. Similarly, ETV1 was enriched in the human ventral thalamic nuclei (ventral anterior, ventral posterior, and ventral lateral), consistent with non-human primates, but distinct from rodents where expression is largely restricted to the medial habenula and parafascicular nucleus. Together, these findings defined a set of spatiomolecular markers for the human MD and neighboring thalamic nuclei that enable reproducible anatomical validation for large-scale spatial transcriptomic studies while highlighting species-specific features of thalamic molecular organization.

Disclosures: F. Siewe: None. **S.V. Bach:** None. **S.E. Maguire:** None. **V. Mallepalli:** None. **H.A. AlGrain:** None. **S.V. Maurer:** None. **R.A. Miller:** None. **R. Bharadwaj:** None. **J.E. Kleinman:** None. **T.M. Hyde:** None. **S.C. Page:** None. **G. Pergola:** None. **K. Martinowich:** None. **K.R. Maynard:** None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.09/KK37

Topic: J.03. Anatomical Methods

Support: Purposeful Growth-Proteomics Initiative, and PAUL G. ALLEN FAMILY FOUNDATION. This research was supported by the Allen Institute, founded by Jody Allen – chair and co-founder of Allen Family Philanthropies, and the late Paul G. Allen – investor, phil

Title: Technical Optimization of 3-Dimensional iPSC Derived Lumenoid Collection and Processing for Spatial Transcriptomics and Immunohistochemistry.

Authors: *A. RUIZ[1], A. KOESTER[2], J. ARIZA TORRES[3];
[1]Mol. Biol., [2]Cell Sci., [3]Histology, Allen Inst., Seattle, WA

Abstract: The use of induced pluripotent stem cells (iPSCs) as a model system allows for the study of many in vivo neuronal cell types, that can be further specialized by deriving PSCs from human tissue to further study disease processes, cellular and genetic mechanisms in a controlled environment. iPSCs are a great model system for studying neurodevelopment and neurodegenerative diseases as they can be induced from specific donor tissue and require less time, resources and processing than traditional model organisms such as mouse or non-human primate. Spatial Transcriptomics and immunohistochemistry techniques can be employed to analyze iPSCs or hiPSCs that have been induced to grow into 3-dimensional lumenoids to study neurodevelopment, cell to cell interaction, as well as neurological disease state. Here, we describe a workflow for maintaning sample integrity by cryoprotecting fixed 3D iPSC derived lulumenoids in 10% sucrose and extracting intact plated samples for cryosectioning and long-term storage.
Unlike the traditional paraffin embedded techniques, that require sample pelleting and extensive

handling, this approach enables direct processing of whole lumenoid cultures while minimizing specimen manipulation. Samples can be cryoprotected, rapidly frozen, sectioned using a cryostat, and mounted onto a desired medium, reducing processing time while preserving morphology and reducing risk of loss or damage to the sample.
We demonstrate that the use of a cryostat is not limited to the sectioning of whole tissue and can be used to section iPSCs that are cultured into 3D lumenoids or single cell monolayers; maintaining sample integrity while preserving 3D spatial morphology. We provide a practical workflow for consistent, reproducible processing of well-plated iPSC cultures for downstream applications such as immunohistochemistry, in situ hybridization, and 3D reconstructive spatial transcriptomic analysis.

Disclosures: A. Ruiz: A. Employment/Salary (full or part-time):; Allen Institute. **A. Koester:** A. Employment/Salary (full or part-time):; Allen Institute. **J. Ariza Torres:** A. Employment/Salary (full or part-time):; Allen Institute.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.10/KK38

Topic: J.03. Anatomical Methods

Support: NSERC
FRQNT

Title: Neuronal quantification in the primary motor cortex of human brains fixed with solutions used in gross anatomy laboratories

Authors: *A. GÉRIN-LAJOIE[1], E.-M. FRIGON[3], D. BOIRE[2], J. MARANZANO[2,4]; [2]Anat., [1]UQTR, Trois-Rivières, QC, Canada; [3]Douglas Res. Centre, McGill Univ., Montreal, QC, Canada; [4]Neurol. and Neurosurg., McGill Univ., Montreal, QC, Canada

Abstract: Background. Brain banks provide small blocks of tissue fixed with neutral-buffered formalin (NBF), whereas gross anatomy laboratories could offer full brains fixed with other fixatives, such as a saturated salt solution (SSS) or an alcohol-formaldehyde solution (AFS). While the macroscopic properties of SSS- and AFS-fixed brains are ideal for dissection and teaching, it is unknown whether the chemicals in their composition impact the antigenicity and cell morphology of the tissue. Therefore, the objective of this study is to compare the quantitative effects of the NBF, SSS and AFS at the microscopic level. To do so, we analyzed the number and size of neurons in the primary motor cortex of brains fixed with each solution. **Methods**. Blocks from 18 human brains (N=6/fixative) were cut into 40-µm sections and mounted on slides to perform an antigen retrieval and an immunohistochemistry protocol targeting neurons. Photomicrographs of 5 regions of interest (ROIs) (60X) in layer 3 of the primary motor cortex were taken with a brightfield microscope (Olympus-BX51W1). Using the

Neurolucida (MBF Bioscience) and Display (MINC Toolkit) softwares, we measured various quantitative variables in each ROI: 1) the total and individual cell surfaces, 2) the number of labeled neurons, and 3) the large and small neuronal diameters. The three groups were compared using ANOVA or Kruskal-Wallis. **Results**. The total cell surface was significantly lower in SSS-fixed specimens compared to NBF- (p=0.002) and AFS-fixed specimens (p=0.045). The individual cell surface was not significantly different between the fixatives ($H(2)=2.137$; p=0.343). There were significantly less labeled neurons in SSS-fixed brains compared to NBF- (p=0.003) and AFS-fixed brains (p=0.001). The NBF-fixed cells had slightly larger small diameters than those measured for the SSS- (p=0.005) and AFS-fixed cells (p=0.011). **Conclusion**. SSS-fixed brains were shown to be less ideal for quantitative immunohistochemical research. However, AFS-fixed brains produced results comparable to those of NBF-fixed brains, which are the gold standard in brain banks.

Disclosures: A. Gérin-Lajoie: None. **E. Frigon:** None. **D. Boire:** None. **J. Maranzano:** None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

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Program #/Poster #: PSTR037.11/KK39

Topic: J.03. Anatomical Methods

Support: Medical Research Council Grant MR/Z504555/1
Diamond Light Source for time on I12 Beamline under proposal MG41088-1.

Title: Full-length synchroton micro-CT of the human vagus nerve reveals continuous fascicular mapping for selective neuromodulation

Authors: *M. GUTIERREZ[1], I. JONES[2], A. LIPTAK[3], K. ARISTOVICH[2], N. THOMPSON[2], G. BURCA[4], D. HOLDER[2];
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Abstract: Understanding the functional anatomy of the human vagus nerve (VN) may enable selective VN stimulation via targeting of organ-specific fascicles. This has previously been achieved using iodine-stained laboratory-based micro-computed tomography (uCT) of entire pig and human VNs from end-organ to cervical segments. Although ~5 µm resolution was achieved, this approach was limited by low signal-to-noise ratio (SNR), inconsistent contrast, and the need for 5 cm sectioning with computational realignment due to restricted field of view (FOV). The purpose of this study was therefore to compare these findings with synchrotron uCT (SR-uCT), which uses a high-flux, collimated X-ray beam from a synchrotron source, enabling improved imaging performance, beam stability, and optical resolution. This yields higher SNR, improved

contrast uniformity, and faster acquisition. Beam geometry and extended FOV allow continuous imaging of ~40 cm nerves without subdivision. We assessed whether these advantages were realised and whether additional anatomical features could be resolved compared with prior work in human VN.
Twenty human VNs (nodose to celiac ganglion) were dissected with major branches preserved, formalin-fixed, stained with Lugol's iodine, and mounted in 3D-printed holders. Imaging was performed at the Diamond Light Source I12 beamline (EH2) using 53 keV X-rays and optical module 2 (3.2 µm pixel size). Full-length imaging was achieved using 32 vertically offset scans, automatically stitched post-reconstruction into contiguous 3D volumes. Reconstructions used HTTomo; fascicle segmentation and trajectory analysis were performed in Avizo and Dragonfly. SR-uCT generated continuous datasets from 20 VNs from 10 donors, mean length 43.7±4.2 cm (36-50 cm). Full scans required 1-2 h at 3.2 µm isotropic resolution, a 9-18× reduction in acquisition time versus laboratory uCT (>18 h). Uniform contrast was maintained along full nerve length with improved SNR and reduced artefacts, preserving continuity without physical sectioning or post-hoc registration. The datasets enabled detailed visualisation of fascicular trajectories, branching, and recurrent merging and splitting events.
This is the first application of SR-uCT for long-range VN fascicle tracing. The method improved SNR and image quality, delivered ~10× higher throughput, and eliminated stitching artefacts associated with FOV limits in laboratory-based µCT. Collectively, these advances enhance continuity, efficiency, and rigour in fascicular tracing. Future work will assess whether individual myelinated and unmyelinated fibres can be resolved.

Disclosures: M. Gutierrez: None. **I. Jones:** None. **A. Liptak:** None. **K. Aristovich:** None. **N. Thompson:** None. **G. Burca:** None. **D. Holder:** None.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.12/KK40

Topic: J.03. Anatomical Methods

Title: Interleaved whole-hemisphere macaque sectioning enables reproducible in-situ sequencing-based spatial transcriptomics and barcoded connectomics

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Abstract: Sequencing-based neuroanatomical approaches such as barcode tracing (BARseq) and spatial transcriptomics depend on accurate spatial localization of tissue. While these methods have been demonstrated in the brains of smaller species, applying them to macaque tissue remains technically challenging due to the size, anatomical complexity, and difficulty of collecting reproducible sections that accurately represents its spatial context. Existing approaches

often rely on gross sectioning methods or thick tissue collection alone, which can reduce anatomical precision and increase dependence on post hoc atlas comparisons for localization. To address this, we developed an interleaved cryostat-based workflow for reproducible whole-hemisphere macaque brain sectioning that preserves both spatial accuracy and compatibility with downstream molecular applications. Using a Leica CM3050 S cryostat, we established a manual sectioning methodology capable of alternating between 250-300 µm coronal macrosections and 20 µm representative sections collected at defined intervals across approximately 2 cm-thick macaque hemispheric slabs. Method development required iterative optimization of multiple sectioning parameters, including chamber and specimen temperature, anti-roll plate positioning, foundational OCT mix, cutting speed, and localized dry ice. Through these adjustments, we were able to consistently collect intact coronal sections spanning the full hemisphere, producing sections that were sample-specific while minimizing tissue loss and distortion. The interleaved design provides an advantage over workflows that rely solely on thick-section sampling by preserving exact anatomical reference points specific to the specimen throughout the collection process. This enables spatial features of the tissue to be retained and accurately interpreted downstream when undergoing in situ sequencing applications, reducing uncertainty associated with atlas-based inference alone. This method establishes a practical and reproducible approach for whole-hemisphere macaque tissue collection and expands the feasibility of sequencing-based neuroanatomical mapping in larger, anatomically complex brains. More broadly, it demonstrates how adapting conventional histological tools in unconventional ways can help bridge the gap between high-throughput molecular methods and large-scale neuroanatomical precision.

Disclosures: A. Oyama: A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **J. Ariza Torres:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **M. Majeed:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **X. Chen:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science.

Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.13/KK41

Topic: J.03. Anatomical Methods

Title: Technical approaches and diagnostic performance of adult brain examination using minimally invasive tissue sampling (MITS): A systematic review and methodological guide

Authors: *M. REINHARDT[1,3], J. COSTA CRUZ[5,3], P. H. SALDIVA[4], L. T. GRINBERG[1,2]; [1]Dept. of Neurosci., [2]Dept. of Lab. Med., Mayo Clin., Jacksonville, FL; [3]Univ. of Sao Paulo, Sao Paulo, Brazil; [4]Dept. of Pathology, Univ. of Sao Paulo, São Paulo, Brazil; [5]Harvard Univ., Boston, MA

Abstract: Minimally invasive tissue sampling (MITS) offers a technical alternative to complete diagnostic autopsy for postmortem brain investigation when conventional autopsy is not feasible

or is declined. This review aims to synthesize evidence on sampling strategies, diagnostic yield and accuracy, and the suitability of sampled tissue for histological and molecular analyses in adult brain MITS. We systematically included full-text reports of human studies with needle-based postmortem brain sampling in adults and excluded pediatric and neonatal populations because brain access and disease epidemiology differ from those in adults and require specific investigation. PubMed, Embase, and Scopus were searched through May 9, 2026, with backward reference screening. Two reviewers independently screened studies, extracted data, and assessed risk of bias in validation studies using QUADAS-2. Findings were narratively synthesized, with diagnostic metrics reported where MITS was compared with complete diagnostic autopsy. We found 43 records published between 1955 and 2026, with most studies applying MITS to body fluids and key organs, including the brain, for cause-of-death determination. Validation studies showed low to unclear risk of bias, mainly due to patient selection and incomplete blinding. Diagnostic yield was highest for disseminated central nervous system processes, including inflammatory, metabolic, and infectious conditions, and lower for focal, vascular, meningeal, and neoplastic diseases. Diagnostic accuracy was generally very high, although microbiological interpretation was sometimes limited by postmortem pathogen translocation and contamination during sampling. Postmortem imaging played two complementary roles in MITS by guiding targeted biopsies and providing structural context for interpretation. Several studies indicated that MITS can provide tissue suitable for microbiology, histology, and molecular analyses when postmortem interval is minimized. In conclusion, adult brain MITS is a technically promising approach for postmortem investigation, particularly when imaging-guided targeting is used and tissue integrity is prioritized. Standardized validation is still needed to define its performance across disease types and sampling conditions.

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Poster

PSTR037: Sample Preparation and Novel Probes

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.14/KK42

Topic: J.03. Anatomical Methods

Support: KAIST Grant G04230041
KAIST Graduate student Grant N10250118

Title: Engineered DARPins as a third-generation labeling platform for large-volume neural tissue imaging

Authors: *B. CHEONG[1], C. PARK[1], H. PARK[1], R. RAHMAN[1], H.-W. SHIH[2], J. KIM[1], J. MONTCLARE[2], Y.-G. PARK[1], D. CHURCHILL[1], R. SCHUBERT[1];
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Abstract: Recent advances in tissue clearing, light-sheet microscopy, and AI-driven image analysis have transformed volumetric imaging, enabling cellular-resolution visualization of intact tissues and large specimens. Modern workflows integrate tissue preparation, clearing, imaging, and computational reconstruction to generate three-dimensional maps of complex systems. Despite progress in instrumentation, clearing chemistry, and analysis, molecular labeling remains comparatively unchanged and continues to limit large-volume imaging. Current strategies rely mainly on antibodies and, more recently, nanobodies. Although specific, these reagents can restrict uniform labeling of thick tissues and cleared specimens. Designed Ankyrin Repeat Proteins (DARPins) are compact engineered binders with small size, high stability, modular design, and straightforward bacterial expression, positioning them as a third-generation platform for deep tissue imaging. Here, we developed and validated DARPin probes targeting GFP and HER2 to establish a broadly applicable framework for volumetric imaging. For GFP benchmarking, anti-GFP DARPins were engineered as a genetically encoded mNeptune-fusion probe and a single-cysteine probe conjugated with Alexa Fluor 647; LC-MS confirmed expected molecular weights. In GFP-positive and GFP-negative HeLa cells, confocal imaging and flow cytometry showed selective GFP-dependent labeling with no detectable signal in negative controls. Four dilutions were tested in triplicate, and a 1:20 dilution from a 0.5 mg/ml stock produced strong target-specific signal with low background. Following cellular benchmarking, DARPins were compared with antibody and nanobody probes in neural tissues. Both DARPin formats labeled GFP-positive neural structures in PFA-fixed 200 µm Thy1-GFP-M mouse brain slices. In passive diffusion assays using cleared 500 µm brain sections, Alexa Fluor 647-conjugated DARPin penetrated the full thickness, whereas monoclonal antibody and nanobody probes reached only approximately 200 µm and 180 µm, respectively. To evaluate broader workflow compatibility, ongoing studies extend DARPin labeling to post-clearing 500 µm and 1 mm brain slices prepared by CLARITY- and DISCO-based methods and HER2-positive organoid and tumor models. Together, these studies establish DARPins as a versatile molecular imaging platform that complements advances in tissue clearing, imaging hardware, and computational analysis. By addressing a bottleneck in molecular labeling, DARPins provide a scalable framework for next-generation volumetric imaging of neural tissues, organoids, and intact specimens.

Disclosures: B. Cheong: None. **C. Park:** None. **H. Park:** None. **R. Rahman:** None. **H. Shih:** None. **J. Kim:** None. **J. Montclare:** None. **Y. Park:** None. **D. Churchill:** None. **R. Schubert:** None.

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.01/KK43

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

Title: Development of a Unique Mouse Model of In Vivo Tau Propagation for Evaluating Efficacy of Anti Tau Antibodies

Authors: *L. NORWOOD[1], R. CHANG[1], Y. E. LEE[1], H. SANDERS[1], N. ROMANUL[1], K. YANAMANDRA[1], M. SCHMITT[2], A. STANEK[2], C. KLEIN[2], X. LANGLOIS[1], E. H. KARRAN[1], T. DELLOVADE[1];
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Abstract: One of the hallmarks of Alzheimer's disease (AD) is the progressive accumulation of abnormally phosphorylated tau protein in neurons, forming neurofibrillary tangles. During AD progression, tau pathology spreads throughout the brain along synaptically connected pathways. To support development of therapeutics aimed at reducing the spread of tau pathology, a model of tau propagation was developed in hTau transgenic mice that express all six isoforms of human tau (3R and 4R tau) without a mutation on a mouse tau KO background. Characterization of this model revealed that aggregated tau is not detected at up to 21 months of age. To develop a model of tau propagation, Sarkosyl insoluble tau lysate extracted from AD brain tissue (AD-SP lysate) was injected into the olfactory bulb (OB). Two well-studied projection pathways were examined for evidence of tau pathology following seeding: 1) the OB mitral and tufted cells projecting to the piriform cortex (synapse 1) and the piriform cortex neurons projecting to the thalamus (synapse 2) and 2) the OB mitral cells projection to entorhinal cortex (synapse 1) and the projection of these neurons to the CA1 hippocampus (synapse 2). A time course study revealed that immunoreactivity for aggregated tau (AT100-IR) was detected in 1st synapse brain regions by 4 weeks post-injection and in 2nd synapses regions by 6 - 8 weeks post-injection. Characterization of the AD-SP lysate revealed that seeding and propagation can be induced with a mixture of lysates from multiple donors and the level of tau pathology correlates with the concentration of insoluble tau in the lysate. The model was further standardized for efficacy studies using the anti-tau antibody, PHF1. These studies found that AT100 IR in the 2nd synapse regions could be significantly reduced when weekly IP doses started 7-days post-seeding. This is also the first evidence of an anti-tau antibody reducing tau propagation in vivo with prophylactic dosing and highlights the utility of this model for development of tau-targeting therapies.

Disclosures: L. Norwood: A. Employment/Salary (full or part-time):; AbbVie. **R. Chang:** A. Employment/Salary (full or part-time):; AbbVie. **Y.E. Lee:** A. Employment/Salary (full or part-time):; AbbVie. **H. Sanders:** A. Employment/Salary (full or part-time):; AbbVie. **N. Romanul:** A. Employment/Salary (full or part-time):; AbbVie. **K. Yanamandra:** A. Employment/Salary (full or part-time):; AbbVie. **M. Schmitt:** A. Employment/Salary (full or part-time):; AbbVie. **A. Stanek:** A. Employment/Salary (full or part-time):; AbbVie. **C. Klein:** A. Employment/Salary (full or part-time):; AbbVie. **X. Langlois:** A. Employment/Salary (full or part-time):; AbbVie. **E.H. Karran:** None. **T. Dellovade:** A. Employment/Salary (full or part-time):; AbbVie.

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.02/KK44

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

Support: NIH P50 HD103536-7954
NIH R21EB033122
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NIH P50 HD103536

Title: Tracking spatiotemporal dynamics of myelination deficit and glial activation in the Free sialic acid storage disorder R39C knock-in mouse model

Authors: *Y. DING[1], A. SOLORZANO[2], V. PRIFTI[5], H. CHANG[5], S. SPALLINA[3], K. WANG[4], E. G. FREEDMAN[6], J. J. FOXE[7];
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Abstract: Free sialic acid storage disorder (FSASD) is a rare lysosomal storage disorder (LSD) caused by pathogenic variants in the *SLC17A5* gene, which encodes the lysosomal sialic acid transporter sialin. FSASD patients show progressive neurological impairments including developmental delay, motor dysfunction, and hypomyelination. Despite increasing knowledge of FSASD pathology, sensitive biomarkers capable of tracking disease progression and therapeutic outcomes remain limited. In this study, diffusion magnetic resonance imaging (dMRI) was performed in the FSASD R39C knock-in (KI) mice, a mouse model that carries the most prevalent *SLC17A5* variant associated with the milder clinical spectrum of FSASD in humans. dMRI revealed widespread microstructural alterations and myelination deficits across major white matter tracts and gray matter regions, consistent with neuroimaging findings reported in FSASD patients. To validate these observations, immunohistochemical (IHC) analyses were conducted and demonstrated significantly reduced myelin basic protein (MBP) and oligodendrocyte transcription factor 2 (Olig2) staining, confirming impaired myelin integrity. IHC also revealed marked astrocyte and microglial activation throughout affected brain regions, indicating robust neuroinflammatory responses associated with disease pathology. Together, these findings establish dMRI as a sensitive, non-invasive approach for detecting myelin abnormalities in FSASD. The convergence of neuroimaging and histopathological evidence highlights myelination deficits and neuroinflammation as key pathological features of FSASD. These biomarkers provide valuable tools for longitudinal disease monitoring and offer a translational framework for evaluating therapeutic efficacy in FSASD and related lysosomal storage disorders.

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Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.03/KK45

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

Title: Neural activity and functional connectivity changes during agitation induction in rats assessed by awake fMRI

Authors: *M. ONDA, Y. MASAKI, M. ITO, S. OHNAMI, N. TAKAI, S. MOMOSAKI; Shionogi & Co., Ltd., Osaka, Japan

Abstract: Agitation in dementia significantly impairs the quality of life of patients and caregivers, underscoring the need for effective therapies. The neural basis of agitation remains unclear, however several clinical fMRI studies have suggested correlations between agitation and activity in specific brain regions. In this study, to evaluate clinically suggested neural activity changes in a nonclinical setting, we utilized an awake fMRI system capable of recording stimulus-evoked emotional responses and assessed blood oxygenation level-dependent (BOLD) signals and functional connectivity (FC) changes associated with agitation. In this study, fMRI scans were conducted using a 7T MRI system on awake rats habituated to the imaging environment. To apply awake fMRI to translational research, we examined whether pharmacological activation by ketamine induces BOLD signal changes consistent with those reported in clinical studies. Intravenous administration of ketamine in awake rats resulted in increased BOLD signals in multiple brain regions, including the insular cortex, in line with previous clinical findings. Subsequently, BOLD signal changes associated with agitation-inducing stimuli were assessed. Prior to fMRI scanning, male and female rats were pair-housed for at least one week. The female was temporarily removed, and a novel male intruder was introduced into the home cage to identify males exhibiting high levels of agitation, which were subsequently selected for imaging. Male rats were subjected to fMRI scanning while being presented with either a female partner alone or a female partner together with a male intruder to induce agitation. This resulted in significant BOLD signal increases in regions, including the amygdala and anterior cingulate cortex. Quantitative evaluation of FC revealed a significant increase in connectivity within sensory integration-related networks, including the temporal association cortex (FDR adjusted $p < 0.05$). In addition, exploratory analysis ($p < 0.01$) without corrections for multiple comparisons indicated that the number of FCs involving the amygdala is the mostly observed. These results demonstrate that the brain regions exhibiting changes in both BOLD activity and functional connectivity correspond to those clinically implicated in agitation (e.g., the amygdala), while revealing network-level alterations. This study suggested the translational relevance of the awake fMRI system across nonclinical and clinical settings, as well as its potential contribution to the development of novel therapeutic strategies.

Disclosures: M. Onda: A. Employment/Salary (full or part-time):; Shionogi & Co., Ltd. **Y. Masaki:** A. Employment/Salary (full or part-time):; Shionogi & Co., Ltd. **M. Ito:** A. Employment/Salary (full or part-time):; Shionogi & Co., Ltd. **S. Ohnami:** A. Employment/Salary (full or part-time):; Shionogi & Co., Ltd. **N. Takai:** A. Employment/Salary (full or part-time):; Shionogi & Co., Ltd. **S. Momosaki:** A. Employment/Salary (full or part-time):; Shionogi & Co., Ltd..

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.04/KK46

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

Title: Deep, reproducible cerebrospinal fluid proteomics at clinical scale: a platform for target engagement, pharmacodynamic readout, and biomarker discovery in CNS drug development

Authors: F. PEROCCHI[1], J. GROSSKREUTZ[2], Y. CHENG[1], S. WALIA[1], *M. JAIN[3], J. WATROUS[3];
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Abstract: Introduction. CNS drug programs increasingly require fluid pharmacodynamic readouts to support dose selection, target engagement, and patient stratification. Immunoassay panels cover only a narrow slice of the active target landscape, and conventional mass spectrometry workflows have lacked the depth, reproducibility, and throughput needed for clinical-scale cerebrospinal fluid (CSF) studies.
Methods. We address this gap with an automated CSF proteomics workflow that pairs a CSF-optimized magnetic nanoparticle capture-and-hold enrichment with single-fraction, single-injection DIA-PASEF mass spectrometry on a Bruker timsTOF HT operated at 60 samples per day. The workflow uses less than 50 microliters of CSF per sample and is fully automated end to end. The same pipeline was applied to a multi-site clinical CSF cohort of healthy controls and patients with neurological disease.
Results. Across 100 non-selected human CSF samples, the workflow quantified 3,642 protein groups (~33,800 peptides), with a minimum of 2,498 protein groups in any single sample, 2,895 protein groups in at least half of samples, and a median technical CV of 11.3%. The quantified proteome includes free, exosomal, and membrane-bound proteins, established and novel post-translational modifications, and members of more than 35 CNS-relevant signaling cascades (including complement, microglial signaling, MAPK, PI3K/AKT/mTOR, NF-kB, interferon, TGF-beta, Wnt/beta-catenin, integrin, and synaptic vesicle cycling). The platform directly quantifies approved and clinical-stage neurodegenerative drug targets including APOE, APP, TREM2, MAPT (tau), SOD2, SNCA, BST1, and the full neurofilament subunit family (NEFL, NEFM, NEFH). In the clinical cohort, the workflow recovered established markers of axonal injury (neurofilaments) and microglial activation (CHIT1, CHI3L1/YKL-40, CHI3L2) and surfaced additional candidate disease-associated proteins.
Conclusions. This is a single CSF assay that delivers target engagement, downstream pathway response, and exploratory biomarker output from one small-volume aliquot. The combination of depth, reproducibility, throughput, and biological breadth supports target identification, biomarker discovery, mechanism-of-action work, and pharmacodynamic measurement in CNS drug development, including dose-ranging studies and trial-embedded biomarker strategies, and provides a tractable platform for deep interrogation of human CNS biology.

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Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.05/KK47

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

Title: Differential Relationship Between DTI-ALPS and Motor Improvement Across STN and GPi Deep Brain Stimulation Targets in Parkinson's Disease

Authors: *G. CHEN[1], J. CHA[1], J. DE BRUIN[1], B. KOPELL[2], H. S. MAYBERG[3], K. CHOI[4]; [1]Radiology, Neurol., [2]Neurosurg., [3]Neurol., [4]Radiology, Neurosurg., Nash Family Ctr. for Advanced Circuit Therapeutics, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: The glymphatic system is the brain's waste-clearance pathway, and its dysfunction is implicated in Parkinson's disease (PD). The DTI-ALPS index is widely used as a non-invasive proxy for glymphatic clearance, though its sensitivity remains debated due to potential confounds from surrounding white matter microstructures. Despite these limitations, previous studies consistently demonstrated clinical relevance, correlating DTI-ALPS with PD severity. However, its prognostic relationship to motor improvement following deep brain stimulation (DBS) remains unexplored. Given that STN DBS typically reduce reliance on dopaminergic medication, while GPi DBS is preferred for severe dyskinesia, these targets may interact differently with the integrity of pathways measured by the DTI-ALPS index.
We analyzed 95 PD patients who underwent DBS (STN=82, GPi=13). Motor improvement was defined as the change in MDS-UPDRS III scores from baseline to 6 months of chronic DBS. ROIs for pre-surgical DTI-ALPS indices were automatically generated and manually verified using 2.5 mm spheres within the projection and association fiber regions adjacent to the medullary veins. A generalized linear model was used to examine the interaction effect between the baseline DTI-ALPS index and 6-month motor improvement UPDRS change. To control for confounds, the analysis focused exclusively on off-medication status UPDRS scores, with age

and sex included as covariates.
There were no group differences in the DTI-ALPS index between the GPi-DBS and STN-DBS groups ($p = 0.726$), and no overall association between DTI-ALPS index and motor improvement ($R = 0.15$, $p = 0.139$). However, we identified a significant interaction effect ($t = -2.154$, $p = 0.034$), indicating that the relationship between baseline DTI-ALPS index and motor improvement depends on the DBS treatment target. Post-hoc correlation analyses revealed a significant positive relationship between baseline DTI-ALPS index and improvement in the GPi-DBS cohort ($R = 0.61$, $p = 0.036$), whereas no significant relationship was found within the STN-DBS cohort ($R = 0.077$, $p = 0.5$).
These findings suggest that baseline DTI-ALPS is strongly associated with motor outcomes following GPi-DBS for PD, whereas the STN-DBS group demonstrated a consistent motor response largely independent of baseline DTI-ALPS. Despite a relatively small GPi-DBS cohort, these results provide testable hypotheses about biological subtypes of PD patients undergoing DBS, contributing a potential novel candidate biomarker to further personalize DBS target selection strategies, where low DTI-ALPS may serve as a negative prognostic marker for GPi-DBS motor response.

Disclosures: G. Chen: A. Employment/Salary (full or part-time):; Icahn School of Medicine at Mount Sinai. **J. Cha:** A. Employment/Salary (full or part-time):; Icahn School of Medicine at Mount Sinai. **J. de Bruin:** None. **B. Kopell:** A. Employment/Salary (full or part-time):; Icahn School of Medicine at Mount Sinai. F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation, Turing Medical. **H.S. Mayberg:** A. Employment/Salary (full or part-time):; Icahn School of Medicine at Mount Sinai. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Abbott Laboratories. F. Consulting Fees (e.g., advisory boards); Abbott Laboratories. **K. Choi:** A. Employment/Salary (full or part-time):; Icahn School of Medicine at Mount Sinai. F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation.

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.06/KK48

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

Title: Screening for Alzheimer's disease biomarkers in CSF using a novel quantitative proteomics platform

Authors: E. A. GIZZIE[1], C. DEMOS[1], J. A. ZHITENEVA[1], M. E. MCCARTHY[1], A. CANO[2,3], J. BROWN[1], B. NGO[1], X. MONTALBAN[2,3], M. SANZ CARTAGENA[2], V. FERNANDEZ[2,3], J. N. WOHLSTADTER[1], A. RUIZ LAZA[2,3], M. BOADA[2,3], ***D. A. ROUTENBERG**[1];
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Abstract: Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder with a decades-long prodromal period, offering a wide window in which to intervene if the underlying biology can be tracked. Monitoring sequential pathological changes in neurodegeneration, inflammation, neurovascular dysfunction, oxidative stress, and metabolic stress may enable intervention before symptom onset and guide more tailored therapy, yet this demands broad, quantitative biomarker measurement. NGS-based immunoassays enable high-multiplex protein detection but lack absolute quantitation and a direct path to focused panels. The ProteinXI platform addresses both gaps, simultaneously quantifying hundreds of proteins—over 300 analytes in just ten microliters of cerebrospinal fluid (CSF)—with a built-in translational route to Meso Scale Discovery's high-throughput electrochemiluminescence (ECL) platform. We evaluated the ProteinXI Discovery CSF panel for analytical sensitivity, precision, reproducibility, and detectability using 40 commercially sourced CSF samples from donors without neurodegeneration, then tested translational relevance in CSF from individuals with AD dementia (n=100), mild cognitive impairment (MCI) progressing to dementia over 3-year follow-up (n=100), MCI non-progressors (n=100), and subjective cognitive decline (n=93), collected by ACE Alzheimer Center Barcelona. Median limit of detection (LOD) was 1.29 pg/mL, with 40 assays reaching LOD ≤20 fg/mL; median dynamic range spanned 4.96 logs and median intraplate CV was 6.55%. 292 analytes were quantifiable in at least half of samples, and 47 were significantly elevated in the combined progressive dementia groups (AD and MCI progressing to AD) versus combined controls (MCI without progression and SCD) using a Wilcoxon rank-sum test with Benjamini-Hochberg correction, FDR<0.05—including Tau, NF-L, GFAP, MIF, YKL-40, and MIP-1a. Each of these was confirmed by individual MSD ECL immunoassays with excellent concordance: Pearson r=0.91-0.98. Eight markers differentiated MCI progressors from non-progressors at AUC>0.75, with Tau performing best (AUC>0.99). This exploratory study shows that ProteinXI delivers robust analytical performance across healthy and AD-spectrum CSF, faithfully recapitulates established biomarkers, and surfaces new candidates for predicting progression—establishing it as a discovery platform with a direct path to clinical research applications.

Disclosures: E.A. Gizzie: A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **C. Demos:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **J.A. Zhiteneva:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **M.E. McCarthy:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC.. **A. Cano:** None. **J. Brown:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **B. Ngo:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC.. **X. montalban:** None. **M. Sanz Cartagena:** None. **V. Fernandez:** None. **J.N. Wohlstadter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Meso Scale Diagnostics, LLC.. **A. Ruiz Laza:** None. **M. Boada:** None. **D.A. Routenberg:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC..

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.07/KK49

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

Support: NIH AG 5549-06
NS1 07265
AG 062135
UG3/UH3 NS 113776
ADDF 291204

Title: Development of Mitochondrial Complex I Modulators for Alzheimer's Disease Therapy

Authors: *S. TRUSHIN, M. OSTROOT, T. NGUYEN, E. TRUSHINA;
Neurol., Mayo Clin., Rochester, MN

Abstract: Mitochondrial dysfunction and impaired adaptive stress responses are early and central features of Alzheimer's disease (AD). We previously identified mitochondrial complex I (mtCI) as a small-molecule druggable target and demonstrated that the tool compound CP2 provides neuroprotection in multiple mouse models of AD. Cryo-electron microscopy studies revealed that CP2 binds to the quinone-binding Q-site of mtCI and weakly inhibits its activity. These findings supported the concept that weak and reversible mtCI inhibition can induce beneficial mitochondrial stress adaptation without causing bioenergetic failure or toxicity. Using CP2 as a tool compound, we performed rational design and structure-activity relationship studies to develop novel classes of weak, reversible mtCI inhibitors with high off-rates, improved functional potency, and favorable drug-like properties. Target engagement, mtCI-binding specificity, selectivity, efficacy, and safety were evaluated using complementary biochemical, mitochondrial, and cellular assays. Lead compounds C458 and C273 were advanced for preclinical characterization. C458 and C273 weakly inhibited mtCI and rapidly dissociated from the Q-site, distinguishing them from high-affinity toxic mtCI inhibitors such as rotenone. Weak mtCI inhibition by C458 and C273 activated AMPK and induced an adaptive neuroprotective stress response characterized by enhanced antioxidant defenses, reduced inflammatory signaling, increased autophagy, and improved mitochondrial biogenesis and turnover. These effects resulted in robust protection against Aβ-induced toxicity. The response was AMPK-dependent and was absent in AMPKα1/α2 knockout fibroblasts. Pretreatment with non-toxic concentrations of rotenone blocked C458 and C273 binding to mtCI and abolished their neuroprotective effects, confirming Q-site-dependent target engagement. In contrast to strong mtCI inhibitors, C458 and C273 showed high off-rates, low mitochondrial toxicity, favorable bioavailability, robust blood-brain barrier penetration, and clean safety profiles in the CEREP 44 panel. These findings demonstrate that weak, reversible mtCI inhibition with high off-rates is sufficient to activate a beneficial AMPK-dependent mitochondrial stress response while preserving bioenergetic integrity. The novel mtCI inhibitors C458 and C273 protect against Aβ toxicity and maintain a wide therapeutic window. Collectively, these data support weak mtCI inhibition as a safe and disease-modifying therapeutic strategy for Alzheimer's disease.

Disclosures: S. Trushin: A. Employment/Salary (full or part-time):; Mayo Clinic. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Some of the authors on this study are named inventors on one or more patent applications owned by Mayo Foundation for Medical Education and

Research. **M. Ostroot:** A. Employment/Salary (full or part-time):; Mayo.Clinic. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Some of the authors on this study are named inventors on one or more patent applications owned by Mayo Foundation for Medical Education and Research. **T. Nguyen:** A. Employment/Salary (full or part-time):; Mayo Clinic. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Some of the authors on this study are named inventors on one or more patent applications owned by Mayo Foundation for Medical Education and Research. **E. Trushina:** A. Employment/Salary (full or part-time):; Mayo Clinic. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Some of the authors on this study are named inventors on one or more patent applications owned by Mayo Foundation for Medical Education and Research.

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.08/KK50

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

Support: Indian council of medical research-Senior research fellowship (2021-2024)
Higher Education and Heath & Family Welfare Departments, Government of Kerala

Title: Mimosine restores labile iron and glutathione homeostasis in cellular and animal models of neurodegeneration

Authors: *H. P. J, R. A. SHENOI, G. CHANDRA, K. MOHANAKUMAR;
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Abstract: Iron overload related neuronal chemical imbalance and neuronal damage is implicated in the pathophysiology of many neurodegenerative diseases. The MPTP-induced cellular model is widely used to study oxidative stress-induced neuronal damage associated with PD. In the present work, we evaluated the therapeutic potential of a plant based molecule mimosine against iron-induced and toxin-induced neuronal damage in cellular and animal models of PD Mimosine formed a stable complex with iron at physiological pH and exhibited iron chelating potential comparable to that of the clinically investigated iron chelator deferiprone. In addition, mimosine exhibited robust antioxidant activity in the ferric reducing antioxidant power assay in cell free system. Mimosine protected differentiated SH-SY5Y cells through chelation of labile iron and restoration of intracellular glutathione levels (GSH), thereby inhibiting iron induced cell death. Furthermore, the antioxidant activity of mimosine confers protection against MPP^+-induced neuronal damage, potentially through the enhancement of intracellular glutathione levels. The GSH level in the control cells was 10.00 ±0.0964 μg/g weight of cell pellet, which decreased to

4.17 ± 0.1 µg/g upon MPP^+ treatment. Co treatment with mimosine restored the GSH levels to 9.46 ± 0.48 µg/g. Similarly upon iron treatment GSH levels decreased to 9.50 ± 0.09 µg/g whereas co-treatment with mimosine restored the GSH levels to 9.79 ± 0.09 µg/g. Our *in vivo* findings form toxin-induced and iron overload models also confirmed the protective effect of mimosine against dopamine depletion. Additionally, we evaluated the effects of mimosine and the PD-neurotoxin MPTP on striatal dopamine levels in C57BL/6 male mice using high-performance liquid chromatography with electrochemical detection. Dopamine levels in the control group were 56.86 ± 2.61 pmol/mg striatum, whereas the MPTP-treated group showed a significant reduction to 13.05 ± 4.17 pmol/mg ($p < 0.05$). In contrast, the mimosine-treated group maintained dopamine levels at 41.83 ± 8.42 pmol/mg, with no statistically significant difference from the control group. Behavioral outcomes from the rotarod, pole test, and open-field test were consistent with the dopamine levels quantified by HPLC, further supporting the neuroprotective effect observed in the study. These results suggest that mimosine does not adversely affect dopamine levels and may exert a protective effect against dopamine depletion.

Disclosures: H.P. J: None.

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.09/KK51

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

Title: Sildenafil/L-Arginine-Enhanced Blood-Brain Barrier Delivery of N-Acetylcysteine Attenuates Cognitive Dysfunction in Alzheimer's Disease and Vascular Dementia

Authors: *Y. LEE, M.-W. CHAO, C.-Y. TSENG;
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Abstract: Dementia is driven by two major pathological mechanisms: abnormal amyloid deposition and vascular dysfunction. Despite decades of research, effective treatments remain limited, largely because most therapeutic agents cannot efficiently penetrate the blood-brain barrier (BBB). Therefore, we investigated a multitarget regimen combining sildenafil, L-arginine, and NAC (SAN), in which sildenafil and L-arginine (SA) were used to transiently modulate BBB permeability and enhance CNS delivery of NAC. In an in vitro human brain endothelial model, SA significantly reduced transendothelial electrical resistance (TEER), disrupted ZO-1 tight-junction continuity, and increased the apparent permeability coefficient (P_{app}) of Lucifer Yellow, indicating a transient BBB-permeability window. In vivo, plasma and cerebrospinal fluid (CSF) NAC concentrations were quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS). SA co-administration significantly increased CSF NAC concentrations, confirming enhanced CNS exposure. We next evaluated SAN efficacy in two adult mouse models: male BALB/c mice subjected to middle cerebral artery occlusion (MCAO) as a vascular dementia model and 5xFAD mice as an AD model. After 4 weeks of daily

SAN treatment, MCAO mice showed significantly improved performance in open-field, eight-arm radial maze, and novel object recognition tests. SAN also increased brain-derived neurotrophic factor (BDNF) signaling and reduced microglial activation (Iba1), as shown by immunohistochemistry and western blotting. In 5xFAD mice, SAN significantly improved Morris water maze performance and reduced cortical and hippocampal AD-related pathology, including amyloid-beta (Aβ) burden, inflammatory markers (interleukin-18 and interleukin-1β), and tau-related pathological ratios. Statistical significance was determined by one-way analysis of variance (ANOVA; $n = 5$, $p < 0.05$). These findings suggest that SA-mediated BBB modulation enhances NAC delivery and potentiates its neuroprotective efficacy, supporting SAN as a promising neurovascular, multitarget strategy for cognitive impairment.

Disclosures: Y. lee: None. **M. Chao:** None. **C. Tseng:** None.

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.10/KK52

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

Support: NIH Grant P50 HD103536-7954
NIH Grant R21EB033122
NIH Grant P50 HD103536
NIH Grant AR069655

Title: Functional ultrasound imaging reveals visually induced somatosensory activation in a mouse model of Cystinosis

Authors: *F. YIN[1], Y. DING[6], H. CHANG[2], J. FENG[7], V. PRIFTI[2], E. G. FREEDMAN[3], J. J. FOXE[4], M. DOYLEY[5], K. WANG[8];
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Abstract: Cystinosis is a rare lysosomal storage disorder (LSD) caused by mutations in the *CTNS* gene and marked by systemic cystine accumulation. Individuals with Cystinosis show growth impairment, kidney issue, and visual complications like photophobia and blepharospasm. However, the neural mechanisms underlying altered visual response in cystinosis remain poorly understood. In this study, functional ultrasound (fUS) imaging was used to investigate central visual processing in a Cystinosis knockout (*CTNS−/−*) mouse model and identify potential neural correlates of visual deficits. Visual stimulation in control mice of both sexes elicited robust activation throughout the canonical visual pathway, including the superior colliculus (SC), lateral geniculate nucleus (LGN), lateral posterior nucleus (LP), and primary and secondary visual cortices (V1/V2). In contrast, *CTNS−/−* mice exhibited altered visually evoked activation,

with abnormal recruitment of somatosensory regions, including the ventral posteromedial nucleus (VPM), posterior nucleus (PO), primary somatosensory cortex (S1) and posterior parietal cortex (PPC), in addition to visual regions. These effects were particularly pronounced in males, suggesting sex-dependent neural circuit dysfunction. The aberrant engagement of somatosensory networks may reflect enhanced processing of aversive sensory signals and provide a neurobiological basis for photophobia. Collectively, these findings reveal significant alterations in sensory network organization in Cystinosis and suggest that visual discomfort may arise from maladaptive central sensory processing.

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Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.11/KK53

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

Title: Laser-induced graphene-based detection of VOC signatures across aging and Parkinson's disease groups

Authors: *M. FULLEM, E. L. STEGEMOLLER;
Kinesiology, Iowa State Univ., Ames, IA

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder typically diagnosed through clinical evaluation after substantial dopaminergic loss has occurred, underscoring the need for non-invasive methods capable of detecting early metabolic changes. Volatile organic compounds (VOCs) emitted from the skin have emerged as promising metabolic biomarkers. This study evaluated the potential laser-induced graphene (LIG) sensors have on detecting naturally emitted VOC-associated electrochemical activity across four groups: healthy young adults (HYA), healthy older adults (HOA), individuals with de novo PD, and individuals with PD receiving dopaminergic medication (PD-on). Cyclic voltammetry measured capacitance at baseline and after 30 minutes of VOC accumulation, and the change in capacitance (ΔC) was calculated to assess dynamic metabolic activity. Kruskal-Wallis analyses revealed a significant main effect of group at baseline ($X^2 = 12.83$, $p = 0.0050$), at 30 minutes ($X^2 = 15.51$, $p = 0.0014$), and for ΔC ($X^2 = 10.34$, $p = 0.016$). Post-hoc Wilcoxon tests with Bonferroni correction showed that de novo participants had higher baseline capacitance values than HYAs ($p = 0.0062$) and PD-on individuals ($p = 0.0028$). At 30 minutes, PD-on participants exhibited lower capacitance than HYAs ($p = 0.0062$), HOAs ($p = 0.0026$), and de novo participants ($p = 0.0022$). At ΔC no pairwise comparisons survived the Bonferroni correction. Jonckheere-Terpstra tests revealed a significant monotonic trend at 30 minutes that aligned with the hypothesized ordering (HYA > HOA > de novo > PD-on; $Z = -2.16$, $p = 0.016$). The capacitance at baseline ($Z = -0.62$, $p = 0.27$) and ΔC ($Z = -1.52$, $p = 0.064$) did not demonstrate a significant ordered trend consistent with the

hypothesized pattern. These results indicate that the expected physiological progression in VOC-associated electrochemical activity emerges after 30 minutes of VOC accumulation, and there may be a different underlying physiological patterning at baseline and ΔC. These findings demonstrate that LIG sensors are sensitive to both static and dynamic VOC-associated electrochemical activity and has the potential to differentiate between aging, early-stage PD, and medicated PD states. LIG-based VOC sensing offers a promising, cost-effective, and non-invasive platform with potential applications in early PD detection, disease monitoring, and personalized treatment assessment.

Disclosures: M. Fullem: None. **E.L. Stegemoller:** None.

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.12/KK54

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

Support: NIH NIDA R21DA058586
R01DA054992

Title: From Literature Mining to Clinical Validation: Repurposing Neuroprotective Therapeutics for HIV-Associated Cognitive Decline

Authors: *A. SIKIRZHYTSKAYA[1], I. TYAGIN[6], M. AKSENOVA[2], H. LI[3], V. SIKIRZHYTSKI[1], H. JI[1], E. KORUNOVA[4], J. MAGAGNOLI[1], T. CUMMINGS[1], I. K. SARIYER[7], R. M. BOOZE[8], I. SAFRO[6], M. WYATT[1], M. SHTUTMAN[5];
[2]Dept. of Drug Discovery and Biomed. Sci., [3]Psychology, [1]Univ. of South Carolina, Columbia, SC; [4]Univ. of South Carolina, COLUMBIA, SC; [5]Drug Discovery and Biomed. Sci., Univ. of South Carolina, Columbia, SC; [6]Univ. of Delaware, Newark, DE; [7]Temple Univ., Philadephia, PA; [8]Dept Psychol, Univ. South Carolina, Chapin, SC

Abstract: HIV-associated neurocognitive disorders (HAND) remain prevalent despite effective antiretroviral therapy and are exacerbated by comorbid substance use disorders. Therapeutic development has been limited by the complexity of neuroinflammatory mechanisms underlying neuronal dysfunction and cognitive decline. We applied an integrated discovery framework combining artificial intelligence (AI)-based literature mining, clinical data analysis, and experimental validation to identify repurposable neuroprotective therapies for HAND.
The AGATHA literature mining platform was used to prioritize relevant drug candidates associated with neuroinflammation, synaptic dysfunction, and neurodegeneration. Candidate compounds were evaluated in primary cortical neuron and microglial cultures exposed to HIV Tat and cocaine. Neuronal integrity, inflammatory signaling, transcriptomic responses, and microglial morphology were assessed. Independent retrospective analyses of Veterans Affairs cohorts were used to examine neurocognitive outcomes associated with blood-brain barrier

(BBB)-penetrant renin-angiotensin-aldosterone system (RAAS) inhibitors in people with HIV. AI-guided prioritization identified Amlexanox, Senicapoc, and Tazemetostat as candidate neuroprotective agents targeting complementary inflammatory and epigenetic pathways. Combined HIV Tat and cocaine exposure induced pronounced synaptic loss, inflammatory activation, and microglial morphological remodeling. Treatment with Amlexanox and Senicapoc substantially preserved synaptic integrity, reduced inflammatory responses, and partially restored homeostatic microglial phenotypes. Transcriptomic analyses demonstrated modulation of pathways associated with neuroinflammation and cellular stress. Literature mining highlighted BBB-penetrant RAAS inhibitors as potential modifiers of neurocognitive decline. Retrospective clinical analyses demonstrated reduced risk of dementia and HAND among people with HIV receiving BBB-penetrant ACE inhibitors compared with non-BBB-penetrant agents. Consistent with these findings, RAAS inhibitors reduced HIV-associated neuronal injury and transcriptomic dysregulation in human cerebral organoids.
These findings demonstrate that integrating AI-driven hypothesis generation with clinical and experimental validation can identify therapeutically actionable pathways for HAND. Convergent evidence supports both modulation of microglial inflammatory signaling and targeting of central RAAS pathways as promising strategies for reducing HIV-associated neurocognitive injury and cognitive decline.

Disclosures: A. Sikirzhytskaya: None. **I. Tyagin:** None. **M. Aksenova:** None. **H. Li:** None. **V. Sikirzhytski:** None. **H. Ji:** None. **E. Korunova:** None. **J. Magagnoli:** None. **T. Cummings:** None. **I.K. Sariyer:** None. **R.M. Booze:** None. **I. Safro:** None. **M. Wyatt:** None. **M. Shtutman:** None.

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.13/KK55

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

Support: NIH Grant AG062543

Title: Theta burst stimulation modulates hippocampal perfusion in mild cognitive impairment

Authors: *R. HICKEY[1], H. ZHANG[2], Y.-C. CHEN[2], Y. LIU[2], C. UGONNA[2], L. HAAHEIM[2], H. SIU[2], N.-K. CHEN[2], L. RYAN[3], Y.-H. CHOU[2];
[1]Psychology, Univ. of Arizona, Tucson, IL; [3]Evelyn F. McKnight Brain Inst., [2]Univ. of Arizona, Tucson, AZ

Abstract: BACKGROUND: Theta-burst stimulation (TBS) is a noninvasive neuromodulation protocol with therapeutic promise for mild cognitive impairment (MCI). Improvements in memory symptoms have been shown following TBS applied to the parietal lobe; however, it is not yet established if these behavioral improvements reflect physiological changes within the

hippocampus. This study investigates whether tractography-guided TBS delivered to the left parietal cortex alters hippocampal perfusion and modulates perfusion-memory coupling in MCI. **METHODS:** Forty-five individuals with MCI completed a 10-session course of intermittent TBS (iTBS), continuous TBS (cTBS), and sham, in a randomized, double-blind, within-subject crossover design. Cerebral blood flow (CBF) was quantified using pseudo-continuous arterial spin labeling (ASL), and associative memory was assessed with the Face-Name task. Outcomes were assessed before and after each treatment condition. Perfusion changes within the left hippocampus, cortical stimulation site, and the medial prefrontal cortex were assessed using a Bayesian mixed-effects model to evaluate the protocol, timepoint, their interaction, and covariates (i.e., age, mean framewise displacement, global gray matter CBF, and regional gray-matter fraction). A three-way mixed model tested whether protocol-related perfusion changes in the hippocampus were associated with within-subject changes in memory performance. Exploratory analyses were also conducted to evaluate perfusion-memory relationships beyond the left hippocampal region of interest. **RESULTS:** Relative to sham, iTBS produced a reliable 12.8% increase in left hippocampal CBF ($\Delta = 0.120$, 95% CrI [0.005, 0.263]). cTBS did not show reliable hippocampal CBF change, but did show a 13.5% reduction in CBF at the stimulation site ($\Delta = -0.145$, 95% CrI [−0.284, −0.008]) and -10.0% in the medial prefrontal cortex ($\Delta = -0.105$, 95% CrI [−0.197, −0.014]) relative to sham. Post-stimulation, both active TBS protocols showed stronger CBF-memory associations, where sessions with improved associative discrimination also showed increased left hippocampal CBF (iTBS: $\beta = 0.676$, 95% CrI [0.006, 1.365]; cTBS: $\beta = 0.988$, 95% CrI [0.307, 1.685]). **CONCLUSIONS:** Tractography-guided TBS applied to parietal sites resulted in hippocampal perfusion changes and produced memory-relevant network effects. These quantitative ASL results support the framework that physiological changes underlie the behavioral outcomes from targeted neurostimulation protocols, and provide promising mechanistic evidence for intervention protocols for MCI.

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Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.14/KK56

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

Support: DBT, India, BIRAC- BIG

Title: From de-novo molecule design to behavior and transcriptomics: An in-silico:in-vivo integrated platform for pre-screening neurodegenerative disease drugs

Authors: *A. AGGARWAL[1,2], L. BAWEJA[2], D. BASU[1], K. SACHDEVA[1];
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Abstract: Neurodegenerative disease drug discovery is hindered by high attrition and late-stage failures, underscoring the need for rapid *in-vivo* systems that can triage drug candidates before mammalian testing. This work establishes a *Drosophila*-based pre-screening platform for Parkinson's disease (PD) that integrates *in-silico* drug designing platform with *in-vivo* toxicology, survival, locomotor behavior, and transcriptomics. To validate the *in-vivo* pipeline, clinically informed drug selection included successful translational compounds (Levodopa, Amantadine, Pramipexole), failed phase III candidates (4-Aminopyridine, Isradipine), and Rasagiline as a translational control, given its efficacy in mammals but absence of a suitable molecular target in *Drosophila*. Logistic-model based lethality assays in wild-type flies defined non-lethal exposure windows, which were then applied to a $LRRK^{ex1/+}$ PD model to quantify dose-dependent effects on survival and locomotor behavior using a highly sensitive fly locomotor assay.Age-resolved transcriptomic profiling at behavioraly characterized timepoints is incorporated to capture drug-induced molecular trajectories across early, mid, and late disease-like stages in the fly, providing a basis for comparison with stage-matched transcriptomic signatures derived from PD mouse models. These cross-species comparisons enable assessment of whether molecular rescue in flies predicts mammalian, age-aligned responses. Building on this benchmarked framework, an *in-silico* pipeline is used to design, generate, and prioritize *de-novo* small molecules targeting pathways implicated in the transcriptomic analyses. Candidates are filtered by predicted pharmacokinetic and safety profiles, then advanced into the proprietary *Drosophila* platform for toxicology, survival, behavior, and transcriptomic readouts, creating a closed loop *in-silico:in-vivo* validation. Together, this integrated platform offers a scalable, mechanistically informed strategy for pre-screening both known and *de-novo* molecules for neurodegenerative disease pipelines.

Disclosures: A. Aggarwal: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Scikal Life Technologies. **L. Baweja:** A. Employment/Salary (full or part-time):; Scikal Research. **D. Basu:** A. Employment/Salary (full or part-time):; Scikal Life Technologies. **K. Sachdeva:** A. Employment/Salary (full or part-time):; Scikal Life Technologies.

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.15/KK57

Topic:

Title: Progranulin Upregulation by Translation-Enhancing Antisense Oligonucleotides for the Treatment of PGRN-Deficient Neurodegenerative Diseases

Authors: *H. ZHOU[1], L. ZHANG[1], S. JAIN[1], J. LI[1], P. YIN[2], R. THAI[1], X. YU[1], Y. WANG[1], X. LIANG[1];
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Abstract: Background: Loss-of-function mutations in GRN cause progranulin (PGRN) deficiency, which is a major genetic cause of frontotemporal dementia (GRN-FTD). Reduced PGRN disrupts lysosomal function, leading to impaired protein clearance, neuroinflammation, synaptic dysfunction, and neuronal degeneration. Microglial activation and astrogliosis are prominent features of PGRN deficiency and are thought to accelerate disease progression further. Moreover, studies have shown that increasing PGRN expression is protective in multiple neurodegenerative disease models, including Alzheimer's disease, supporting PGRN restoration as a promising therapeutic strategy. **Method:** Novel antisense oligonucleotides (ASOs) were developed to increase PGRN protein expression in vitro and in vivo. These ASOs utilize Arnatar's proprietary ACT-UP1 (Antisense Coupled Translation Upregulation) platform, in which ASOs selectively bind to the 3′ UTR of GRN mRNA and increase recruitment of endogenous translation enhancing proteins to boost protein synthesis. The ASOs were designed to target GRN mRNA sequences conserved across human, non-human primate, mouse, and rat transcripts. Effects on PGRN expression and function were evaluated by Western blotting and ELISA in human cell lines and rodent models. **Results:** In human U937 cells, GRN-targeting ASOs dose-dependently increased PGRN protein levels up to approximately 3-fold. Increased PGRN expression by ASO treatment was also observed in human SH-SY5Y neuroblastoma cells and in primary fibroblasts derived from FTD patients carrying heterozygous GRN mutations (nonsense or frameshift). Subcutaneous administration of ASOs also increased PGRN protein in mouse liver. The ASO-induced PGRN was functionally active, as demonstrated by activation of the AKT signaling pathway. In addition, intracerebroventricular administration of ASOs in Sprague-Dawley rats produced dose-dependent increases in PGRN protein levels across multiple CNS regions, including cortex, cerebellum, hippocampus, and brainstem. Elevated PGRN expression was sustained for more than 6 weeks following a single dose. At last, GRN-targeting ASOs demonstrate a strong preclinical safety profile suitable for further development as therapeutics. **Conclusion:** ACT-UP1 ASOs can increase PGRN protein expression across multiple in vitro and in vivo models. These findings support the therapeutic potential of PGRN-targeting ASOs for PGRN-deficient neurodegenerative disorders.

Disclosures: H. Zhou: A. Employment/Salary (full or part-time):; Arnatar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Arnatar Therapeutics. **L. Zhang:** A. Employment/Salary (full or part-time):; Arnatar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Arnatar Therapeutics. **S. Jain:** A. Employment/Salary (full or part-time):; Arnatar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Arnatar Therapeutics. **J. Li:** A. Employment/Salary (full or part-time):; Arnatar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Arnatar Therapeutics. **P. Yin:** A. Employment/Salary (full or part-time):; Arnatar Therapeutics. **R. Thai:** A. Employment/Salary (full or part-time):; Arnatar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Arnatar Therapeutics. **X. Yu:** A. Employment/Salary (full or part-time):; Arnatar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Arnatar Therapeutics. **Y. Wang:** A. Employment/Salary (full or part-time):; Arnatar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

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

Poster

PSTR038: Neurodegenerative Diseases (AD, PD, MS, Stroke)

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.16/KK58

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

Support: Intramural Research Program of the National Institutes of Health (NIH)

Title: Neuroplasticity Enhancement from Cognitive Training Reinforced by Psilocybin (NECTAR) Study Design

Authors: *N. NEUHALFEN[1], D. KAPOGIANNIS[2], A. MANOLOPOULOS[1];
[1]Natl. Inst. on Aging, Natl. Inst. of Hlth., Baltimore, MD; [2]BSU, NIA/NIH, Baltimore, MD

Abstract: Despite recent advancements, treatment options for Alzheimer's disease (AD) remain limited to symptomatic relief and fail to adequately address ongoing neurodegeneration. Beyond AD, sub-clinical cognitive decline occurs in normal aging motivating a search for pro-cognitive interventions. Cognitive training has shown promise in enhancing cognitive function in both normal aging and AD. However, its benefits are marginal and may be constrained by age-related declines in neuroplasticity mechanisms. Psilocybin, a serotonergic psychedelic drug, has been shown to promote neuroplasticity at multiple levels, including synaptogenesis, dendritic remodeling and biogenesis and brain network re-organization. We designed the Neuroplasticity Enhancement from Cognitive Training Reinforced by Psilocybin (NECTAR) study, a phase 2a, randomized, open-label, parallel-group trial with two arms, to evaluate whether psilocybin can augment the neuroplastic and cognitive-enhancing effects of cognitive training in two populations, 40 adults 65 years and older with normal cognition and 40 individuals with early-stage AD. Participants in both populations will be randomized 1:1 to receive either two oral doses of 25 mg of psilocybin, administered two weeks apart, plus daily cognitive training for four weeks or cognitive training alone. We hypothesize that psilocybin plus cognitive training will enhance neuroplasticity, as measured by a Neuroplasticity Composite Score (NPCS), compared to cognitive training alone. The NPCS comprises measures of cognitive performance (assessed by a Tablet-Based Cognitive Assessment Tool), functional connectivity coefficient for the Default Mode Network on resting state fMRI, individualized pace of brain aging (brain-age-gap estimate from structural MRI), and plasma levels of brain-derived neurotrophic factor. Additionally, we hypothesize that psilocybin plus cognitive training will induce beneficial changes in cognitive, neuroimaging, EEG, psychological (anxiety, depression), and biomarker outcomes compared to cognitive training alone. This is the first study to examine the synergistic effect of psilocybin plus cognitive training on neuroplasticity and will open the way to studying

the neuroplastic effects of psychedelics as a novel therapeutic approach to AD and brain aging. The trial will be conducted at the NIA Clinical Unit in Baltimore, MD.

Disclosures: N. Neuhalfen: None. **D. Kapogiannis:** None. **A. Manolopoulos:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.01/KK59

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

Title: Optimising cAMP signalling with isoproterenolenables a robust human iPSC-derived neuron-astrocyte-microglia tri-culture

Authors: M. RIOS DE ANDA[1], T. TATAR OZKAN[1], S. HUSSAIN[1], P. BARTON[1], E. YATES[1], C. ARUTHAN[1], H. GARNETT[1], N. JAMES[2], J. HUNDLING[1], I. FERREIRA[1], *A. TURNER[1], B. NEWMAN[1], K. FIRTH[1], G. MASTROGIOVANNI[1], T. OOSTERVEEN[3], W. BERNARD[1];
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Abstract: In neurodegenerative diseases, impaired neuronal function leads to the loss of cognition, memory, and motor control. While research has traditionally been neuron-centric, glial cells are now recognised as critical drivers of disease progression via phenotypic shifts from a neuroprotective to neurotoxic states. Developing therapies requires high-throughput, complex in vitro systems to model these interactions robustly. Although human iPSC-derived cells are promising, their utility is often limited by high manufacturing variability and their conflicting media requirements when generating complex cell models. To address these limitations, we used deterministically programmed human iPSCs to develop robust protocols for complex models, including a tri-culture of ioGlutamatergic Neurons, ioAstrocytes, and ioMicroglia. Tri-culture development was initially hindered by high cAMP requirements (500 mM) for ioAstrocytes, which compromised ioMicroglia viability. We optimised the media using isoproterenol, a beta-adrenoceptor agonist that increases intracellular cAMP levels and induces a stellar morphology in astrocytes. Supplementing with 5 mM isoproterenol reduced exogenous cAMP ioAstrocyte requirements 2- to 5-fold depending on the cell densities. The addition of isoproterenol preserved the ioAstrocytes identity as shown by the expression of VIM and S100B, and their stellar morphology, while maintaining healthy IBA1 expressing ioMicroglia. Incorporating genetically matched disease model cells into this protocol can readily expand this system into a highly reproducible, scalable platform for modelling specific CNS pathologies to advance drug discovery.

Disclosures: M. Rios de Anda: A. Employment/Salary (full or part-time):; bit.bio. **T. Tatar Ozkan:** A. Employment/Salary (full or part-time):; bit.bio. **S. Hussain:** A. Employment/Salary (full or part-time):; bit.bio. **P. Barton:** A. Employment/Salary (full or part-time):; bit.bio. **E.**

Yates: A. Employment/Salary (full or part-time):; bit.bio. **C. Aruthan:** A. Employment/Salary (full or part-time):; bit.bio. **H. Garnett:** A. Employment/Salary (full or part-time):; bit.bio. **N. James:** A. Employment/Salary (full or part-time):; bit.bio. **J. Hundling:** A. Employment/Salary (full or part-time):; bit.bio. **I. Ferreira:** A. Employment/Salary (full or part-time):; bit.bio. **A. Turner:** A. Employment/Salary (full or part-time):; bit.bio. **B. Newman:** A. Employment/Salary (full or part-time):; bit.bio. **K. Firth:** A. Employment/Salary (full or part-time):; bit.bio. **G. Mastrogiovanni:** A. Employment/Salary (full or part-time):; bit.bio. **T. Oosterveen:** A. Employment/Salary (full or part-time):; bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time):; bit.bio.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.02/KK60

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

Support: AMED 26be1004103

Title: A Multi-Platform Microphysiological System-MEA Approach Using Conventional MEA and CMOS-MEA Systems: Application to CNS Circuit, NMJ, and Peripheral Neuropathy Models

Authors: *M. YAMANAKA, X. HAN, R. YOKOI, N. MATSUDA, B. NODA, I. SUZUKI; Tohoku Inst. of Technol., Sendai, Japan

Abstract: Microphysiological systems integrated with microelectrode arrays (MPS-MEA) enable label-free electrophysiological monitoring of human-relevant neural circuits, yet no single MEA platform addresses all application demands. We developed a two-compartment MPS device connected by micro-channels that minimize inter-compartment fluid exchange, allowing independent use of different cells, media, and compounds in each compartment. The device was fabricated from cyclic-olefin polymer (COP) and first bonded to Alpha MED Scientific (AMS) glass-substrate MEA to establish the process, then extended to three additional systems: Axion BioSystems for high-throughput multiwell testing, MaxWell Biosystems CMOS-MEA (26,400 electrodes; 1,020 simultaneously recordable) for detailed synaptic propagation analysis at single-unit resolution, and Sony UHD-CMOS-MEA (236,880 electrodes) for simultaneous full-array large-area recording. This platform was validated across three neural models using rat primary neurons and human iPSC-derived cells. In a CNS circuit model on AMS and Axion, hippocampal and cortical neurons in opposing compartments showed directional burst propagation; unilateral picrotoxin increased activity bilaterally, and CNQX reduced hippocampal bursts to approximately 13% of baseline, confirming cortex-to-hippocampus signal propagation. Electrical stimulation of cortical neurons evoked measurable hippocampal responses, enabling calculation of inter-regional synaptic propagation velocity. MaxWell CMOS-MEA enabled detailed analysis of synaptic propagation along micro-channels at single-unit resolution. In an

NMJ model on AMS and Axion, skeletal muscle responses to motor neuron inputs confirmed functional NMJ formation after four weeks of co-culture. In a peripheral neuropathy model, Sony UHD-CMOS-MEA independently enabled simultaneous large-area tracking of action potential propagation along axons with single-spike resolution across the full array. These results highlight a practical framework for platform selection in MPS-MEA assay design: conventional MEA systems offer the throughput needed for multi-compound screening applications, whereas CMOS-MEA systems provide the spatial resolution essential for higher-order functional analyses requiring single-unit activity characterization, precise axonal conduction velocity mapping, or large-scale propagation tracking at the single-cell level. Strategic alignment of platform capability with assay requirements provides a scalable foundation for human-relevant disease modeling, drug efficacy evaluation, and neurotoxicity assessment.

Disclosures: M. Yamanaka: None. **X. Han:** None. **R. Yokoi:** None. **N. Matsuda:** None. **B. Noda:** None. **I. Suzuki:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.03/KK61

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

Title: High-Throughput Screening Platform and Orthogonal Assays for Apelin Receptor Discovery

Authors: L. C. D. GIBSON[1], **G. CUCINIELLO**[2], C. BROWN[1], L. J. YUILL[1], J. KEWNEY[3], *L. GERRARD[1];
[1]Sygnature Discovery, Glasgow, United Kingdom; [2]Sygnature Discovery, NOTTINGHAM, United Kingdom; [3]Sygnature Discovery, Troon, United Kingdom

Abstract: The apelin receptor (APLNR, APJ) is a class A G protein-coupled receptor activated by endogenous ligands including apelin peptides and ELABELA. Beyond its established role in cardiovascular physiology and metabolic health, APLNR is increasingly implicated in central nervous system processes, including neurodevelopment, neuroprotection, angiogenesis, and modulation of neuroinflammation. Notably, receptor activation has been associated with neuroprotective and anti-inflammatory effects, supporting growing interest in the therapeutic potential of APLNR agonists. To enable drug discovery, we have generated and characterised a APLNR stable cell line co-expressing Gqi chimeric protein and developed a high-throughput screening (HTS)-compatible functional assay to measure calcium signalling. This has been established as a primary screening assay for detection of novel APLNR agonists and optimised for sensitivity, robustness, and scalability. To further characterise APLNR pharmacology, orthogonal assays employing independent readouts were implemented to capture distinct signalling outputs, enabling assessment of pathway engagement and support hit confirmation.

Together, this integrated assay framework supports robust investigation of APLNR signalling and enables identification and validation of modulators.

Disclosures: L.C.D. Gibson: None. **G. Cuciniello:** None. **C. Brown:** None. **L.J. Yuill:** None. **J. Kewney:** None. **L. Gerrard:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.04/KK62

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

Support: NINDS Grant T32-NS007413
NIH Grant R35-HL145203
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The UPenn Transdisciplinary Award Program in Translational Medicine and Therapeutics (TAPITMAT)
The CHOP Gene Therapy and Inherited Metabolic Disorders (GTIMD) Frontier program
The Margaret Q. Landerberger Foundation

Title: In vivo adenine base editing of the liver rescues brain biochemistry and improves brain network dynamics in a mouse model of phenylketonuria

Authors: *M. K. GAUTIER[1], S. BHUYAN[1], A. PALMUCCI[1], H. SAID[1], M.-G. ALAMEH[1,2], X. HONG[1], X. WANG[2], K. MUSUNURU[1,2], B. R. WHITE[1,2], R. AHRENS-NICKLAS[1,2]; [1]The Children's Hosp. of Philadelphia, Philadelphia, PA; [2]The Univ. of Pennsylvania, Philadelphia, PA

Abstract: Phenylketonuria (PKU) is an autosomal recessive inborn error of amino acid metabolism affecting roughly 1:24,000 newborns worldwide. Infants lack functional phenylalanine hydroxylase (PAH), a liver enzyme that converts the amino acid phenylalanine (Phe) into tyrosine (Tyr). PAH deficiency leads to a rapid increase in blood Phe levels during the postnatal period, resulting in neurotoxic injury. Clinical management focuses on symptom reduction via dietary Phe restriction, a life-long regimen with poor compliance. Patients with insufficient metabolic control are at risk of developing intellectual disability, epilepsy, motor impairments, and psychiatric disorders. Mice homozygous for the common p.P281L (c.842C>T) *PAH* variant develop a severe neurologic phenotype characterized by elevated brain Phe and motor deficits. Using *in vivo* electroencephalogram (EEG) (n=6) and hemodynamic widefield optical imaging (WOI) (n=11), we show P281L mice have abnormal hippocampal circuit dynamics and alterations in resting state functional connectivity between brain regions by

postnatal day 60. To determine whether corrective liver editing improves clinically relevant neurologic phenotypes, we administered an adenine base editor therapy (ABE8.8 mRNA and a variant-specific hybrid guide RNA packaged in lipid nanoparticles) to four-week-old P281L mice via retro-orbital injection. *In vivo* EEG six weeks post-treatment revealed a normalization of slow wave background frequency composition and partial amelioration of network-level brain dysfunction (n=4). Biochemical analysis showed significant reductions in Phe concentrations in plasma (96.8%) and brain cortical tissue (68.7%), as well as increases in plasma and brain tyrosine levels (61.7% and 27.4%, respectively) (n=8). Rebalancing of amino acid levels produced a significant increase in the synthesis of associated neurotransmitters, most prominently serotonin and norepinephrine. Genetic and biochemical correction was accompanied by a rescue of hindlimb spinal reflexes and mobility improvements (n=12). Next-generation sequencing of post-mortem liver tissue from treated mice showed corrective editing that ranged from 10% to 71% of total *PAH* alleles. Our findings further support the viability of corrective editing-based therapeutics for the treatment of monogenic metabolic disorders, but emphasize the importance of early-life correction in conditions with complex neurodevelopmental phenotypes.

Disclosures: M.K. Gautier: None. **S. Bhuyan:** None. **A. Palmucci:** None. **H. Said:** None. **M. Alameh:** None. **X. Hong:** None. **X. Wang:** None. **K. Musunuru:** None. **B.R. White:** None. **R. Ahrens-Nicklas:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.05/KK63

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

Title: Investigating the interaction between neurovascular cells in a co-culture system based on differentially expressed sex-related genes to optimize cell transplantation therapy for brain injury

Authors: *C.-H. CHOU[1,2], R. ADHIKARI[2], Y.-C. CHEN[3];
[1]Neurol., Tri-Service Gen. Hospital, Natl. Def. Med. Center, Taiwan, Taipei City, Taiwan;
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Abstract: Cell selection is a critical issue in optimizing the efficacy of cell therapy. Because cells often share similar morphological characteristics and may exhibit overlapping phenotypic markers or undergo dynamic phenotypic shifts in co-culture systems, reliably identifying and tracking each cell type in subsequent analyses becomes extremely difficult. For example, fluorescent dyes can dilute over time due to cell division, leading to reduced signal intensity and inaccurate identification. Similarly, genetic modifications introducing reporter genes can alter cell behavior or interfere with natural signaling pathways, while surface markers may lack specificity or be significantly influenced by the cell microenvironment or differentiation state. In a neurovascular co-culture system, we co-cultured neural progenitor cells or dentally derived neural crest-like stem cells (NCSCs) with endothelial cells from donors of different sexes, and

applied *EIF1AY* and other sex-related genes to achieve precise identification of the donor origin while integrating single-cell RNA sequencing. Furthermore, we selected the most suitable dental-derived NCSCs to generate the cell sheet for transplantation therapy. We have previously demonstrated that transplantation of the neural progenitor cell-engineered cell sheet (NECS) in a rat model of brain injury promotes *in situ* neurovascular tissue repair and functional improvement. In addition to a significant reduction in modified neurological severity score (2 points in the treatment group, 7 points in the control group), lesion volume was projected to decrease by 38% four weeks after NECS transplantation. These findings demonstrate that sex-specific transcriptomic tracking provides a robust strategy for dissecting neurovascular cell interactions and optimizing cell selection for regenerative therapies. This platform may accelerate the development of vascularized cell-sheet products for the treatment of brain injury characterized by neural tissue loss.

Disclosures: C. Chou: A. Employment/Salary (full or part-time):; NeuSprout LLC. **R. Adhikari:** A. Employment/Salary (full or part-time):; NeuSprout LLC. **Y. Chen:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.06/Web Only

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

Title: Optimization and validation of $GABA_A$ receptor FLIPR membrane potential assay for the detection of positive allosteric modulators for drug forensic applications

Authors: *F. TAN[1], Z. WU[2], Y. NEO[1], C.-M. LOW[2], Y. YONG[1], C. LIM[1];
[1]Forensics Ctr. of Expertise, Home Team Sci. and Technol. Agency, Singapore, Singapore, Singapore; [2]Pharmacol., Yong Loo Lin Sch. of Medicine, Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Recently, there was a surge in the lacing of vape pods with etomidate in the various East and Southeast Asian countries. These laced vape pods represent a problem to society as many times the users themselves are not aware that the vape pods are being laced with an illicit drug. Etomidate is a potent and rapidly acting imidazole-based compound which was previously used as an anesthetic agent due to its minimal effects on breathing and blood pressure. Its ability to target specifically to the β_2 and β_3 subunits of $GABA_A$ receptor as a positive allosteric modulator allows it to account for lower seizure threshold and maintaining cardiovascular stability in patients undergoing anesthesia. Unfortunately, etomidate is also able to suppress the biosynthesis of adrenocortical steroids, resulting in increases morbidity and mortality, particularly in the critically ill. This leads to etomidate being rarely used now as an anesthetic agent. Etomidate, when used as a drug of abuse, has dissociative effects such as hallucinations, altered perceptions and sense of detachment from reality. Frequent abuse of etomidate will further lead to dependence, myoclonus, derealization, and suicidal ideation. Due to the recent

abuse, China, Hong Kong and Singapore, faced with etomidate-related threats, have classified etomidate as a drug of abuse. However, due to the relative ease of synthesis, analogues of etomidate that have equal or higher potency may be easily synthesized as new psychoactive substances (NPS) to evade prosecution. To circumvent the legislation loophole, some countries such as Singapore and UK, have amended their legislation to enable the prosecution of possession of such NPS by determining the substance ability to produce a psychoactive effect rather than by chemical structure alone. This resulted in the need to develop assays to determine if these new substances can trigger similar effects as etomidate.
In this study, we present the use of a FLIPR membrane potential assay as an alternative to patch clamp to allow the detection of the effects of positive allosteric modulator of $GABA_A$ receptors. We further validate the assay using other analogues of etomidate and determine the threshold of detection between HEK cell lines stably expressing $GABA_A$ receptors with the following subtypes $\alpha1\beta2\gamma2$ and $\alpha1\beta3\gamma2$.

Disclosures: F. Tan: None. **Z. Wu:** None. **Y. Neo:** None. **C. Low:** None. **Y. Yong:** None. **C. Lim:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.07/KK64

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

Support: RS-2024-00444687

Title: Transcriptome-Guided In Silico Identification of HTR1B and EFNB2 as Dual Therapeutic Targets in Intervertebral Disc Degeneration

Authors: *H. KIM, J. HONG, H. KIM, W. JEON, J. LEE, C. YEO, Y.-S. LEE;
Jaseng Med. Fndn., Seoul, Korea, Republic of

Abstract: Intervertebral disc degeneration (IDD) is a major cause of chronic low back pain, yet effective disease-modifying therapies remain unavailable. Recent evidence suggests that neurovascular clearance dysfunction and pathological angiogenesis may contribute to disease progression. To explore potential therapeutic targets associated with these processes, we performed transcriptomic analysis of peripheral blood samples from patients with IDD and identified HTR1B, EFNB2, and MMRN1 as significantly upregulated genes. Based on their reported biological functions, we hypothesized that increased HTR1B signaling may contribute to impaired perispinal neurovascular clearance through vasoconstrictive mechanisms, whereas EFNB2 and MMRN1 may promote pathological angiogenic and lymphangiogenic remodeling within the degenerating disc. Together, these pathways could facilitate waste accumulation, immune cell infiltration, and disease progression. Therefore, we selected HTR1B and EFNB2 as dual therapeutic targets for subsequent structure-based virtual screening of natural compounds.

Structure-based virtual screening was conducted using the ZINC Natural Products and TCMNP databases. First, a pharmacophore mapping approach identified 7,770 compounds satisfying binding conditions for key HTR1B residues (Asp129, Trp327). Subsequent standard molecular docking targeting the HTR1B GPCR pocket selected 3,125 superior natural compounds exhibiting strong binding affinities of ≤ -8.5 kcal/mol. Secondary molecular docking against the EFNB2 protein-protein interaction (PPI) interface was performed to prioritize dual-target candidates. To account for structural flexibility and disease-specific binding patterns, selected compounds were further evaluated by molecular dynamics (MD) simulations under both physiological (pH 7.4) and IDD-relevant acidic (pH 6.5) conditions. Trajectory analyses including RMSD, RMSF, and MM-PBSA free-energy calculations were used to evaluate the stability and binding characteristics of candidate compounds under disease-relevant conditions. This study introduces a transcriptome-guided dual-target discovery strategy linking neurovascular clearance dysfunction and pathological angiogenesis in IDD. The identified candidates provide a foundation for future experimental validation and therapeutic development targeting HTR1B- and EFNB2-associated disease mechanisms.

Disclosures: H. Kim: None. **J. Hong:** None. **H. Kim:** None. **W. Jeon:** None. **J. Lee:** None. **C. Yeo:** None. **Y. Lee:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.08/KK65

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

Support: Advanced Research and Invention Agency (ARIA) SCNI-PR01-P014

Title: Multimodal tissue-engineered living electrodes for synaptic-based excitation, inhibition, or modulation of cortical tissue

Authors: *V. ALPIZAR VARGAS[1], D. CHOUHAN[2], S. KARANDIKAR[1], F. VITALE[1], D. CULLEN[3];
[2]Dept of Neurosurg., [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Neurosurg., Univ. of Pennsylvania, Media, PA

Abstract: Conventional neural interfaces can stimulate and record from neural tissue but remain limited in their ability to precisely modulate host circuits, which may require biological integration and cell-type-specific synaptic inputs. Axon-based living electrodes offer a complementary strategy in which defined neuronal populations serve as engineered biological relays for targeted circuit modulation. Here, we are developing so-called tissue-engineered living electrodes, or TELEs, featuring defined populations of human induced pluripotent stem cell (iPSC)-derived neurons and long-projecting, bundled axonal tracts capable of synaptically integrating with - and hence modulating - deep regions in the brain. The current study advances

the first multi-modal TELE comprising glutamatergic, GABAergic, and dopaminergic neurons to enable synaptic-based excitation, inhibition, or modulation of target neurons towards the goal of creating a multimodal biohybrid neural interface. Human iPSC-derived glutamatergic, GABAergic, and dopaminergic neurons were aggregated and embedded within three-dimensional hyaluronic acid hydrogel microcolumns to form elongated axon-rich microtissues. These TELEs were evaluated for survival, axonal outgrowth, neuronal phenotype, and functional maturation using viability, immunocytochemistry and activity assays. TELEs have exhibited robust viability, maintained phenotypic identity, supported aligned axonal extension through the microcolumn, and displayed functional activity consistent with their potential use as living neuromodulatory interfaces. Comparative analysis of TELEs with various neuronal subtypes will determine their effects on microtissue formation, axonal architecture, maturation, and functional signaling. By engineering TELEs from distinct human neuronal populations, this work establishes a foundation for multimodal living electrodes capable of delivering a range of neuromodulatory inputs. Integration with cortical organoids or other target tissues will allow us to test how defined axonal inputs regulate human network activity in a controlled *in vitro* system. This approach may provide a scalable platform for studying circuit-level mechanisms and developing biologically integrated interfaces for neural repair.

Disclosures: V. Alpizar Vargas: None. **D. Chouhan:** None. **S. Karandikar:** None. **F. Vitale:** None. **D. Cullen:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.09/LL1

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

Title: Spatially Resolved Detection of Dystrophin Isoforms Using BaseScope™ Duplex Fluorescent Assay

Authors: *S. A. DESHPANDE[1], A. J. Y. LING[1], J. A. YU[1], M. SAMBHI[1], L.-C. WANG[2]; [1]Bio-techne, Newark, CA; [2]Bio-Techne, Minneapolis, MN

Abstract: Genetic alterations in mammalian genes, including exon skipping, play a crucial role in various diseases, treatment outcomes, and prediction of patient survival. Mutations in the DMD gene result in cognitive and neuropsychiatric complications due to the essential roles of these isoforms in brain function. Mutations located near the 5' end of the DMD gene predominantly affect full-length isoforms like Dp427c with mild cognitive phenotype, whereas downstream mutations disrupt shorter isoforms such as Dp71, leading to more severe cognitive and behavioral manifestations. Furthermore, the spatial heterogeneity of brain tissue highlights the importance of cell type- and region-specific gene functions, providing insights into the mechanisms underlying neuropsychiatric disorders. We developed a next-generation, manual and fully automated fluorescent assay on the Leica platform that enables highly specific and

simultaneous detection of closely related RNA targets, specifically isoform-specific exon-exon junctions. This assay utilizes new BaseScope™ technology to visualize single RNA molecules in FFPE tissues and cell pellets. To validate this workflow, we detected endogenous control genes using 1zz probes on HeLa cell pellets and mouse multi-tissue arrays. To visualize Dp71 and Dp427c isoforms, junction-specific probes were designed using new BaseScope™ chemistry and applied to mouse brain tissue sections. Further, Dp71 and Dp427c exon junction-specific probes were multiplexed and co-detected with Rbfox3 RNAscope probe for neurons, and Aqp4 RNAscope probe for astrocytes, in mouse brain tissue using the BaseScope™ Expansion Pack and RNAscope™ Multiomic assay. Signal intensity, measured as dot counts per cell from control genes using the new BaseScope™ Duplex Fluorescent assay, was comparable to that obtained with the original BaseScope™ assay. Multiplexing of Dp71 and Dp427c exon junction probes with neuronal and astrocyte markers revealed region-specific expression patterns of each dystrophin isoform in wild-type mouse brain tissue. These findings demonstrate the efficacy of the BaseScope™ Duplex Fluorescent assay for simultaneous, same-slide detection of cells expressing highly similar RNA targets. The BaseScope™ Duplex Fluorescent assay offers spatial resolution of isoform- specific gene expression, representing a powerful tool for investigating cell-type-specific transcript variants in defined brain regions. This technology holds significant potential to advance precision neuroscience research by enabling detailed characterization of disease-associated transcript isoforms at cellular resolution.

Disclosures: S.A. Deshpande: None. **A.J.Y. Ling:** None. **J.A. Yu:** None. **M. Sambhi:** None. **L. wang:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.10/LL2

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

Support: NIH Grant R01AG074092
U19AG060917
R01DK107670
R01AI161363

Title: A humanized follicle stimulating hormone blocking antibody as a therapeutic strategy for osteoporosis, obesity, and Alzheimer's disease

Authors: *A. PALLAPATI, F. KORKMAZ, S. ROJEKAR, S. SIMS, J. GIMENEZ ROIG, D. VASILYEVA, U. CHELIADINOVA, F. SULTANA, A. GUMEROVA, T. FROLINGER, T. YUEN, M. ZAIDI;
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Abstract: Growing evidence supports direct actions of follicle-stimulating hormone (FSH) on tissues other than the ovaries and testes. Genetic or pharmacologic FSH blockade protects mice against bone loss (1,2), fat gain (3), and memory loss (4), and attenuates Alzheimer's disease (AD)-like features—conditions that converge in postmenopausal women. We thus developed a first-in-class, humanized, epitope-specific humanized FSH-blocking antibody—MS-Hu6— with a K_D of 7.52 nM (5) as a lead therapeutic for three diseases of public health magnitude—osteoporosis, obesity and Alzheimer's disease (AD) that track together in post-menopausal women. We solved the crystal structure of MS-Hu6 bound to FSH, resolving the antibody-antigen interface in atomistic detail. A single injection of ^{89}Zr-labeled MS-Hu6 yielded a ß-phase t½ of 89 h in female and 131 h in male mice, with retention in regions of interest. The murine equivalent, Hf2, rescued recognition memory and spatial learning deficits in a context- and time-dependent manner in AD-prone 3xTg and APP/PS1 mice. These cognitive benefits occurred alongside reduced free (bioavailable) FSH and unperturbed estrogen, and were accompanied by dose-dependent reductions in body weight (7%) and body fat (33%) in female mice. To assess translatability, MS-Hu6 was given to African green monkeys (8 mg/kg intravenously, then subcutaneously at monthly intervals). It was well tolerated, with no effects on vitals, blood chemistries, or blood counts; a ~4% weight loss followed the first injection in all four animals and persisted in two. Using our Good Laboratory Practice (GLP) platform (21CFR58), we formulated MS-Hu6 and the murine equivalent Hf2 at an ultra-high concentration; both formulated antibodies displayed enhanced thermal and colloidal stability. Together, these data identify FSH as a tractable target for cognitive decline and show that a structurally defined, brain-retained FSH-blocking antibody treats memory deficits across two AD mouse models, with a supportive safety profile in non-human primates. [1]*Cell*, 2006; [2]*PNAS*, 2018,[3] *Nature*, 2017; [4]*Nature*, 2022; [5]*PNAS*, 2020.

Disclosures: A. Pallapati: None. **F. Korkmaz:** None. **S. Rojekar:** None. **S. Sims:** None. **J. Gimenez Roig:** None. **D. Vasilyeva:** None. **U. Cheliadinova:** None. **F. Sultana:** None. **A. Gumerova:** None. **T. Frolinger:** None. **T. Yuen:** None. **M. Zaidi:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.11/LL3

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

Support: NIH R01 CA284075

Title: Identification of a high-affinity receptor for CART II neuropeptide

Authors: *N. CORVALAN CABANAS[1], C. MILIANO[1], I. S. LEVINE[1], L. MURDAUGH[2], Y. DONG[1], S. BISWAS[1], S. VIJAYAN[1], A. M. PICKRELL[1], N. SUTO[3], A. GREGUS[1], M. W. BUCZYNSKI[1];
[1]Neurosci., Virginia Polytechnic Inst. and State Univ., Blacksburg, VA; [2]Anesthesiol.,

Pennsylvania State Univ. Col. of Med., Hershey, PA; [3]Dept. of Mol. Pharmacol. & Exptl. Therapeut., Mayo Clin., Rochester, MN

Abstract: Cocaine- and amphetamine-regulated transcript (CART) prepropeptides have been implicated in multiple pathologies including obesity, nociception, mood disorders, diabetes mellitus, and drug addiction, yet the absence of validated receptors has hampered the mechanistic interrogation and therapeutic application of the two principal peptides, CART I (CART 55-102) and CART II (CART 62-102). Both CART I and CART II have been proposed to bind to G-protein coupled receptors (GPCR) to elicit wide-ranging behavioral and physiological effects, such as appetite suppression and thermal analgesia. Accordingly, an orphan GPCR, GPR160, has been reported as a common receptor for both CART I and CART II, hence the first and only receptor identified for any CART peptides to date. However, CART I produces more potent anxiogenic effects than CART II, while CART II produces more potent anorexic and analgesic effects than CART I, suggesting separate receptors for these two CART peptides. Here, we used high-throughput cell-based GPCR screening technology (Presto-TANGO) to identify LPAR2 as the high affinity receptor for CART II, and secondary functional assays and whole-cell ELISA binding assays to confirm these findings. Genetic (LPAR2 knockout mice) and chemical (LPAR2 antagonist H2L5186303) tools validated that the established analgesic and anorexic behavioral effects of CART II - but not CART I - in the brain are specifically mediated by LPAR2, confirming it as the physiologically relevant receptor for this neuropeptide. Collectively, these findings demonstrate LPAR2 is the endogenous CART II receptor in the brain, enabling the interrogation of CART II-specific neurobiology and the development of therapeutic interventions.

Disclosures: N. Corvalan Cabanas: None. **C. Miliano:** None. **I.S. Levine:** None. **L. Murdaugh:** None. **Y. Dong:** None. **S. Biswas:** None. **S. Vijayan:** None. **A.M. Pickrell:** None. **N. Suto:** None. **A. Gregus:** None. **M.W. Buczynski:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.12/LL4

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

Title: Novel tools for spatial profiling of protein glycosylation in cancer biology

Authors: *E. LEONARD[1], S. CHEN[2], S. CHOUDHURY[3];
[1]Res. & Develop., [2]Product Mgmt., Vector Laboratories, Inc, Newark, CA; [3]Vector Laboratories, Inc, San Ramon, CA

Abstract: Glycan modifications play critical roles in cell function in both healthy and diseased states, from controlling proliferation to modulating the immune response. Lectins are glycan-binding proteins that recognize specific glycan structures. Their glycan-specific nature makes

them important tools to profile, characterize, and capture the complexity of glycans in biological systems.
To explore the complexity of glycan modifications, Vector Laboratories provides Glysite™ Scout Glycan Screening Kits, which are fully integrated kits for the detection of glycan expression in tissue sections. Our curated lectin selection enables the detection of the major glycan motifs including sialylation, fucosylation and galactosylation, for the evaluation of glycan distribution in a target specimen. Here, we established a standard workflow of lectin-integrated tissue immunoassays. Formalin-fixed, paraffin-embedded (FFPE) tissue sections were prepared from a selected panel of normal and cancerous tissues including colon, pancreas, breast, kidney, brain, and lung. Our lectin histochemical analysis revealed tissue-dependent glycopatterns, and our result was aligned with morphological changes observed in disease progression. We then utilized Glysite Explorer in situ PLA Glycan Detection Kit, a novel proximity-based detection technology, to investigate protein-specific glycosylation changes from healthy to diseased tissues. Our findings highlight distinct glycosylation patterns associated with pathological conditions, including cancer, underscoring the relevance of glycosylation in disease mechanisms. In summary, Glysite™ Scout Glycan Screening Kits are easily plugged into day-to-day tissue immunoassays that allow comprehensive screening of N- and O-glycan profiles in various tissue sections. In addition to glycan expression, Glysite Explorer Kit can be used to explore the glycosylation changes of specific biomarkers in cancer tissues. Altogether, this new data will add to the growing understanding of the impact of protein glycosylation on cancer biology.
This tool enriches biomarker discovery and therapeutic targeting, thus emphasizing the transformative potential of glycosylation-focused research in advancing precision medicine.

Disclosures: E. Leonard: A. Employment/Salary (full or part-time):; Vector Laboratories Inc. **S. Chen:** A. Employment/Salary (full or part-time):; Vector Laboratories Inc. **S. Choudhury:** A. Employment/Salary (full or part-time):; Vector Laboratories Inc.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.13/LL5

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

Title: SimpleStep™ Ignite: A 55-Minute Chemiluminescent ELISA Platform Delivering Broader Range, Faster Results and More Sensitive Quantification SimpleStep™ Ignite: A 55-Minute Chemiluminescent ELISA Platform Delivering Broader Range, Faster Results and More Sensitive Quantification

Authors: *E. SWANSON, M. MOHAMMADI, J. S. MONETTE, A. HEUBERGER, J. HEATH;
Abcam, Eugene, OR

Abstract: The SimpleStep® ELISA platform utilizes Abcam's CaptSure™ technology to simplify traditional ELISA workflows into a rapid, single-wash format. This semi-homogeneous design, which uses a single step to form the antibody-antigen complex and bind it to the plate with an affinity tag, reduces protocol complexity, minimizes operator-dependent variability, and improves reproducibility. Sequence-defined recombinant rabbit monoclonal antibodies also contribute to consistent performance, high specificity, and lot-to-lot reproducibility. Building on this foundation, we have recently advanced the technology to create the SimpleStep Ignite platform, which incorporates the same universal plate architecture while further shortening assay time and expanding dynamic range through a highly sensitive chemiluminescent output. Here we demonstrate that after optimizing the components and workflow of the SimpleStep platform for this new readout, we reduce the lower limit of quantification of the chemiluminescent assay by an average of six-fold relative to the colorimetric assay, coupled to an average increase in the overall range of the assay by a factor of 32. Additionally, we were able to shorten the total assay time by more than 30 minutes, achieving an automation-friendly runtime of less than one hour. With higher sensitivity and increased operational simplicity, this suite of assays provides researchers with rapid, robust, and reproducible tools across a wide range of applications, from screening to functional validation.

Disclosures: E. Swanson: A. Employment/Salary (full or part-time):; Abcam. **M. Mohammadi:** A. Employment/Salary (full or part-time):; Abcam. **J.S. Monette:** A. Employment/Salary (full or part-time):; Abcam. **A. Heuberger:** A. Employment/Salary (full or part-time):; Abcam. **J. Heath:** A. Employment/Salary (full or part-time):; Abcam.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.14/LL6

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

Title: Live cell high-content imaging enables scalable kinetic screening of microglial phagocytosis and morphology

Authors: *M. BOISVERT, L. HERNANDEZ;
Araceli Biosci., Tigard, OR

Abstract: Microglial dysfunction is increasingly implicated in neurodegeneration, aging, and inflammation-associated cognitive decline, making microglial phagocytosis and activation a promising target to address cognitive decline. However, there is a gap in high throughput in vitro drug discovery and screening assays when it comes to this model: endpoint and slow kinetic assays miss dynamic and heterogeneous cellular responses and lack the throughput screening requires. Here, we demonstrate a live-cell high-content imaging workflow for scalable kinetic analysis of microglial phagocytosis and morphology. Using 384-well plates, we image hundreds of thousands of iPSC-derived microglia at 5-minute intervals with submicron resolution across

the majority of each well, acquiring both fluorescence and brightfield channels. This combination of temporal resolution, spatial resolution, and well coverage enables quantitative analysis of bead uptake kinetics, morphology, and population heterogeneity at the scale required for screening.
We applied this ultra-fast high content methodology to measure microglial responses to inflammatory stimulation and drug treatment. Following LPS treatment, kinetic imaging revealed an early responding subpopulation with activation-associated morphological changes, consistent with heterogeneous microglial responses to inflammatory challenge. In a bead-based phagocytosis assay, the platform quantified microglial uptake dynamics, showing drug-induced inhibition of microglial phagocytosis. Subsequent hourly imaging further identified and characterized a population of microglia that remained non-phagocytic after 24 hours. Combining high temporal resolution, subcellular spatial resolution, and 384-well throughput, this approach supports scalable discovery of modulators of microglial phagocytosis, activation, and morphology.

Disclosures: M. Boisvert: A. Employment/Salary (full or part-time):; Araceli Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Araceli Biosciences. **L. Hernandez:** A. Employment/Salary (full or part-time):; Araceli Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Araceli Biosciences.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.15/LL7

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

Support: New Investigator Grant (no. NI22-1106) from the SickKids Foundation
CIHR Project Grant (PJT no. 191866)
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Azrieli Center for Autism Research
Canada First Research Excellence Fund and HBHL
Integrated Program in Neuroscience (Molson Neuro-engineering Award)
CIHR (Canada Graduate Scholarship - Doctoral)

Title: A compact single-AAV gene restoration platform via CRISPR activation for neurodevelopmental disorders

Authors: *R. SURESH[1], X. TAN[1], L. CONG[2], G. A. ROULEAU[1], Y. ZHOU[1];
[1]Neurol. and Neurosurg., Montreal Neurolog. Inst. and Hospital, McGill Univ., Montréal, QC, Canada; [2]Pathology, Stanford Univ., Stanford, CA

Abstract: Numerous neurodevelopmental disorders (NDDs) arise from haploinsufficiency. However, many causal genes are too large, dosage-sensitive, or utilize multiple promoters, making them unsuitable for single-adeno-associated virus (AAV) gene replacement. Although mitigating strategies, including dual-AAV recombination, are under development, technical barriers remain before their effective application *in vivo*. The goal of this project is to engineer an AAV- and CRISPR-based gene-restoration platform that can upregulate large genes implicated in NDDs. CRISPR activation (CRISPRa) offers an alternative approach by upregulating the wild-type copy of the disease-associated gene to compensate for mutant-allele loss. Nevertheless, it remains a challenge to integrate all essential CRISPRa elements into a single AAV vector for efficient, neuronal-specific transduction *in vivo*. Creating a single AAV-based CRISPRa system would pave the way for clinical translation by improving efficiency, eliminating the need for co-transduction with multiple AAVs, and reducing viral load to mitigate toxicity. In this study, we constructed a compact and potent CRISPRa-based gene restoration platform that fits all required elements within a single AAV vector. We first designed a synthetic guide RNA (gRNA) expression cassette that is smaller than conventional gRNA expression systems, allowing for multiplexing of multiple gRNAs within a single AAV vector. We then rationally engineered compact, robust transactivation motifs capable of activating gene transcription at the protein level when placed in tandem. Finally, after incorporating a neuron-specific promoter, we demonstrated this single AAV vector's efficacy in upregulating mRNA and protein expression of *Syngap1* and *Scn1a*, two large genes implicated in severe NDDs, *in vivo*. In a *Scn1a*$^{+/-}$ mouse model of Dravet syndrome (DS), intravenous delivery of AAV-CRISPRa restored *Scn1a* mRNA and NaV1.1 protein brain-wide to near-physiological levels and markedly improved the associated premature mortality phenotype. These results highlight the potential of applying these synthetic modules and single-AAV platform to develop therapeutic interventions for genetic disorders caused by haploinsufficiency. Ongoing work focuses on rescuing neural and behavioural phenotypes in mouse models of severe NDDs caused by genetic haploinsufficiency.

Disclosures: R. Suresh: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PCT filed in the WIPO with McGill University. **X. Tan:** None. **L. Cong:** None. **G.A. Rouleau:** None. **Y. Zhou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PCT filed in the WIPO with McGill University.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.16/Web Only

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

Support: Eye Hope Foundation
Life Science Research Partners
Snow Foundation
Wolfram UK
Association Syndrome Wolfram

Title: A proof-of-concept study for single-nucleotide base editing to prevent vision loss in a Wolfram syndrome mouse model

Authors: S. BERGMANS, M. BULCAEN, F. FATEMEHAREFEH, M. CARLON, C. VERFAILLIE, L. MOONS, ***L. DE GROEF**;
KU Leuven, Leuven, Belgium

Abstract: Wolfram syndrome (WS) is a rare, fatal neurodegenerative disorder caused by loss-of-function variants in *WFS1*, with no disease-modifying therapy. This study aimed to (i) define the visual neurodegenerative phenotype of a novel *Wfs1*^{Q670X} mouse model and (ii) test the feasibility and therapeutic impact of adenine base editing (ABE) as a mutation-specific gene correction strategy. Male and female *Wfs1*^{Q670X} mice and wild-type littermates were followed from 2 to 7.5 mo. Males developed diabetes by 2 mo and females by 4 mo, and failed to gain weight; male survival was reduced by ~50% at 4 mo. Visual acuity declined from 4 mo (15%; $p < 0.0001$; $N \geq 33$), accompanied by age-dependent loss of retinal ganglion cell (26%; $p = 0.0006$) and photoreceptor (15%; $p = 0.0394$) function measured by electroretinography ($N \geq 17$). At 6 mo, post mortem analyses revealed increased immune cell infiltration (50%; $p = 0.0007$; $N = 7$) and microglial activation (17%; $p = 0.0036$; $N = 7$) (IBA1), and upregulation of the unfolded protein response (70%, $p = 0.02$; $N = 7$) (BiP) in the retina, consistent with progressive neurodegeneration linked to metabolic dysfunction, as observed in WS patients.To address the causal mutation, we evaluated ABE-based gene correction. Building on prior work demonstrating efficient ABE-mediated restoration of WFS1 protein in WS patient-derived induced pluripotent stem cells and differentiated neural cells, we first validated a dual AAV2/2-hSYN1 split-intein ABE9 system in vitro. Mixed retinal neuronal cultures derived from *Wfs1*^{Q670X} mice (P3-P4) were transduced and analyzed at DIV12. qPCR on genomic DNA showed a significant reduction (41%; $p = 0.0362$) in mutant allele signal ($N = 8$ with $n = 4$ per experiment), indicating successful gene correction.For in vivo testing, female *Wfs1*^{Q670X} mice were injected intravitreally at 2 mo and followed at 4, 6, and 7.5 mo. Ca. 70% of retinal ganglion cells were co-transduced by both vectors ($N = 4$). Treated mice showed a significant delay in visual acuity decline ($N \geq 4$) and preservation of retinal ganglion cell function compared with untreated controls ($N \geq 4$). Immunostainings demonstrated partial restoration of WFS1 protein expression in the retina ($N = 4$). Age-matched untreated and vector-only controls were included.Together, these results establish the *Wfs1*^{Q670X} mouse as a robust and clinically relevant model of WS and provide the first in vivo evidence that precise ABE-mediated correction can restore disease protein expression and slow neurodegeneration. This work highlights base editing as a groundbreaking, mutation-specific therapeutic strategy with broad implications for previously untreatable rare neurodegenerative diseases.

Disclosures: S. Bergmans: None. **M. Bulcaen:** None. **F. Fatemeharefeh:** None. **M. Carlon:** None. **C. verfaillie:** None. **L. Moons:** None. **L. De Groef:** None.

Poster

PSTR039: Gene, Protein, or Cell Based Approaches

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.17/LL8

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

Title: High plex proteomics illuminate the functional layers of microglial biology: post-transcriptionally regulated activation states, high-throughput secretome profiling reveals immunomodulatory efficacy, and cross-organ toxicity.

Authors: *A. ROSENBLOOM[1], N. ROBICHAUD[2], K. EDWARDSON[3], N. RASHIDI[2], M. KAMPMANN[4], M. DAGHER[2];
[1]Nomic Bio, Woodinville, WA; [2]Nomic Bio, Montreal, QC, Canada; [3]Nomic Bio, Toronto, ON, Canada; [4]Inst. for Neurodegenerative Dis., UCSF, San Francisco, CA

Abstract: Microglial dysregulation is implicated in neurodegeneration. Defining microglial function in response to perturbation and identifying safe immunomodulatory therapies requires capturing the breadth of inflammatory proteins, and concurrent signals of toxicity, inaccessible with conventional proteomic technologies. Here we apply high-throughput proteomics (Nomic Omni 1000, >1000 proteins) to capture the microglial activation and response. Selective modulation of activation states is a potential therapeutic target. We collaborated with Martin Kampmann at UCSF to use CRISPRi screens in microglia to identify gene targets that regulate 6 distinct microglial states, including interferon responsiveness state and chemokine expressing state. Transcriptomics identified 3 gene hits with broad effects across multiple activation states, but not the chemokine expressing state, and were profiled with Omni 1000 to investigate proteomic changes invisible to transcriptomics. The effect of all 3 hits on the interferon-responsive state was validated by both mRNA and protein. However, transcriptomics was blind to the chemokine state. We observed that each hit produced robust regulation of secreted chemokines detectable only by proteomics, alongside protein-specific cell death markers and soluble shed receptors; and therefore, missed post-transcriptionally regulated proteins, yielding high false-negative rates for functionally relevant hits. In a perturbation screen of 510 bioactive compounds in LPS-stimulated microglia (>6.5 million data points), LPS induced expected TNFα, IL1β, IL6, IL12 p40, and ISG15. Approximately 1/3 of compounds suppressed inflammation; 1/4 of those showed cytotoxicity, distinguishable by leakage of intracellular proteins. This resolution separated mechanistically distinct hits: methylprednisolone selectively blocked cytokine expression, whereas staurosporine, a potent TNFα inhibitor, instead drove broad intracellular protein release (cell death). Critically, protein profiling across organ specific cell lines was able to predict cross-organ safety liabilities. The HSP90 inhibitor onalespib reduces LPS-induced inflammation, but in cardiomyocytes, cell death associated proteins were highly detected, consistent with class-wide HSP90 cardiotoxicity. In hepatocytes, methylprednisolone produced paradoxical induction of IL6 and SAA, recapitulating the hepatic immune activation reported with high-dose systemic exposure. These results establish functional proteomics as a necessary data layer; simultaneously resolving post-transcriptional regulation, compound efficacy, and multi-organ safety.

Disclosures: A. Rosenbloom: A. Employment/Salary (full or part-time):; Nomic Bio. **N. Robichaud:** A. Employment/Salary (full or part-time):; Nomic Bio. **K. Edwardson:** A. Employment/Salary (full or part-time):; Nomic Bio. **N. Rashidi:** A. Employment/Salary (full or part-time):; Nomic Bio. **M. Kampmann:** None. **M. Dagher:** A. Employment/Salary (full or part-time):; Nomic Bio.

Poster

PSTR040: Optogenetic

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.01/LL9

Topic: J.08. Methods to Modulate Neural Activity

Support: NRF RS-2022-NR067861
NRF RS-2020-NR048354

Title: Imaging electrically evoked retinal activity in degenerated retina of rd1 blind mice using genetically encoded fluorescent indicators

Authors: Y. JUNG[1], B. J. BAKER[1], ***Y.-K. SONG**[2,3];
[1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Applied Bioengineering, [3]Res. Inst. for Convergence Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Retinal prostheses seek to restore vision by electrically activating surviving neurons in degenerated retina, but improvement requires tools that reveal how retinal circuits respond to stimulation with cellular and temporal precision. Here, genetically encoded fluorescent indicators were used to map activity in retinal ganglion cells (RGCs) from photoreceptor-degenerated rd1 blind mice. The voltage indicator Bongwoori-R3 [1] and calcium indicator GCaMP6f [2] were virally expressed in RGCs and imaged with high-speed one-photon fluorescence microscopy during simultaneous patch-clamp recording or epi-retinal microelectrode stimulation. Both indicators reported current-evoked activity, but they provided complementary information. GCaMP6f produced large calcium-dependent fluorescence changes associated with action potential firing, whereas Bongwoori-R3 directly tracked membrane voltage with faster kinetics and millisecond-scale resolution. Bongwoori-R3 imaging detected somatic action potentials, subthreshold depolarization, hyperpolarization, and voltage propagation into axon bundles, responses that are difficult to resolve with calcium imaging alone. Voltage imaging also revealed spatially distributed activity, including responses in neighboring RGCs during stimulated firing and evidence of electrical coupling consistent with gap-junction communication. [3] Frame-subtraction analysis separated voltage-dependent membrane signals from slower pH-related fluorescence changes, improving interpretation of recordings in retinal explants. During epi-retinal stimulation, Bongwoori-R3 reported spatially defined responses while avoiding stimulus artifacts that often limit electrophysiology. The optical responses depended on pulse phase, duration, and frequency, demonstrating the ability of voltage imaging to visualize spatiotemporal activation across degenerated retinal tissue. These results show that genetically encoded voltage

and calcium indicators are complementary tools for dissecting retinal circuit function in disease models. Bongwoori-R3-based voltage imaging provides a direct, artifact-resistant approach for monitoring electrically evoked membrane dynamics with cellular precision and may guide stimulation strategies for next-generation visual prostheses.
References: [1] S. Lee et al., *Sci. Rep.* 2017, **7**, 8286. [2] Y.-C. Chang et al., *J. Neural Eng.* 2019, **16**, 026017. [3] Y. Jung et al., *ACS Chem. Neurosci.* 2025, **16**, 4711−4724.

Disclosures: Y. Jung: None. **B.J. Baker:** None. **Y. Song:** None.

Poster

PSTR040: Optogenetic

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.02/LL10

Topic: J.08. Methods to Modulate Neural Activity

Support: NIMH Grant 1R43MH139287

Title: High-bandwidth all-optical electrophysiology using s-TeFo imaging and 3D holography

Authors: B. OZBAY[1], Y. ATLAS[2], O. ASSAYAG[2], ***K. KILBORN**[1];
[1]3i, Denver, CO; [2]Intelligent Imaging Innovations SAS, Paris, France

Abstract: In systems neuroscience, one kind of ideal experiment involves being able to record the activity of thousands of neurons *in vivo*, across multiple cortical layers or subcortical regions, while also selectively inducing activity patterns in subsets of these same neurons. While advances in genetically-encoded calcium indicators and optogenetics make such experiments theoretically possible, readily-available optical microscopes necessary to fully support these experiments do not yet exist.
Significant academic research has already been conducted in two distinct areas of photonics: 1) volumetric imaging of neuroactivity at physiologically relevant rates and cellular resolution, and 2) using computer-generated holography to selectively activate optogenetically-labeled neurons within similar volumes. However, most work in volumetric functional imaging has not included real-time optical neuro-stimulation, and most work in 3D stimulation has been paired with conventional single-plane imaging.
We present a microscope design that combines fast, unbiased, volumetric imaging using scanned temporal focusing (s-TeFo) two-photon imaging with two different forms of scanless 3D holography, 3D-SHOT and MTF-CGH, to address this technical need.
The underlying principle of s-TeFo is to use a high-pulse-energy laser to create a larger laser illumination spot (on the order of the size of a soma), while maintaining the axial confinement needed for optical sectioning. Compared to typical scanning with a close-to-diffraction-limited spot, s-TeFo allows for much faster scanning and more efficient multiphoton excitation under the "one-pulse-per-pixel" principle. By conceding spatial resolution and focusing on somatic cell activity, tens of frames can be acquired per volume and thousands of neurons can be recorded at

rates consistent with genetically-encoded calcium indicators.
Solutions to technical challenges will be presented that 1) ensure that stimulation patterns that closely mimic physiologically observed patterns can be produced that minimally interfere with recording, 2) stimulation targets can be identified and visualized at different resolutions and scanning modalities, 3) volumetric recording parameters can be optimized to record only from planes of interest, and 4) and power delivered to each target can be closely calibrated.

Disclosures: B. Ozbay: A. Employment/Salary (full or part-time):; 3i. **Y. Atlas:** A. Employment/Salary (full or part-time):; 3i. **O. Assayag:** A. Employment/Salary (full or part-time):; 3i. **K. Kilborn:** A. Employment/Salary (full or part-time):; 3i. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 3i.

Poster

PSTR040: Optogenetic

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.03/LL11

Topic: J.08. Methods to Modulate Neural Activity

Support: JSPS KAKENHI Grant Number 23H03416
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Hokkaido University—Hitachi Collaborative Support Program

Title: Modulation of mouse auditory cortical activity by optogenetic theta-burst stimulation

Authors: *T. YOSHIKAWA[1], T. TATENO[2];
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Abstract: Repetitive brain stimulation is a promising approach for treating neurological disorders. Among stimulation paradigms, theta-burst stimulation (TBS; 50-Hz triplet bursts repeated at 5 Hz) is particularly attractive because it can induce post-stimulation modulation lasting approximately 20 min after a brief 40-s protocol, potentially shortening treatment sessions. However, the mechanisms underlying the rapid effects of TBS remain unclear and require further investigation in animal models. In rodents, most TBS studies have focused on the motor cortex, whereas studies in the auditory cortex (AC), a region critical for sound processing, remain comparatively scarce. Moreover, most TBS studies infer circuit mechanisms indirectly, and optogenetic identification of candidate cell types involved in TBS effects remains rare. Here, we used cell-type-specific theta-burst optogenetic stimulation (TBOS) of CaMKIIα-expressing pyramidal neurons to test whether excitatory cortical drive modulates sound-evoked responses in the mouse AC. An adeno-associated viral vector (AAV9-CaMKIIα-hChR2(H134R)-EYFP) was injected into the AC of C57BL/6J mice. Four to five weeks after injection, mice were anesthetized, and extracellular recordings were performed from the exposed AC using a 16-

channel silicon probe. We compared three TBOS conditions within each animal in a counterbalanced order: intermittent TBOS (iTBOS; 2-s bursts delivered every 10 s for a total of 200 s), continuous TBOS (cTBOS; bursts delivered continuously for 40 s), and sham stimulation (0-mW illumination). Sound-evoked activity was quantified by measuring frequency response areas (FRAs), defined as peak negative local field potential amplitudes evoked by tone bursts spanning 4-32 kHz at multiple intensities, before and after each TBOS intervention. Per-pair Δ values (post − pre) of peak FRA amplitude were compared across TBOS conditions. iTBOS significantly reduced peak FRA response amplitude relative to sham. In contrast, cTBOS did not significantly differ from sham. This reduction in sound-evoked responses after iTBOS differs from the facilitatory effect of conventional magnetic iTBS, suggesting that TBOS of pyramidal neurons may engage distinct circuit mechanisms in the AC, possibly through recruitment of compensatory inhibition. Ongoing work will increase the sample size and compare effects across additional cell types. These findings may help clarify TBS mechanisms and inform the optimization of TBS-based interventions for hearing disorders.

Disclosures: T. Yoshikawa: None. **T. Tateno:** None.

Poster

PSTR040: Optogenetic

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Topic: J.08. Methods to Modulate Neural Activity

Support: Max Planck Society
BMBF Grant ME1ZEUS006

Title: Laser-integrated nanophotonic neural probes for dual-color optogenetics

Authors: *D. A. ROSZKO[1,2,3], J. N. STRAGUZZI[1], A. A. LAKUNINA[4], H. CHUA[5], S. KITAMURA[6], K. YANO[6], R. LAWROWSKI[7], M. Z. KHALID[1], F. WEISS[1], M. G. JAMA[7], M. HAGIMOTO[6], G. LO[5], T. A. VALIANTE[8,3,2], J. K. S. POON[2,3], J. H. SIEGLE[4], W. D. SACHER[1,3];
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Abstract: Implantable neural probes for delivering precise optogenetic stimulation enable the control and study of genetically-distinct neural populations in behavior and disease, yet it remains challenging to realize systems with sufficient spatiotemporal resolution, optical power, and usability. To address this, we have developed dual-color laser-integrated nanophotonic neural probes, which feature hybrid-integrated AlGaInP and InGaN laser diodes (LDs), two 16-

channel thermo-optic photonic switching trees with grating coupler emitters (pitch: 130 µm, span: 2 mm) along an implantable silicon shank (length: 6.6 mm, width: 74 µm, thickness: ~110 µm) for addressable photostimulation, 31 TiN electrodes (pitch: 65 µm, span: 2 mm) for electrophysiological recording, and on-chip sensors for optical power monitoring and temperature sensing. Devices were fabricated at a commercial silicon photonics foundry, enabling scalable manufacturing volumes. For control and data acquisition, we also developed a programmable circuit board featuring an Artix-7 field-programmable gate array (FPGA), 4-channel laser diode driver (LDD), three 16-channel digital to analog converters (DACs) for controlling the photonic switches, and four analog to digital converters (ADCs) for measuring electrophysiological, photodetector, and thermistor signals. Using laser surface roughening, we reduced electrode impedances from a nominal impedance of 17.7 ± 7.3 MΩ (mean ± SD; n=93 electrodes from 3 probes) to 0.67 ± 0.33 MΩ (n=93 electrodes from 3 probes) to improve recording signal quality. Using an external optical power meter, we measured the emitter optical power for blue and red photostimulation as 8.6 ± 1.8 µW (n=42 emitters from 3 probes, LD current: 80 mA) and 77 ± 26 µW (n=58 emitters from 4 probes, LD current: 70 mA) respectively, with variability primarily related to LD alignment for each device. We present preliminary results using nanophotonic probes in combination with Neuropixels 2.0 to investigate the effects of activating dorsal striatum D1 or D2 medium spiny neurons on spiking activity in substantia nigra pars reticulata (n=2 mice expressing CoChR, n=1 mouse expressing ChRmine). In future work, we envision that these laser-integrated nanophotonic neural probes and their associated data acquisition system will enable experiments involving high-resolution optogenetic circuit mapping and sub-millisecond closed-loop photostimulation.

Disclosures: D.A. Roszko: None. **J.N. Straguzzi:** None. **A.A. Lakunina:** None. **H. Chua:** None. **S. Kitamura:** None. **K. Yano:** None. **R. Lawrowski:** None. **M.Z. Khalid:** None. **F. Weiss:** None. **M.G. Jama:** None. **M. Hagimoto:** None. **G. Lo:** None. **T.A. Valiante:** None. **J.K.S. Poon:** None. **J.H. Siegle:** None. **W.D. Sacher:** None.

Poster

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Program #/Poster #: PSTR040.05/LL13

Topic: J.08. Methods to Modulate Neural Activity

Title: Genotyping-Free Identification of ChR2 Mice by noninvasive optogenetic Activation of Vibrissa

Authors: M. SAHIN[1], B. SOLGUN[2], H. EREN[3], E. ERDENER[2], *T. DALKARA[1];
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Abstract: Accurate identification of opsin-expressing transgenic animals is essential for optogenetic studies. Because PCR-based genotyping may be affected by technical and handling errors and does not directly assess transgene function, we developed a rapid, minimally invasive method for identifying Thy1-channelrhodopsin-2 (ChR2)-yellow fluorescent protein (YFP) mice using non-invasive optical stimulation of the facial nerve. Optical access to the proximal facial nerve was achieved through an optical fiber positioned in the external auditory canal. Blue light stimulation (450 nm, 1-10 Hz, 1-10 ms, 1.1-10 mW) evoked immediate, stereotyped ipsilateral whisker movements, confirming functionally sufficient ChR2 expression. Optically evoked responses were readily distinguished from spontaneous whisking by their temporal locking to stimulation frequency and remained evident at the lowest tested parameters (1.1 mW, 1 ms, 1 Hz). Responses were observed in homozygous, heterozygous, and juvenile Thy1-ChR2-YFP mice (4-24 weeks of age) of both sexes following stimulation through external auditory canal on both sides. Functional screening of 58 animals showed complete concordance with confirmed genotype assignment. The procedure was effective in both anesthetized (isoflurane or ketamine) and awake animals without causing pain or parasympathetic responses. As an anatomical correlate of functional screening, endogenous ChR2-YFP fluorescence was visualized in peripheral axons by confocal imaging of whole-mount auricular preparations. Robust YFP-positive axons were readily detected without immunohistochemical processing of semi-transparent PFA-fixed pinna. These findings demonstrate that transgene expression can be verified within seconds through direct functional assessment rather than inferred from genotype assignment. This approach may prevent the inclusion of incorrectly classified animals in optogenetic experiments and assist in the establishment of breeding colonies. The ability to repeatedly and non-invasively assess facial nerve function may also provide a useful tool for longitudinal studies of peripheral nerve injury and regeneration.

Disclosures: M. Sahin: None. **B. Solgun:** None. **H. Eren:** None. **E. Erdener:** None. **T. Dalkara:** None.

Poster

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Program #/Poster #: PSTR040.06/LL14

Topic: J.08. Methods to Modulate Neural Activity

Support: HHMI Janelia
HHMI

Title: Raster photostimulation of large-scale neural populations

Authors: *P. K. LAFOSSE[1], D. FLICKINGER[1], G. JAINDL[2], A. DRINNENBERG[3], S. GRØDEM[4], K. K. LENSJØ[4], L. SIVERTS[5], H. ZENG[5], B. TASIC[5], T. L. DAIGLE[5], M. FYHN[4], K. DEISSEROTH[3], C. STRINGER[1], M. PACHITARIU[1];

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Abstract: Neural computations underlying behavior and cognition are carried out by neural populations distributed across the brain. The ability to record and control activity at a large scale is thus critical for understanding how these computations are implemented across brain networks. State-of-the-art photo-activation experiments allow for causal manipulations of select neurons, but these methods have generally been limited to small numbers of neurons or small areas in the brain. To greatly increase the number of photo-activated neurons, we developed a new raster photostimulation system to control thousands of neurons across a large 5 mm field-of-view using a two-photon mesoscope. We routed the photostimulation laser into the same optical path used for imaging, independently gating it to activate specific neurons during recordings. Our method allows for pixel-level precision to photostimulate patterns containing thousands of neurons in a single imaging frame, and the ability to update patterns on a frame-by-frame basis. In mice expressing a GCaMP indicator and ChRmine opsin in neurons, we show successful photoactivation in a majority of neurons using patterns of more than 1,000 targets. Further, we demonstrate that we can successfully activate neurons using different point-spread functions and also using a standard, commercial two-photon microscope, indicating our approach works well across different systems. While raster photostimulation lacks the same temporal control relative to other methods due to the nature of the scanning, it provides an easy-to-use system with high spatial precision, low relative cost, and the ability to photostimulate up to and beyond thousands of neurons.

Disclosures: P.K. LaFosse: None. **D. Flickinger:** None. **G. Jaindl:** A. Employment/Salary (full or part-time):; MBF Biosciences. **A. Drinnenberg:** None. **S. Grødem:** None. **K.K. Lensjø:** None. **L. Siverts:** None. **H. Zeng:** None. **B. Tasic:** None. **T.L. Daigle:** None. **M. Fyhn:** None. **K. Deisseroth:** F. Consulting Fees (e.g., advisory boards); Stellaromics, Maplight Therapeutics. Other; Modulight.bio, RedTree. **C. Stringer:** None. **M. Pachitariu:** None.

Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: DFG Walter Benjamin MA10161/1-1

Title: High fidelity all-optical manipulation of Drosophila brain across scales , from neuronal populations to neuronal sub-compartments

Authors: *N. MANCINI[1], I. A. OLDENBURG[2], H. ADESNIK[3], S. S. BIDAYE[4];
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[3]Univ. of California, Berkeley, Berkeley, CA; [4]Max Planck Florida Inst. For Neurosci., Jupiter, FL

Abstract: We leverage a new experimental platform that allows simultaneous two-photon holographic stimulation with fast volumetric imaging in the tractable brain of *Drosophila melanogaster*. Formerly used in mice, this strategy helps us to calibrate our stimulation parameters, stimulate specific neuronal compartments (i.e. dendrites, soma, spike initiation zone), and address how specific neuronal activity profiles in these compartments causally relate to complex and potentially previously uncharacterized behaviors in a tractable model organism such as the fruit fly. Using ex-vivo fly brain preparations, we first characterize various light-activated Channelrhodopsin variants (CsChrimson, ChrimsonR, Chrome, Chrome2f, Chrmine) by targeting a population of olfactory projection neurons (PNs). We then generate high-fidelity activity patterns in the PNs and simultaneously perform volumetric imaging. Finally, we validate our approach by specifically targeting sub-neuronal compartments of a command-like neurons to elicit specific maneuvers in intact, tethered behaving flies.

Disclosures: N. Mancini: None. **I.A. Oldenburg:** None. **H. Adesnik:** None. **S.S. Bidaye:** None.

Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: DFG grant (ZA990/1-)
ZIAMH002838
ZIAMH002898
ZIAMH002899

Title: Brain-wide optogenetics fMRI and electrophysiology mapping in the marmoset through transcranial light stimulation

Authors: *D. ZALDIVAR[1], M. EPSTEIN-O'ROURKE[3], L. IVES[4], A. RIBEIRO GOMES[5], C. C.-C. YEN[6], L. BAWEKE[7], K. CAMERON[3], C. ROOD[2], D. IDE[8], D. A. LEOPOLD[9]; [1]Natl. Inst. of Mental Hlth. Div. of Intramural Res., Bethesda, MD; [2]Natl. Inst. of Mental Hlth. Div. of Intramural Res., National Institute of Mental Health Division of In, MD; [3]Natl. Inst. of Mental Hlth., Bethesda, MD; [4]NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD; [5]Lab. of Neuropsychology / Section on Cognitive Neurophysiol. and Imaging, Natl. Inst. of Mental Health, Natl. Inst. of Hlth., Bethesda, MD; [6]NINDS, Natl. Institues of Hlth., Bethesda, MD; [7]NIH, Bethesda, MD; [8]NIMH, Bethesda, MD; [9]NIMH, Bethsda, MD

Abstract: Mapping functional connections across the brain requires methods to measure the downstream effects of local neural excitation. Optogenetic fMRI offers local neural excitation

combined with whole-brain imaging, thus enabling the systematic mapping of brain-wide functional networks. However, optogenetic experiments often require one or more craniotomies. In primate experiments, for example, they are required both to deliver opsins using a virus and to later stimulate the transduced brain tissue with light. These constraints restrict the range of accessible stimulation regions and limit the suitability of this approach for longitudinal studies. Here, we present a minimally invasive transcranial optogenetic mapping approach in the common marmoset that requires no craniotomy and is thus suited for both broad optogenetic mapping and stable, longitudinal studies. Opsins were first introduced broadly across the cortex of four animals using a single prenatal viral injection (Ribeiro Gomes et al., 2026). Optogenetic fMRI and electrophysiological mapping experiments were then carried out more than a year later using a transcranial light stimulation approach, leaving the skull intact. Transcranial light stimulation generated spatially localized, time-locked fMRI and EEG responses in the vicinity of the stimulation site, as well as downstream cortical and subcorticial responses in the fMRI data. Light stimulation was shown to be spatially restricted, as nearby cortical stimulation locations (e.g. two portions of cortical area MT) led to distinct and repeatable activation patterns in downstream areas. Together, these findings demonstrate that transcranial optogenetic stimulation combined with fMRI enables minimally invasive, brain-wide causal mapping of functional networks in the primate brain. This scalable platform supports longitudinal physiological and behavioral investigations and provides a powerful framework for studying circuit organization, development, and plasticity in species that lack established genetic tools.

Disclosures: D. Zaldivar: None. **M. Epstein-O'Rourke:** None. **L. Ives:** None. **A. Ribeiro Gomes:** None. **C.C. Yen:** None. **L. Baweke:** None. **K. Cameron:** None. **C. Rood:** None. **D. Ide:** None. **D.A. Leopold:** None.

Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: Government of Canada New Frontiers in Research Fund–Transformation. NFRFT-2020-00238
Canadian Institutes of Health Research. Grant no. 191895

Title: A tether-free and hadstage-free light delivery implant for precision optogenetic modulation with stimulation parameters changeable after implantation in small rodents

Authors: S. SHALILEH[1], S. TRETJAKOV[2], A. MOALLEMI[3], E. MOHSENI VADEGHANI[1], W. TETZLAFF[4], ***D. SHAHRIARI**[5];
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Abstract: A fully implantable and battery-powered device is presented for both brain and spinal cord optogenetic stimulation at precise anatomical locations in mice and rats. The stimulation parameters can be changed on-the-fly without animal restriction or special housing. In addition to be completely free of tethers or a headstage, the implant stimulation parameters in every animal can be separately controlled even when group housed, which uniquely enables social behavior studies. The implant contains 1) neural probes with embedded µLEDs as the light source, 2) an electronic module that separately controls each light source with stimulation parameters changeable by the user and 3) a rechargeable implanted battery to power the entire device. After weeks of stimulation, the implanted battery can be recharged over the skin within 10 minutes without the need to anesthetize the animal while using commercially available chargers. Requiring minimal custom fabrication, the platform can be readily adapted to different stimulation parameters in different neuroscience labs. Data is shown for i*n vivo* studies in both mice and rats, which demonstrated stable operation for over a month. As a functional demonstration, targeted optical activation of inhibitory interneurons in transgenic mice produced reproducible and reversible hindlimb paralysis without operator intervention. Together, this platform provides a completely implantable system for chronic optogenetic neuromodulation in freely behaving animal models.

Disclosures: D. Shahriari: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application holder. Potential commecialization opprotunity.

Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: Air Force Office of Scientific Research FA9550-23-1-0701
Air Force Office of Scientific Research FA9550-26-1-0004 - AFOSR (MURI)
NIH New Innovator Award DP2MH136494

Title: Depth-Resolved Optogenetic Control of Cortical Circuits using MicroLED Integrated Silicon Probes

Authors: *D. MAO[1,2], C. SHR[2], K. JAYANT[2,3];
[2]Weldon Sch. of Biomed. engineering, [3]Purdue Inst. for Integrative Neurosci., [1]Purdue Univ., West Lafayette, IN

Abstract: Dissecting how cortical layers and regions contribute to sensory processing demands tools that combine spatially precise perturbation with simultaneous, depth-resolved recording. We introduce an integrated silicon probe platform supporting high-density electrophysiology alongside single- and dual-color optogenetic stimulation (blue and red LEDs), scalable from

single-region laminar interrogation to multi-region and thalamocortical circuits. In a characterized embodiment — 32 independently addressable blue microLEDs and 64 recording electrodes spanning 1.6 mm of cortical depth — the probe delivers localized stimulation with minimal thermal impact (<1°C) and low electrode impedance (41.0 ± 5.0 kΩ at 1 kHz). Implanted in the primary somatosensory cortex of ChR2-expressing mice, it resolved 34 photo-responsive units across layers 4-6, whose firing-rate gains and activation latencies scaled monotonically with stimulation-recording distance — a direct signature of layer-specific recruitment. During an active whisker-based go/no-go task, layer-selective stimulation produced distinct changes in goal-directed processing, implicating individual cortical layers in sensorimotor control. These results establish integrated multicolor high-density microLED probes as a precision platform for causally linking laminar and interregional circuit dynamics to perception and behavior.

Disclosures: D. Mao: None. **C. Shr:** None. **K. Jayant:** None.

Poster

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Support: NIH Grant RF1NS128895-01
NSF GRFP Fellowship
Ruth K Broad Fellowship SPS 303289
NIH F31 Fellowship 5F31EY037507-02

Title: Optimization of single-neuron and ensemble photostimulation in larval zebrafish

Authors: *O. TRAUBERT[1], J. MORRA[2], J. A. ATKINSON[3], K. FOUKE[4], E. A. NAUMANN[2];
[1]Biomed. Engin., [2]Neurobio., Duke Univ., Durham, NC; [3]Duke Univ., Durham, NC, ; [4]Duke Univ., Durham, NC

Abstract: Holographic two-photon optogenetic photostimulation enables precise targeting of individual neurons, yet identifying stimulation strategies that reliably evoke desired activity while minimizing phototoxicity remains a central challenge. Because physiological neural activity emerges from coordinated firing of neural ensembles, approaches for both single-neuron and ensemble photostimulation are needed. We developed an all-optical approach for simultaneous photostimulation and calcium imaging in translucent larval zebrafish expressing the red-shifted opsin rsChRmine in excitatory neurons and the calcium indicator GCaMP6s panneuronally. To maximize the reliability of above-threshold responses in targeted neurons, we systematically explored the photostimulation parameter space, including laser power, pulse duration, pulse interval, and scan pattern. In addition, we explored strategies for photostimulating

neural ensembles to maximize population response levels and response reliability. Guided by opsin kinetics, we identified a regime in pulse duration and interval that produced consistent effects in targeted neurons and quantified the effects of laser power and scan pattern on photostimulation efficacy. While globally optimal stimulation parameters maximized photostimulation success across the population, cell-specific parameter optimization achieved comparable performance with reduced stimulation requirements. To improve ensemble photostimulation, we devised strategies for selecting neuronal ensembles. We evaluated response reliability within targeted ensembles and compared photostimulation-evoked and physiologically occurring population activity. To efficiently identify optimal parameters during the experiment, we modeled single-neuron responses to photostimulation using Bayesian optimization. This approach identified effective stimulation parameters using substantially fewer test stimulations than exhaustive grid search while maintaining performance comparable to population-optimal parameters. Together, these results establish a framework for efficient calibration of photostimulation parameters and provide a foundation for reproducing physiologically relevant patterns of neural activity with cellular precision.

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Poster

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Program #/Poster #: PSTR040.12/LL20

Topic: J.08. Methods to Modulate Neural Activity

Title: Modeling neuronal diseases with automatically generated iPSC-derived dorsal forebrain 3D organoids

Authors: *O. SIRENKO[1], L. CHEW[2], P. MACHA[1], E. F. CROMWELL[3];
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Abstract: iPSC-derived 3D organoids represent a rapidly advancing technology with significant potential for understanding brain physiology and modeling neurological diseases. However, the development of dorsal forebrain organoids from iPSCs is a complex and variable process, which presents challenges for scalable compound screening. We developed automated workflow for the generation and analysis of neural organoids using the CellXpress.ai system, the FLIPR system, and HCS.ai imaging system. The CellXpress.ai system automates organoid culture, media exchanges, controlled agitation, and monitoring via automated imaging. Morphological characterization of developing organoids was performed using confocal imaging for neural markers TUJ1, MAP2, and GFAP. Functional characterization of spontaneous neuronal activity was assessed through kinetic recording and analysis of calcium oscillations. Calcium dynamics were measured using FLIPR or HCS.ai systems following loading of organoids with Calcium 6

dye. Synchronous activity patterns were analyzed using quantifying peak count, amplitude, and peak width. Organoids displaying asynchronous activity were evaluated using HCS.ai system by imaging and measuring fluorescence intensity fluctuations across regions or individual cells. For pharmacological characterization, organoids exhibiting robust and well-defined synchronous oscillations (approximately 40-50% of samples) were selected. Benchmark compounds demonstrated expected functional responses: AMPA and 4-aminopyridine induced dose-dependent increases in oscillation frequency, while GABA reduced oscillatory activity. Additional compounds, including bicuculline, NMDA, and memantine, produced characteristic modulation of calcium signaling patterns. Furthermore, dorsal forebrain organoids were applied to model neurological conditions such as epilepsy and traumatic brain injury (TBI). Epileptiform activity was induced by 4-AP, resulting in increased oscillation frequency after 30 minutes of exposure, followed by attenuation upon treatment with valproic acid. TBI was modeled by applying pressure pulses (1-3 atm) using a PuMA microfluidic system. TBI-like events significantly disrupted neuronal activity, as evidenced by reduced synchronous calcium oscillations. Notably, neuronal activity was partially restored following treatment with 4-AP. In addition, TBI-like conditions led to a modest decrease in cell viability after 48 hours. This integrated platform combining automated culture and advanced functional analytics demonstrates a scalable solution for disease modeling and compound screening.

Disclosures: O. Sirenko: A. Employment/Salary (full or part-time):; Molecular Devices, LLC. **L. Chew:** A. Employment/Salary (full or part-time):; STEMCELL Technologies. **P. Macha:** A. Employment/Salary (full or part-time):; Molecular Devices, LLC. **E.F. Cromwell:** A. Employment/Salary (full or part-time):; Protein Fluidics.

Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant R01NS118188

Title: Using multi-site optogenetic stimulation to enhance the firing frequency of ChR2 in peripheral nerves

Authors: *T. A. WELTON[1,2], T. R. CURRIE[2], A. FONTAINE[2], J. H. CALDWELL[3], R. F. WEIR[2], D. RESTREPO[1,3], E. A. GIBSON[2];
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Abstract: Optogenetics is being considered as an alternative to electrical stimulation in the field of bioelectric medicine. The maximal stimulation frequency during an optogenetic experiment is limited by the photokinetics of the selected opsin variant. Despite its relatively slow kinetics,

Channelrodopsin-2 (ChR2) is one of the most widely available and commonly used opsin variants in neuroscience research today. In this work, we investigate whether two-site, spatiotemporal optical stimulation can be used to bypass the frequency limits of ChR2 in peripheral nerves. We named this spatiotemporal stimulation technique "Drumbeat" optogenetic stimulation because the light is bounced back and forth between two stimulation sites along the length of the nerve. We evaluated the efficacy of drumbeat stimulation using compound action potential (CAP) recordings from *ex-vivo* sciatic nerves and electrocardiogram recordings from optogenetic vagus nerve stimulation (VNS) in mice expressing ChR2(H134R) in cholinergic neurons. Drumbeat stimulation of *ex-vivo* sciatic nerves significantly reduced the overall decay in the peak amplitude of successive CAPs compared to single site stimulation at frequencies ≥ 30 Hz. Three seconds of drumbeat VNS elicited significantly larger drops in heart rate at both 30 and 60 Hz compared to single site stimulation. At 60 Hz, drumbeat VNS restored the physiological response which was virtually eliminated during single-site VNS. Together these results show that multi-site spatiotemporal stimulation can be used to effectively enhance optogenetic firing of ChR2 in peripheral nerves.

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Poster

PSTR040: Optogenetic

Location: WCC Halls A-C

Time: Saturday, November 14, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.14/LL22

Topic: J.08. Methods to Modulate Neural Activity

Title: State-dependence of closed-loop optogenetic control of mesoscale cortical dynamics

Authors: *A. DEOLE[1], A. LI[4], E. T. SHEA-BROWN[2], N. A. STEINMETZ[3];
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Abstract: Mesoscale cortical activity is typically perturbed open-loop; whether active feedback control can reliably regulate it, and what limits that control, remains unclear. We developed a data-driven, closed-loop optogenetic controller for population activity and used control-theoretic analysis to show its performance is systematically shaped by brain state. Adult transgenic mice co-expressing GCaMP8s and an opsin (ChrimsonR in inhibitory neurons; n=3 mice, 13 sessions). Wide-field calcium imaging (35 Hz) provided real-time feedback of a target cortical region's activity while a galvanometer-steered laser stimulated the region. Trial-averaged responses were well captured by a low-order linear time-invariant (LTI) model fit to impulse- and step-responses (0-1.8 mW, ~90 trials/amplitude; R^2=0.51-0.99). Using the LTI assumptions, we derived a proportional-integral controller to enable closed-loop steering despite deviations from linearity. Such closed-loop control, moreover, enables rejection of 'disturbances' of the target activity, i.e., idiosyncratic fluctuations in activity due to non-linear dynamics, changing

brain states, or external inputs. Using the controller to steer activity along a desired time course (reference tracking), cross-trial variance and per-trial tracking error (MSE) were reduced (40.7%, signed-rank p=0.0005; and 19.3%, p=0.0002). We reasoned that, by the internal model principle, a good regulator implicitly embodies a model of the system, so trials it fails to track correspond to states where dynamics depart from that model. Using this logic, we found that two independent state variables shaped controllability through opposite mechanisms. Disturbances associated with mouse movement (assessed by video of the mouse's face) were rejectable disturbances, in that open-loop tracking degraded as movement increased whereas closed-loop tracking did not, so the closed-loop advantage was greatest during trials with high movement (interaction p=0.039). However, pre-stimulus activity variance was irreducible: high-variance trials tracked worse for both open- and closed-loop conditions (per-session rank correlation p=0.0017, 12/13 sessions; excluding trials with movement). We infer that in these less-predictable states the internal model no longer fits and feedback cannot compensate. In the future, a state-dependent model may therefore improve reference tracking in all states. In sum, the closed-loop controller successfully regulates mesoscale cortical dynamics and reveals a dissociation between state changes corresponding to movement and to spontaneous internal fluctuations.

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Poster

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Topic: I.08. Learning and Memory

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Title: An all-optical platform for naturalistic visual information encoding and decoding in in vitro biological neural networks

Authors: *S. OMIDI[1], Y. BERDICHEVSKY[1,2];
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Abstract: Title: An all-optical platform for naturalistic visual information encoding and decoding in in vitro biological neural networks Organoid Intelligence (OI) proposes that the computational properties of biological neural networks (BNNs) can be used for energy-efficient information processing, with potential advantages over silicon-based artificial systems. In vitro BNNs, with their intrinsic recurrent connectivity, have demonstrated the capacity to perform complex spatiotemporal information processing tasks, such as pattern recognition. In this study, dissociated primary rat cortical neurons were cultured to form BNNs, and interfaced using an all-

optical system for stimulation and recording. An image recognition task was selected as a spatiotemporal encoding and decoding task. Naturalistic images were transformed into 9×9 spatial grids, with luminance values mapped to optical stimulation pulse rates to encode temporal dynamics. A digital micromirror device (DMD) pattern illuminator delivered patterns of optical pulses to Channelrhodopsin (ChR2)-expressing neurons across 20 distinct images, while network activity was simultaneously recorded via calcium imaging using the genetically encoded indicator jRGECO1a. Post-stimulus network activity, recorded during a silent period where no stimulation was delivered, was decoded using a multiclass Support-Vector-Machine (SVM) classifier to assess how long stimulus information remained classifiable. Classification accuracy was significantly above chance (5% for a 20-class dataset), and network activity remained decodable for up to 200 ms following stimulus offset. This demonstrates a fading memory of stimulus identity in the BNN. Memory was further evaluated by calculating separability of network states after delivery of different stimuli. Separability was quantified by calculating the dot-product of each pair of patterns and their respective averages. Inter-pattern discriminability was expressed as a modified Z-score of Fisher LDA separation and was consistent with the SVM classification results. Preliminary pharmacological experiments suggest that blocking NMDA receptors (D-AP5), L-type calcium channels (Nimodipine), and GABA-B receptors (CGP55845) reduces stimulus decoding accuracy and modified Z-score separability analysis, indicating these pathways contribute to stimulus information retention. This all-optical BNN platform provides a framework for spatiotemporal biocomputing with naturalistic sensory inputs and a tool for probing the pharmacological mechanisms underlying biological information processing, contributing toward OI systems.

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