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Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

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

Title: Beyond the Neural Plate: Neurogenic Stem Cell Niches in the Early Human Embryo

Authors: *I. BYSTRON;
Univ. of Oxford, Oxford, United Kingdom

Abstract: Early human embryonic development is characterized by rapid neurogenesis, primarily orchestrated within the neural tube and neurogenic placodes. Here, we present novel data extending our understanding of ectodermal neurogenic fields.We used a battery of markers to reveal the phenotypic characteristics and migratory potential of the earliest neurons of the human forebrain. Embryos from Carnegie stages (CS) 10-18 (29-43 days post-conception) were obtained from the Human Developmental Biology Resource UK. Migratory neurons were reconstructed by rapid, high-resolution volume rendering of multichannel 3D confocal data sets from a Zeiss confocal microscope.Neuronal development in the human retina starts with precocious bipolar neurons invading the retina from the ventral diencephalon. These cells, which we call **Meitar neurons**, are distinct from 'predecessor' cells, the first neurons to migrate into the prospective cortex. Although they don't express axonal markers GAP43 and Tag1, it's possible both populations interact intimately with basal processes of local stem cells. Moreover, we found precocious neurons scattered through the ectoderm surrounding the forebrain. Some of these unusual cells migrate into mesenchyme, extending TU20-positive processes into pigment and neural retina; others penetrate the presumptive cortical wall. Furthermore, the oral ectoderm of the invaginating Rathke's pouch, traditionally non-neurogenic, generates migratory neurons. These TU-20 positive cells resemble early olfactory placode neurons penetrating the brain. Calbindin (CB) immunoreactivity in cycling progenitors of the olfactory placode, dorsal diencephalon, and the ciliary margin of the developing retina suggests newborn neurons here, utilizing CB, contribute to olfactory bulb, thalamus, and retina formation.These results reshape our understanding of neurogenic stem cell niches in early human embryos, revealing novel migratory pathways from previously overlooked ectodermal and brain regions.

Disclosures: I. Bystron: None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant AG060238
NIH Grant AG062251
NIH Grant AG033570
NIH Grant AG076940

Title: Caveolin-1 autonomously regulates neurogenesis via mitochondrial dynamics

Authors: *D. PATEL;
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Abstract: Adult hippocampal neurogenesis (AHN) plays instrumental roles in learning and memory. However, the mechanisms underlying AHN are not fully understood. Understanding the signals that regulate AHN has implications for brain function and therapy. Here we show that Caveolin-1 (Cav-1), a protein that is highly enriched in endothelial cells and the principal component of caveolae, autonomously regulates neurogenesis. CRISPR-sham (Cav-1WT) and CRISPR/Cas9-edited (Cav-1KO) human induced-pluripotent stem cells were differentiated into neural progenitor cells (NPCs), precursor cells and forebrain neurons. Deletion of Cav-1 in neural progenitor cells led to reduced neural stem cells proliferation and enhanced neuronal differentiation. Importantly, Cav-1 was localized to the mitochondria in neural progenitor cells. Proteomic analysis validated that Cav-1 plays a role in mitochondrial pathways in neural progenitor cells. Examination of mitochondrial morphology in Cav-1WT and KO suggests that Cav-1 may modulate mitochondrial fission-fusion, a critical process in neurogenesis. These results suggest that Cav-1 is a novel regulator of AHN and underscore the impact of AHN on cognition.

Disclosures: D. Patel: None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: Apex Biotech Research Pty Ltd: 281589068

Title: Psmd13, a proteasome regulatory subunit identified in miR-29a regulation during neurogenesis

Authors: *D. KURIAKOSE, Z.-C. XIAO;
Monash Univ., Melbourne, Australia

Abstract: miR-29a is a microRNA critical for neuronal development and implicated in neurodegenerative diseases; however, its upstream regulatory mechanisms remain unclear. To elucidate regulators of miR-29a, we leveraged the genetic diversity of 54 Collaborative Cross (CC) mouse strains and performed miR expression profiling with Quantitative Trait Locus (QTL) mapping. A significant QTL on chromosome 7 was identified, and Psmd13, a non-ATPase subunit of the 26S proteasome, emerged as a top candidate. RNAi-mediated knockdown of Psmd13 in mouse neural precursor cells (mNPCs) enhanced neuronal differentiation and modulated miR-29a expression in a differentiation-dependent manner: upregulated in undifferentiated cells and downregulated upon differentiation. Co-immunoprecipitation revealed Psmd13 associates with Dicer, and ChIP-seq demonstrated Psmd13-Dicer co-binding at miR-29a loci and other genomic sites enriched for chromatin and neuronal activity functions. This co-binding was dynamic and differentiation dependent. Small RNA sequencing confirmed widespread miR dysregulation after Psmd13 depletion, with greater changes in the differentiated state. Psmd13 knockdown altered Dicer localization and reduced its binding at miR-29a in differentiated cells. Moreover, proteasome inhibition using MG132 decreased Psmd13 and Dicer levels, downregulated miR-29a, and impaired neuronal differentiation. These findings reveal a proteasome-linked regulatory axis wherein Psmd13 modulates Dicer stability and chromatin association to control miR-29a expression and neuronal differentiation. This work uncovers a novel, differentiation-dependent mechanism of miR-29a transcriptional regulation, positioning Psmd13 as a key integrator of proteasomal activity, miR biogenesis, and neurodevelopmental homeostasis.

Disclosures: D. Kuriakose: A. Employment/Salary (full or part-time): Full-time, Monash University. **Z. Xiao:** A. Employment/Salary (full or part-time): Monash University, Zhejiang University.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Title: Defining alpha-B Crystallin (Cryab) expression in progenitor subtypes of the developing mouse neocortex

Authors: *Z. SHOKOOHI, Z. LI, T. F. HAYDAR;
Anat. & Neurobio., Boston Univ. Sch. of Med., Boston, MA

Abstract: The developing neocortex contains a diverse array of progenitor subtypes, including apical intermediate progenitors (aIPCs), basal radial glia (bRG), and truncated radial glia (tRG),

some of which have been primarily associated with gyrencephalic species. However, emerging evidence suggests that precursor morphotypes such as bRGs and short progenitors also exist in lissencephalic brains, prompting interest in molecular markers like *Cryab* that may distinguish these populations. While *Cryab* is reportedly expressed by tRG in primate and ferret cortical development, its expression pattern and cell-type specificity in the mouse forebrain remains poorly defined.To address this gap, we developed and validated a novel Cre plasmid tool driven by the *Cryab* promoter, and have used it together with a CAG-Stoplight dual reporter, to genetically label *Cryab*-expressing cells via in utero electroporation (IUE) at E14 in mouse fetal neocortex. After 24 hours, we analyzed electroporated brains using immunohistochemistry (IHC) and RNAscope for known progenitor markers (e.g. Sox2, Tbr2) to determine the spatial distribution and cell-type identity of *Cryab*$^+$ cells in the ventricular (VZ) and subventricular zones (SVZ). Our analysis reveals that *Cryab* is expressed across multiple progenitor subtypes, including both radial glia and IPCs, with no apparent specificity for aIPCs, suggesting that *Cryab* may have a broader biological role in progenitor dynamics than previously hypothesized.To identify *Cryab*-expressing cells not accessible by IUE, we will leverage our single-nucleus RNA sequencing (snRNA-seq) dataset from the mouse telencephalon to map *Cryab* expression across defined cell clusters. This multi-modal strategy will allow us to quantitatively define the timing, distribution, and identity of *Cryab*$^+$ progenitors during mouse cortical development. By resolving *Cryab* expression patterns in the lissencephalic brain, our work provides insight into the evolutionary conservation of progenitor diversity.

Disclosures: Z. Shokoohi: None. **Z. Li:** None. **T.F. Haydar:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: Canadian Institutes of Health Research Grant 264872

Title: Dennd5b regulates neural progenitor cell proliferation and differentiation

Authors: *L. AGUILERA LUNA[1], G. KULASEKARAN[2], P. S. MCPHERSON[3];
[1]Integrated Program in Neurosci., [2]McGill Univ., Montreal, QC, Canada; [3]Dept Neurol. & Neurosurg., Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: Rab GTPases cycle between active (GTP-bound) and inactive (GDP-bound) states, promoting membrane trafficking in their active states. DENN domain-containing proteins activate Rabs via guanine nucleotide exchange factor (GEF) activity, catalyzing the removal of GDP leading to binding of GTP. DENND5B, a DENN family member, has recently been linked to severe neurodevelopmental delay and early-onset seizures in humans. Patient-derived variants span the coding sequence, potentially contributing to observed phenotypic heterogeneity and

variable disease severity. However, the molecular mechanisms and developmental role of DENND5B remain poorly understood. We examined DENND5B expression in mouse brain lysates (E12-P60) and found it is predominantly expressed during early brain development. Using human iPSC-derived neural progenitor cells (NPCs) and lentiviral expression of shRNA, we discovered that DENND5B KD led to an ~20% (mean 18.1%, SD ± 6.8) reduction in NPC proliferation and induced elongated βIII-tubulin-positive processes with growth cone-like structures at their tips, suggesting premature neuronal differentiation. To map its Rab GTPase network, we developed a cell-based Rab recruitment assay and identified 13 Rab GTPases recruited by DENND5B, including Rab6A, Rab6B, Rab15, and Rab33A — many of which are involved in Golgi-mediated trafficking. A catalytically impaired DENND5B mutant revealed that DENND5B functions as a GEF for Rab15, while other Rabs likely serve as binding partners or components of a shared molecular complex. Notably, patient-derived mutations in the RUN1 domain of DENND5B impaired Rab recruitment, pointing to disrupted intracellular trafficking in disease. Our findings demonstrate that DENND5B is essential for maintaining the proliferative capacity of NPCs and preventing premature neuronal differentiation, likely through the regulation of membrane trafficking events. Additionally, the disrupted Rab interactions caused by pathogenic mutations offer mechanistic insights into the neurodevelopmental impairments seen in affected patients.

Disclosures: L. Aguilera Luna: None. **G. Kulasekaran:** None. **P.S. McPherson:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: HD0099813

Title: D-fructose exposure impairs neuronal development in mouse neural progenitor cells

Authors: *J. HERNANDEZ[1], M. BAQUEIRO[2], L. BORA[1], G. HAN[1], M. G. ROSS[3], M. DESAI[1];
[1]Women & Children's Hlth., The Lundquist Inst. at Harbor-UCLA, Torrance, CA; [2]Sch. of Applied Sci., Univ. of Campinas (UNICAMP), Limeira, SP, Brazil; [3]Dept. of Obstetrics & Gynecology, Univ. of California Los Angeles, Los Angeles, CA

Abstract: Introduction: During gestation, the fetus relies on the maternal nutritional environment, which plays a crucial role in shaping its epigenome, nervous system development, and metabolism. Research by Barker et al. introduced the concept of developmental programming, demonstrating that maternal malnutrition can predispose offspring to adult-onset diseases. This theory has gained substantial support, particularly in the context of maternal obesity (OB) and high-fructose diets. Notably, in utero exposure to maternal obesity combined

with excessive fructose intake impairs learning, memory, and cognitive function in mouse offspring. **Aim:** This in vitro study aims to investigate the cellular effects of fructose exposure on neuronal development, with a specific focus on the neuron/astrocyte ratio and neuritic extension growth in mouse neuronal stem cells. **Methods:** Neural progenitor cells (NPCs) were derived from the ganglionic eminence of E12.5 C57BL/6 mouse embryos. **Results:** Upon differentiation, embryonic NPCs exhibited a reduced neuron-to-astrocyte ratio following treatment with either 5 mM (1.4 ± 0.1 vs. 1.9 ± 0.1, $p = 0.02$) or 12.5 mM D-fructose (1.5 ± 0.1 vs. 1.9 ± 0.1, $p = 0.02$). Additionally, preliminary analysis revealed a statistically significant reduction in neuritic length following fructose exposure. The average neuritic length was 35.9 µm in the 5 mM treatment ($p = 0.0036$) and 34.8 µm in the 12.5 mM treatment ($p = 0.0005$), compared to 40.9 µm in the control group. **Conclusions:** In vitro findings suggest that prenatal exposure to fructose disrupts the hippocampal neuron-to-astrocyte ratio, with heightened vulnerability observed during fetal development. This shift toward excessive gliogenesis at the expense of neurogenesis may contribute to long-term cognitive impairments. Additionally, these findings reveal that even low-dose fructose exposure can impair fetal neuritic outgrowth, potentially compromising hippocampal synaptic plasticity and, consequently, learning and memory. The observed reduction in neuritic extension may hinder effective neuronal communication due to reduced neurotransmitter delivery. Future work will assess neuronal functionality by analyzing electrical signaling between the fructose and control groups. Given the widespread consumption of D-fructose in modern industrialized diets, these results underscore the importance of addressing its neurodevelopmental risks.

Disclosures: J. Hernandez: None. **M. Baqueiro:** None. **L. Bora:** None. **G. Han:** None. **M.G. Ross:** None. **M. Desai:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 1R15HD114135-01

Title: The Roles of the tweety Genes in the Notch Signaling Pathway

Authors: *G. E. HUSSEY[1], M. O. ROYSTER[1], M. S. SAHA[2];
[2]Biol., [1]Col. of William and Mary, Williamsburg, VA

Abstract: The Notch signaling pathway is highly conserved in neural development due to its role in the maintenance and differentiation of neural stem cells (NSC). One gene identified as a target of Notch signaling is ttyh1, a member of the tweety gene family. The tweety genes- ttyh1, ttyh2, and ttyh3- demonstrate strong central nervous system (CNS) expression, particularly ttyh1 in actively-dividing NSCs and ttyh3 in post-mitotic neural cells. Misregulation of tweety is

associated with neurological pathologies and cancers. Despite its implication in NSC regulation and disease, whether ttyh1 acts upstream or downstream or both of Notch signaling has not been determined. Additionally, interaction between ttyh3 and Notch has not been explored. To elucidate these relationships, we hyperactivated the Notch pathway and used in situ hybridization (ISH) to observe spatiotemporal changes in ttyh1 and ttyh3 expression. Additionally, we observed the effect of ttyh1 and ttyh3 overexpression or knockout on the expression of two marker genes in neural development: SRY-box 2 (Sox2), expressed in neural progenitor cells, and neural beta tubulin (tubb2b), expressed in post-mitotic neurons. This is accomplished by injecting Xenopus laevis embryos at the two-cell stage with Notch intracellular domain (ICD) for hyperactivation, tweety capped mRNA synthesized from cDNA for overexpression, or Cas9 with sgRNA targeting the ttyh1 or ttyh3 coding region for knockout. Our results suggest that ttyh1 and ttyh3 have distinct mechanisms of interaction with the Notch pathway. ISH of ICD-injected embryos reveals broader ttyh1 expression beginning in neurula stages, supporting previous literature suggesting ttyh1 is a downstream target of Notch. Conversely, ISH following ttyh1 overexpression shows broader CNS expression of Sox2 and less broad expression of tubb2b, suggesting reciprocal interaction between Notch and ttyh1. Unlike ttyh1, our findings do not support an interaction between Notch and ttyh3. ISH following Notch hyperactivation reveals no distinct spatiotemporal changes in ttyh3 expression, and ttyh3 overexpression resulted in no changes in Sox2 or tubb2b expression. These findings suggest that ttyh1 and ttyh3 have distinct and complex roles in the Notch signaling pathway, regulating their mediation of neurogenesis.

Disclosures: G.E. Hussey: None. **M.O. Royster:** None. **M.S. Saha:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: NRF-2022R1A6A1A03053343
2021M3E5E5096464
RS-2023-00248303
RS-2024-00433755

Title: Catalpol promotes the generation of cerebral organoids with oRGs through activation of STAT3 signaling

Authors: *Y.-J. LEE[1], J. KIM[2];
[1]Dongguk Univ., Seoul, Korea, Republic of; [2]chemistry, Dongkuk Univ., Seoul, Korea, Republic of

Abstract: The generation of human cortical organoids containing outer radial glia (oRG) cells is crucial for modeling neocortical development. Here we show that Catalpol, an iridoid glucoside

derived from *Rehmannia glutinosa*, significantly enhances the generation of cerebral organoids with expanded oRG populations and increased neurogenic potential. Catalpol-treated organoids exhibited thicker ventricular zone/subventricular zone (VZ/SVZ) and outer subventricular zone (oSVZ) regions, with increased numbers of SOX2+HOPX+ and SOX2+TNC+ oRG cells and elevated expression of oRG markers HOPX and FAM107A. We found that Catalpol promoted oRG generation through non-vertical divisions of ventricular radial glia (vRG) cells, indicating enhanced oRG generation via asymmetrical divisions. Furthermore, we demonstrated that Catalpol augmented oRG cell numbers through activation of the STAT3 signaling pathway. These findings highlight Catalpol's potential in promoting the generation of cerebral organoids with expanded oRG populations and increased neurogenic potential through STAT3 activation, offering new insights into neocortical development modeling.

Disclosures: Y. Lee: None. **J. Kim:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS082174

Title: Visualization of ocular motor neuron subpopulations during development

Authors: *S. SANTOS[1], M. F. ROSE[2];
[2]Pathology and Lab. Med., [1]Univ. of California Irvine, Irvine, CA

Abstract: Motor neuron development involves cell proliferation, specification, and migration in the central nervous system and axon targeting to specific muscles in the periphery. A subset of the brainstem oculomotor neurons (cranial nucleus 3, CN3), which control eye movement, migrate across the midline in a rare process. This subpopulation is selectively vulnerable in the childhood neurologic disease “Congenital fibrosis of the extraocular muscles type 1” (CFEOM1), where mutations in the kinesin KIF21A cause axon stalling and resulting deficits in upward gaze. The unique genes that direct each of these processes in the various motor neuron types and subpopulations, and their contributions to selective vulnerability in disease remain to be fully defined. We have adapted an ex vivo slice culture live imaging platform to visualize motor neuron development at single cell resolution. We use a combination of in vivo mouse genetic reporters to label the motor neurons, including the transgene Isl1-GFP and Cre lines such as Phox2b-cre and Isl1-cre in combination with the fluorescent cre reporter ROSA-tdTomato. We plan to intersect these tools and tissue clearing approaches to visualize motor neuron processes both during normal development and in disease models. In addition, we and colleagues have generated an atlas of developing motor neuron gene expression from which we have identified candidate genes of CN3 motor neuron subpopulations during differentiation. To

determine the extent to which the candidate genes are critical for ocular motor neuron development, we will disrupt their expression using CRISPR-Cas9, followed by analysis with our imaging pipeline. We also analyze motor neuron migration using a local thresholding mask to track cell movement. Overall, visualization of the dynamic behaviors among the CN3 motor neuron subpopulations and their progenitors will better define their population-specific choices during development and selective vulnerability in disease, and clarify the timing and function of gene expression that could inform future regeneration protocols.

Disclosures: S. Santos: None. **M.F. Rose:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI (21K07274)

Title: Activity-dependent immediate early expression of Gpr3 and its regulatory role in neuronal gene expression

Authors: *S. TANAKA[1], F. IKAWA[2], H. SHIRAKI[3], K. HARADA[4], N. SAKAI[5];
[1]Hiroshima Univ. Grad. Sch. of Biomed. and Hlth. Sci., Hiroshima, Japan; [2]Dept. of Mol. and Pharmacol. Neuros, Hiroshima City/Hiroshima Prefecture, Japan; [3]Hiroshima Univ. Grad. Sch. of Biomed. & Hlth. Sci., Hiroshima, Japan; [4]Mol. and Pharmacol. Neurosci., Hiroshima Univ., Hiroshima, Japan; [5]Dept Pharmacol Neurosci, Grad Sch. of Biomed & Hlth. Sci, Hiroshima Univ., Hiroshima-Shi, Japan

Abstract: Recent studies have identified a group of constitutively active G protein-coupled receptors (GPCRs) that activate G proteins independently of ligand binding. Among these, GPR3, GPR6, and GPR12—members of the class A rhodopsin-like GPCR family—are known to be abundantly expressed in neurons (Tanaka et al., JBC 2007). We have demonstrated that GPR3 constitutively activates Gαs, elevates basal intracellular cAMP, and promotes neurite outgrowth, neuronal survival, and axon regeneration (Tanaka et al., 2007, 2014, 2021; Masuda et al., 2022). In a more recent study, we found that GPR3 expression is rapidly induced within 30 minutes by NGF or cAMP stimulation through evolutionarily conserved cAMP response elements (CREs) in its 5′ promoter region (Manuscript in submission). To further investigate the role of GPR3 in transcriptional regulation, we aimed to define the transcriptional programs modulated by GPR3 during neuronal differentiation. PC12 cells were transfected with control or GPR3-targeting siRNA, and RNA-seq was performed 48 hours after NGF stimulation (n = 2 per group). Notably, GPR3 knockdown led to downregulation of several genes, including *Contactin 4*, *Stra6*, *Aplnr*, and *Nr4a3*. Since Nr4a family genes (*Nr4a1-3*) harbor multiple CRE motifs and act as typical IEGs induced by cAMP-CREB signaling, we hypothesized that GPR3 may regulate their delayed

expression through this pathway. To test this, we conducted RT-PCR analysis of *Nr4a1-3* mRNA levels over 96 hours following NGF-induced differentiation. In control siRNA-transfected cells, *Nr4a1*, *Nr4a2*, and *Nr4a3* mRNA levels gradually increased over time. However, GPR3 knockdown significantly suppressed this upregulation, especially between 48 and 96 hours. The suppression was most pronounced for *Nr4a1* and *Nr4a3*. Conversely, GPR3 overexpression under normal serum conditions robustly increased *Nr4a1-3* mRNA levels within 12 hours after transfection, even in the absence of external differentiation stimuli. Furthermore, GPR3 induction modulates *Synapsin1* expression in an NR4A1-dependent manner. Finally, to assess the functional consequence of this regulation, we examined primary cortical neurons derived from GPR3 knockout mice. Consistent with the molecular findings, these neurons exhibited a reduced density of Synapsin1-positive vesicles during differentiation. Taken together, these results suggest that GPR3 acts as an IEG-like, activity-dependent cAMP modulator that links extracellular signals to CREB-mediated transcription of neuronal genes, potentially regulating neuronal differentiation and synaptic plasticity.

Disclosures: S. Tanaka: None. **F. Ikawa:** None. **H. Shiraki:** None. **K. Harada:** None. **N. Sakai:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.11/A11

Topic: A.01. Neurogenesis and Gliogenesis

Title: Neuronal Precursor Diversity Predicts Pyramidal Neuron Heterogeneity in the Adult Hippocampus via Tbr2-Based Lineage Mapping

Authors: *K. CINTOLO;
Anat. and Neurobio., Boston Univ., Boston, MA

Abstract: Heterogeneity of neurons in the hippocampus is a critical feature that supports its complex and multifaceted functions. However, how and when this diversity arises remains to be fully understood. T-box brain 2 (Tbr2), one of the earliest markers of precursor variation in the neocortex, has been shown to demarcate lineage-specific aspects of neocortical excitatory neuron development. Tbr2 is also expressed by progenitors in the hippocampal primordium, but whether mechanisms identified in the neocortex similarly contribute to hippocampal neuronal identity has not been explored. We investigated whether the activity of a diverse pool of neuronal precursors during prenatal development gave rise to the heterogeneity observed among pyramidal neurons in the adult hippocampus. We first sought to validate a Tbr2 genetic labeling tool, previously used in the neocortex, to fate-map and characterize neurons generated during prenatal neurogenesis. Our results suggest that distinct regulatory elements around the Tbr2 gene locus are required for efficient labeling in the hippocampus. To identify and characterize these elements, we developed additional Tbr2 transfection tools incorporating combinations of three

highly conserved cis-acting Tbr2 regulatory elements. These tools enabled efficient simultaneous labeling of separate precursor lineages. Notably, we found that Tbr2 (4.5 kb)-Cre labels a greater percentage of Tbr2-lineage neurons compared to Tbr2 (2.5 kb)-Cre. Our findings confirm that distinct regulatory elements contribute to the expression of Tbr2 in neocortical versus hippocampal progenitor cells. Future experiments are underway to refine our ability to faithfully label intermediate progenitors and assess the abundance of precursor cells and their neuronal progeny in the hippocampus, with the goal of delineating potential differences in their gene expression profiles and, ultimately, their functional properties in the mature brain. Successful characterization of this pool of neuronal precursor cells and determining how it is regionally regulated is key to a deeper understanding of how these cells impact memory, learning, and behavior.

Disclosures: K. Cintolo: None.

Poster

PSTR100: Neuronal Differentiation

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Program #/Poster #: PSTR100.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: SECIHTI Grant 319578
SECIHTI Posgradueted studies fellowship of O.R. L.-M.

Title: Characterization of the conditioned medium from human olfactory neuroepithelium derived cells and evaluation of its trophic potential in neural precursor cell cultures

Authors: *O. LORA-MARIN[1,2], M. SILVA-LUCERO[2], J. PADILLA-MENDOZA[2], M. CARDENAS-AGUAYO[2];
[1]Natl. Autonomous Univ. Mexico (UNAM), Ciudad de México, Mexico; [2]Physiology, Lab. of Cell. Reprogramming, Sch. of Medicine, Natl. Autonomous Univ. of Mexico (UNAM), Ciudad de Mexico, Mexico

Abstract: Background Precursor cells communicate via the secretion of diffusible chemokines, which regulate various cellular processes. Aging is linked to altered proliferation, diminished stem cell pluripotency, and an increased proinflammatory state—changes that may be due to age-related shifts in chemokine secretion. The in vitro isolation of these secreted factors, known as conditioned medium (CM), has been widely studied. Notably, CM derived from young neural precursor cells (NPCs) has been shown to exert beneficial effects on these processes. Thus, further characterization of CM composition and age-dependent changes in NPC chemokine secretion is warranted. Human olfactory neuroepithelial neural precursor cells (hONE-NPCs) constitute a suitable model for studying the components of CM. **Objectives** To perform a proteomic characterization of conditioned medium (CM) derived from human olfactory neuroepithelium neural precursor cells (hONE-NPCs) obtained from healthy donors aged 30-40

(G30) and 50-60 (G50). Additionally, we aim to assess the CM's trophic effects by using it as a culture supplement for NPCs.**Methods** Proteins present in the hONE-NPC-CM were identified by mass spectrometry. An in silico analysis was then performed to generate a differential expression analysis of the identified proteins. Subsequently, the conditioned medium was used at a 30% concentration as a supplement for NPC cultures. Activation of the TrkB receptor was assessed by Western blot, and the effect of the CM on cell proliferation and neurogenic processes was evaluated. **Results** The CM contained trophic factors involved in cell proliferation, mainly associated with the MAPK and TrkB signaling pathways. Sustained activation of both the signaling pathway and the TrkB receptor was observed in the presence of CM from both G30 and G50 groups. An increase in cell proliferation was detected in cell treated with both CM. However, in the CM from the G50 group, proteins associated with cell differentiation processes were also identified. **Conclusions** This study identified trophic factors in hONE-NPC-CM that activate TrkB/MAPK pathways, enhancing NPC proliferation in both age groups (G30/G50). While younger CM (G30) showed stronger pro-proliferative effects, older CM (G50) contained differentiation-associated proteins, suggesting age-dependent functional shifts. These findings support the therapeutic potential of hONE-NPC-CM, although age-related secretory changes require further exploration.

Disclosures: O. Lora-Marin: None. **M. Silva-Lucero:** None. **J. Padilla-Mendoza:** None. **M. Cardenas-Aguayo:** None.

Poster

PSTR100: Neuronal Differentiation

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.13/A13

Topic: A.01. Neurogenesis and Gliogenesis

P30EY031631

Title: Rbpms is necessary for retinal ganglion cell development and function

Authors: *E. QUAINOO[1], X. XIE[1], B. MYSONA[2], X. CLARK-WALKER[3], R. ANITHADEVI SIVAKUMAR[3], K. BOLLINGER[2], L. GAN[1];
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Abstract: RNA-binding protein with multiple splicing (RBPMS) is a member of the single RNA recognition motif family of RNA-binding proteins and is expressed in many tissues in mice. In the CNS, RBPMS is known to be expressed in retinal ganglion cells (RGCs) soon after their specification and throughout maturity. RNA-binding proteins controls post-translational gene regulatory processes including RNA splicing, transport, localization, and translation, and RBPMS as an RNA-binding protein is known to regulate alternative splicing events in vascular smooth muscle cells and cardiomyocytes. The role of RBPMS in mammalian RGC development and function is, however, not known. Our objective in this study was to utilize a Cre-Lox

recombination approach to knock out *Rbpms* specifically in RGCs to determine its role in mammalian RGC development and function. To achieve this, we developed and crossed *Rbpms-DreFlex-pA* knock-in C56BL/6 background mice with *Six3-Cre* mice of the same background to induce Cre recombination and termination of *Rbpms* transcription in developing RGCs in the embryonic neuroretina. We then characterized RGC phenotype in adult (2-3 months) homozygous and heterozygous *Rbpms*-KO mice as well as wildtype mice of either sex using immunohistochemistry, electron microscopy, and ERG test (n=4). We observed RBPMS loss in the central one-third to half RGCs in developing and adult homozygous *Rbpms*-KO mice retinas. We also found a reduction in optic nerve size with significant loss of RGC axons in the adult homozygous *Rbpms*-KO mice (mean±SEM: wildtype vs *Rbpms*-KO; 69218±1491 vs 46592±2164, $p<0.0001$, Ordinary one-way ANOVA). Immunohistochemistry characterization of RGCs in the adult mouse retina also showed approximately 50% loss of POU4F2+ homozygous *Rbpms*-KO RGCs (mean±SEM: wildtype vs *Rbpms*-KO; 2361±74.87 vs 1127±91.66, $p<0.0001$, Ordinary one-way ANOVA). Consequently, adult homozygous *Rbpms*-KO mice showed significant reduction in pattern ERG P1 (mean±SEM: wildtype vs *Rbpms*-KO; P1 = 19.12±0.62 vs 10.97±1.23, $p=0.0014$, Ordinary one-way ANOVA) and N2 (mean±SEM: wildtype vs *Rbpms*-KO; N2 = 31.58±1.84 vs 21.59±1.54, $p=0.0044$, Ordinary one-way ANOVA) wave amplitudes indicating deficit in RGC electrophysiological activity. These findings suggest RBPMS critical role in structural and functional development of mammalian RGCs - possibly through its maintenance of post-translational gene regulatory mechanisms.

Disclosures: E. Quainoo: None. **X. Xie:** None. **B. Mysona:** None. **X. Clark-Walker:** None. **R. Anithadevi Sivakumar:** None. **K. Bollinger:** None. **L. Gan:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.14/A14

Topic: A.01. Neurogenesis and Gliogenesis

Title: Identification and Validation of Transitional Cerebellar Progenitors (TCP) in the Human Fetal Cerebellum

Authors: Y. LIN[1], W. ZHOU[1], ***R. Q. LU**[2];
[1]Children's Hosp. of Fudan Univ., Shanghai, China; [2]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

Abstract: The developing human cerebellum comprises a series of transient progenitor states that are essential for generating diverse neural subtypes, yet the identity and validation of intermediate cell populations bridging stem-like and lineage-committed neuronal precursors remain limited. In our previous single-cell transcriptomic study, we identified a distinct transitional cerebellar progenitor (TCP) population enriched in specific progenitor domains such as the rhombic lip during human fetal cerebellar development. Here, we provide additional

multimodal validations of this population. Rigorous reanalysis of our single-cell transcriptomic data, applying stringent quality control measures, validated the quality of TCP cells and their classification as a transcriptionally distinct population. Orthogonal validation of TCP signature genes (SOX11 and HNRNPH1) using RNAscope in situ hybridization and immunohistochemistry on additional fetal cerebellar samples demonstrated the consistent presence of TCPs in the rhombic lip, transitioning from $PRTG^{+}$ stem-like zones in the ventricular zone at early developmental stages to the subventricular zone overlapping with $EOMES^{+}$ unipolar brush cell precursors at later stages. TCP-like populations were also independently identified in two fetal cerebellar single-nucleus transcriptomic atlases, and their gene signature was enriched in a cell population associated with aggressive medulloblastomas. Collectively, these multimodal validations confirm the existence of a transitional progenitor population in the human fetal cerebellum, with implications for cerebellar lineage progression and medulloblastoma origin.

Disclosures: Y. Lin: None. **W. Zhou:** None. **R.Q. Lu:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.15/A15

Topic: A.01. Neurogenesis and Gliogenesis

Support: MNS Research Expenses

Title: Origins and developmental mechanisms of Purkinje cells and eurydendroid cells in the zebrafish cerebellum

Authors: *Y. KOYAMA-FUJII, E. ULZII, T. SHIMIZU, M. HIBI;
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Abstract: The cerebellum plays key roles in skilled movement, motor learning, and cognition. Its neural circuitry is broadly conserved across vertebrates. Granule cells (GCs) and Purkinje cells (PCs) receive extracerebellar inputs. PCs integrate this information and relay it to output neurons. In mammals, these outputs are carried by deep cerebellar nuclei (DCN) neurons. In zebrafish, however, output neurons are located near PC somata and extend long dendrites receiving inputs from both PCs and GCs; these are known as eurydendroid cells (ECs). PCs are GABAergic neurons derived from progenitors expressing the proneural gene *pancreas associated transcription factor 1a* (*ptf1a*) in the ventricular zone (VZ), while GCs are glutamatergic and arise from progenitors expressing the proneural genes *atonal bHLH transcription factor 1a/b/c* (*atoh1a/b/c*) in the upper rhombic lip (URL). In contrast to PCs and GCs, the origin and specification of ECs remain poorly understood. Furthermore, the transcriptional programs governing the differentiation of PCs and ECs are not fully defined. We found that progenitors expressing the proneural gene *oligodendrocyte lineage transcription*

factor 2 (*olig2*) give rise to PCs, and that PCs are strongly reduced in *olig2;olig3* mutants. *olig2* and *olig3* are expressed in the VZ, suggesting that Olig2/3 function in VZ progenitors to promote PC differentiation. We also found that transcription factors in the forkhead box P (Foxp), SKI family transcriptional corepressor (Skor), LIM homeobox (Lhx), RAR-related orphan receptor (Ror), and EBF transcription factor (Ebf) families act downstream of Ptf1a. Some, but not all, are also regulated by Olig2/3, suggesting that Olig2/3 function in parallel with Ptf1a. We further found that ECs originate from progenitors expressing *olig2* but not *ptf1a* or *atoh1c*, which is one of the *atoh1* family genes. Interestingly, *olig2* and *atoh1a*—another member of the *atoh1* gene family—are co-expressed in a subset of progenitors, so we speculate that ECs arise from *olig2/atoh1a* double-positive progenitors, which are distinct from those that generate either PCs or GCs. In mammals and birds, there is only a single *Atoh1* gene, and DCN neurons are derived from $Atoh1^{+}$ progenitors. Therefore, our findings suggest that teleost cerebellar output neurons differ in developmental origin from those of other vertebrates. In summary, we present recent insights into the development of PCs and ECs in zebrafish, highlighting the role of $olig2^{+}$ progenitors in generating these cell types.

Disclosures: Y. Koyama-Fujii: None. **E. Ulzii:** None. **T. Shimizu:** None. **M. Hibi:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.16/A16

Topic: A.01. Neurogenesis and Gliogenesis

Title: Developing a biofunctional xeno-free hydrogel platform for long-term 3D neuronal differentiation and maintenance

Authors: *A. FERRER DIAZ, J. HUANG;
TheWell Biosci. Inc, Monmouth Junction, NJ

Abstract: The development of in vitro systems for long-term neuronal differentiation and survival is crucial for understanding both physiological processes and disease states. While traditional two-dimensional (2D) neuron models have been instrumental in neuroscience research, these systems fail to maintain neuron viability over extended periods, impeding prolonged neuronal maturation. One reason for this limitation is that 2D-based models misrepresent the in vivo microenvironment by lacking an extracellular matrix (ECM) and tissue-specific cells, negatively affecting cell survival, differentiation, and behavior. As a solution to these challenges, three-dimensional (3D) culture systems have emerged as a superior approach for performing in vitro studies that are more physiologically relevant. However, these models often use animal-based ECM derived from murine tumors, which are temperature sensitive, contain over 2,000 undefined components, and, as a result, introduce experimental variability and affect reproducibility, hindering potential lab automation capabilities and clinical applications. In this study, we developed VitroGel Neuron, a novel xeno-free hydrogel platform

with bio-functional modifications that resemble the native ECM to assess long-term neuronal maturation and survival. Both human and rat neuronal neuroblasts were embedded in the hydrogel matrix for 3D culture. In addition to the 3D hydrogel neuron culture system, we developed the 2D hydrogel covering “blanket” method. This culture method consists of adding a thin layer of hydrogel on top of a monolayer of neuronal neuroblasts to promote prolonged neuron differentiation. Neuronal neuroblasts were differentiated into mature neurons by removing the serum from the cultures or supplementing the medium with retinoic acid. Immunofluorescence staining was performed on the cultures on days 7, 14, 21, and 30 to evaluate the presence of beta-III-tubulin, a marker expressed in mature neurons. Interestingly, we showed that the hydrogel facilitates long-term neuronal neuroblast differentiation and maturation, as confirmed by the positive beta-III-tubulin staining. Overall, this study demonstrated that the xeno-free 3D hydrogel platform is an effective tool for neuronal differentiation and maturation, highlighting its potential for clinical applications.

Disclosures: A. Ferrer Diaz: A. Employment/Salary (full or part-time): TheWell Bioscience Inc. **J. Huang:** A. Employment/Salary (full or part-time): TheWell Bioscience Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TheWell Bioscience Inc.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.17/A17

Topic: A.01. Neurogenesis and Gliogenesis

Title: The Growth and Neuronal Differentiation of Human Induced Pluripotent Stem Cells in Xeno-Free Functional Synthetic Hydrogel

Authors: R. I COHEN[1], *J. HUANG[2];
[1]TheWell Bioscience, Inc., Monmouth Junction, NJ; [2]TheWell Biosci. Inc, Monmouth Junction, NJ

Abstract: Human induced pluripotent stem cells (iPSCs) offer a powerful starting point to study the molecular dynamics of the developing nervous system. Further, they provide an invaluable tool to develop patient specific models for studying diseases process. Therefore, optimizing their growth in a defined and native 3D state is of paramount importance to both guide and allow for polarizing events that favor differentiation into highly connected neuronal networks. In this study, we used **VitroGel-STEM®**, a synthetic functionalized and xeno-free hydrogel, to support robust iPSC expansion, maintenance of pluripotency, and initial steps of neuronal lineage induction. Subsequently, newly differentiated neuronal stem cells, as single cells or neurospheres were transitioned to **VitroGel-Neuron**, a specialized hydrogel designed to facilitate neuronal adhesion, outgrowth, and synaptic connectivity. The studies were conducted using two iPSC lines generated using episomal plasmids; one derived from human foreskin fibroblasts, and the

second from CD34+ hematopoetic stem cells. IPSCs grown for 7days on 2D vitronectin coated plastic were dissociated into single cells using Accutase, and embedded into VitroGel-STEM® matrix at a density of 300 cells/mm^3 (80,000 cells per well of 24 well plate). Metabolic health was estimated using Alamar Blue dye, sphere diameter using microscopy, and cell number by automated cell counting protocols. After 3-4 days numerous colonies of IPSCs with diameter of 50 microns (~65,000 um^3 or 125 cells) were observed, mushrooming by day 11 to over 10 fold in number and 250 microns (~15k cells) in diameter. iPSCs were retrieved from 3D gel using VitroGel Organoid Recovery Solution, and Accumax dissociation and plated onto 2D surfaces to observe expected colony morphology, and canonical Tra-1-60 and Oct4 positive staining. Parallel cultures were used to derive neural stem cells using step wise small molecule cocktail to generate spheres of Floor Plate Neuroepithelia, which were recovered and embedded into VitroGel-STEM for EGF/FGF-2 expansion, or into VitroGel-Neuron™ for differentiation. In EGF/FGF-2 model, neurospheres were formed and expanded over several passages. Likewise, in VitroGel-Neuron™, robust 3D axonal projections were observed forming within 7 days in media containing a cocktail of pro-differentiation growth factors and small molecules. Further work is aimed at characterizing the types of neurons generated in this paradigm, and potential use in animal models of nervous system injury.

Disclosures: R. I Cohen: None. **J. Huang:** A. Employment/Salary (full or part-time): TheWell Bioscience Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TheWell Bioscience Inc.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.18/A18

Topic: A.01. Neurogenesis and Gliogenesis

Support: New Jersey Health Foundation Grants (Z.L.M., V.M.)
Connecticut Science Fund Grant (V.M.)

Title: Multiple neurons, interconnected via tunneling nanotubes, form a syncytium that may facilitate rapid spreading of pathogenic species in neurodegenerative diseases

Authors: P. VAID[1], Z. MURESAN[1], *V. MURESAN[2];
[1]Pharmacology, Physiol. and Neurosci., New Jersey Med. School, Rutgers Univ., Newark, NJ;
[2]New Jersey Med. School, Rutgers, Newark, NJ

Abstract: Neurodegenerative diseases, such as Alzheimer's disease (AD), typically lead to the abnormal aggregation of neuronal proteins that interfere with neuronal function and ultimately cause neuronal death. We recently proposed that the locus coeruleus-derived, mouse neuronal cell line CAD constitutes an excellent, yet simple, "sporadic Alzheimer's-in-a-dish" model. Differentiated, metabolically stressed CAD neuronal cells (i.e., cultured in the absence of serum)

spontaneously accumulate oligomeric amyloid-β (Aβ) and aggregates of phosphorylated Tau (pTau), as do neurons in the brain regions afflicted by AD pathology. We previously showed that the CAD cells that contain such aggregates usually appear in islet-like clusters segregated from the dominant, conventional cells. Here, we asked what could explain the accumulation of pathogenic aggregates in groups of neighboring cells. A likely explanation could be that the Aβ and pTau aggregates are first produced in one cell and then translocate to neighboring cells via thin, channel-like connections, known as tunneling nanotubes (TNTs). TNTs are thought to be generated via two different mechanisms: (1) extension of a filopodium from one cell to another, followed by membrane fusion; and (2) membrane fusion between two cells in close contact, followed by distancing of the connected cells. Recently, we identified a novel mechanism of generation of cell-to-cell connections that structurally resemble TNTs. We found that such connections form between daughter cells that fail to complete cytokinesis after mitosis and remain permanently connected. Such TNTs, identified via the acetylated microtubules that persist in the region of the midbody, form while CAD cells proliferate, and are maintained after differentiation. While the TNTs are established between two cells, we found that a single cell often connects via TNTs to more than one cell. Often, several CAD cells are connected via TNTs in a complex way, leading to the formation of syncytia, where the cytoplasm of the cells forms a single, interconnected cytoplasmic mass. Moreover, the TNTs connecting the cells are of different types: conventional or formed as a result of incomplete cytokinesis between postmitotic daughter cells. We propose that the pathogenic species produced in one cell could rapidly translocate to all cells interconnected via TNTs. We also propose that similar syncytia, formed by neurons interconnected via a network of TNTs, could be common in the normal brain, and serve as a way of neuron-to-neuron communication, in addition to synaptic communication. We propose that the networks of TNT-connected neurons are fundamental to how brains function.

Disclosures: P. Vaid: None. **Z. Muresan:** None. **V. Muresan:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.19/A19

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH T32HD055164

Title: Birth order-dependent modulation of Collier (EBF/Olf1/UNC-3 homolog) activity drives acquisition of cell identity in a Drosophila lineage

Authors: *Z. MARSHALL[1], E. HECKSCHER[2];
[1]Neurobio., [2]MGCB, Univ. of Chicago, Chicago, IL

Abstract: Neural stem cells divide in a sequential, stereotypic manner to produce daughter neurons, forming a lineage. Yet, there is no simple one-lineage-to-one-neuron-type relationship.

Instead, neuron identity can be determined by birth order (e.g., first-born, second-born, etc.). However, how gene expression is coordinated to assign birth order-specific identities remains poorly understood. Collier/Olf1/EBF (COE) proteins are a conserved family of transcription factors critical for neural differentiation. In the spinal cord, COE proteins are expressed in immature neurons until terminal differentiation and are required for normal marker expression. When expressed precociously in motor neuron domains, COE homologs can reprogram cells to express interneuron markers. In the Drosophila nerve cord (spinal cord analog), the sole COE ortholog, Collier (Col), is promoted by temporal cues in certain lineages and activates terminal identity genes. Thus, Collier likely collaborates with temporal information to guide neuron identity. Yet, these studies do not resolve how birth order within a lineage may coordinate Collier-dependent cell identity, as Collier was studied either in neurons of similar birth order or where birth order couldn't be precisely tracked. To address this, I investigate the Drosophila neuroblast 3-3 (NB3-3) lineage, which produces two types of Even-skipped(+) Lateral interneurons (ELs)—early-born and late-born. Both express Even-skipped (Eve) from birth and maintain its expression. Strikingly, Col is required for Eve expression only in late-born ELs, despite being present in both. In contrast, early-born ELs require Col later in differentiation to express the terminal identity factor, Acj6. These data show that birth order and Collier expression interact to drive birth order-specific gene expression within a lineage. Surprisingly, these interactions appear minimally influenced by known temporal cues. Thus, our findings suggest that birth order alone can modulate how Collier directs distinct transcriptional programs, revealing an underappreciated layer of developmental regulation where neuron birth timing shapes transcription factor activity to diversify neural identities.

Disclosures: Z. Marshall: None. **E. Heckscher:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.20/A20

Topic: A.10. Schizophrenia

Support: R01MH125528 EH21-0016

Title: Loss-of-function mutations in SETD1A disrupt cortical development and neuronal function in human cerebral organoids

Authors: *G. C. TRACY[1], K. MENDEZ-MALDONADO[3], H. ZHANG[2], Y. HONG[4], S. ZHANG[5], Z. P. PANG[6], H. SONG[7], G.-L. MING[8], J. DUAN[9];
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Neurosci, Univ. of Pennsylvania, gladwyne, PA; [9]NorthShore Univ. HealthSystem/University of C, Evanston, IL

Abstract: SETD1A, a component of the Complex Proteins Associated with Set1 (COMPASS) complex responsible for methylation of histone 3 lysine 4 (H3K4), has been implicated in schizophrenia through rare, dominant loss-of-function mutations. To model the impact of these mutations on human cortical development, we generated cerebral organoids from human induced pluripotent stem cells (iPSCs) carrying patient-specific SETD1A mutations across two genetic backgrounds (11C and CD07). These include an exon 2 (4 bp insertion), exon 16 (2 bp deletion), and a CRISPR-engineered 1 bp insertion in CD15 exon 16. Using a slicing protocol adapted from Qian et al. (2020), we cultured organoids to day 150 without necrotic core formation, enabling prolonged structural and functional analyses. Quantitative PCR and Western blot across timepoints revealed varying degrees of SETD1A reduction. The 11C exon 2 mutant (C11Kle2) showed up to ~50% reduction in protein expression. The 11C exon 16 mutant (C11Kle16) showed a 30-70% reduction in SETD1A expression across development. The CD07 exon 16 mutant (C7Kle16) showed ~55% reduction in gene expression and ~50% reduction in protein at day 70. The 1 bp insertion line (C15Δe16) exhibited a 50% decrease in SETD1A expression (qPCR) and ~40% reduction in protein (Western). Together, these results demonstrate that SETD1A mutations reduce gene dosage and alter molecular features of cortical development. Functional assays revealed impaired neuronal differentiation and excitability. The C11Kle2 line had reduced percentages of SATB2- and TBR1-positive neurons at days 103 and 120, indicating disrupted cortical layer development. Calcium imaging of C11Kle2 and C15Δe16 at days 120-130 showed reduced spontaneous firing rate and amplitude, supporting impaired neuronal function across mutations and backgrounds. These combined results indicate that dominant mutations in SETD1A impair neuronal differentiation and excitability, disrupting both protein expression and cortical layer formation across genetic backgrounds. Ongoing single-cell RNA sequencing and single-cell CUT&Tag profiling of histone H3 lysine 4 mono- and tri-methylation (H3K4me1 and H3K4me3) will characterize genome-wide transcriptional and epigenetic dysregulation associated with SETD1A mutations in human cortical development.

Disclosures: G.C. Tracy: None. **K. Mendez-Maldonado:** None. **H. Zhang:** None. **Y. Hong:** None. **S. Zhang:** None. **Z.P. Pang:** None. **H. Song:** None. **G. Ming:** None. **J. Duan:** None.

Poster

PSTR100: Neuronal Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.21/A21

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

Support: NIH T32 Grant 5T32NS105607-07

Title: Exploring the sex- and cell-type specific role of Tet3 in the mouse brain using spatial transcriptomics

Authors: *J. GROSS[1], H.-T. HUANG[2], K. MORRIS-BLANCO[3];
[1]Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA; [2]Life Sci., [3]Cell and Developmental Biol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: The ten-eleven translocase (TET) family of enzymes plays a crucial role in epigenetics by regulating the DNA methylome. TETs oxidize the repressive 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) or further oxidize 5hmC to mediate DNA demethylation. Both TETs and 5hmC are associated with increased gene expression. Importantly, Tet3 is highly expressed in neurons and is associated with neuroprotection in several neurological disorders. Despite the critical function of Tet3 in neurodevelopment and brain disease, Tet3 has not been thoroughly investigated in a sex- or cell-type-specific manner. To address this knowledge gap, we investigated neuronal, astrocyte and microglial Tet3 expression in the male and female mouse brain using immunofluorescence and spatial transcriptomics. Immunofluorescence in young adult Tet3-FLAG knock-in male and female mice revealed co-expression of FLAG in microglia, astrocytes, and neurons. We further found evidence of sex-specific differences in neuronal and glial Tet3 expression in the mouse brain. Next, to assess the role of neuronal and microglial TET3 on gene expression, we developed two conditional $Tet3^{fl/fl}$ knockout mouse lines to reduce Tet3 in excitatory neurons ($Camk2a^{CreER}$) and microglia ($P2ry12^{CreER}$). Spatial transcriptomics performed on coronal sections from male and female neuronal (Camk2a-$CreER^{+/-}$ :: $Tet3^{Flx/Flx}$) and microglial (P2ry12-$CreER^{+/-}$ :: $Tet3^{Flx/Flx}$) Tet3 knockout cohorts identified sex- and cell-specific differentially expressed genes (DEGs) related to learning, memory, and neural activity. Finally, we observed brain-region specific changes within the DEGs. The results from this study provide a basis for further understanding the sex and cell-type role of Tet3 in the brain. Given that 5mC and 5hmC epigenetic modifications are reversible, cell-specific modulation of Tet3 represents an attractive therapeutic target for neurological diseases.

Disclosures: J. Gross: None. **H. Huang:** None. **K. Morris-Blanco:** None.

Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.01/A22

Topic: A.06. Developmental Disorders

Support: SECIHTI Grant 827864

Title: Relationship between symptom severity, social communication prerequisites and neurophysiological activity in children diagnosed with Autism Spectrum Disorder

Authors: P. A. BATIZ FLORES[1,2], ***C. VEGA MICHEL**[3];
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Neurociencia Aplicada (INNA), Guadalajara, Mexico; [3]Escuela de Pedagogía y Psicología, Univ. Panamericana, Zapopan, Mexico

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with one of the largest increases in prevalence worldwide in recent years. People with ASD present difficulties in the development of social communication from the first months of life, as well as restricted and repetitive behavior patterns. Symptoms manifest within a continuum of severity and significant differences are observed between low and high functioning cases. Although distinct patterns of brain activity have been found in the evaluation of individuals with ASD compared to typically developing individuals, there is no brain marker due to heterogeneity of symptoms and differences in age and diagnostic criteria in the populations evaluated. The objective of this research was to know the relationship between symptom severity, social communication prerequisites and neurophysiological activity in children diagnosed with ASD; seeking an approach to describe the neural mechanism underlying ASD and a potential biological marker of it, through the detailed description of symptoms and developmental abilities according to their ages. Forty-four children with suspected or diagnosed ASD, from 2 to 5 years of age, recruited from the waiting list of a public center specialized in the evaluation and diagnosis of autism in Mexico, participated in the study. The MCHAT screening test was used for 2- and 3-year-old children and the SRS screening test for 4- and 5-year-old children. The Structured Interview CRIDI-Autism Spectrum Disorders was applied, the results of which yield algorithms according to the DSM 5, DSM-IVR, ICD 10 and ICD 11 manuals. The recording of brain electrical activity in the awake state was carried out for 20 to 30 minutes to obtain approximately 2 minutes of artifact-free recording for brain mapping. Children with higher severity level of ASD diagnosis were found to have lower developmental age, mainly in the area of communication, lower relative power in the frontal alpha band, higher relative power of the frontal delta band, and increased coherence of the delta, theta, and alpha bands of the frontotemporal region. The results contribute to a better understanding of the brain pattern underlying ASD symptoms at different levels of severity.

Disclosures: P.A. Batiz Flores: None. **C. Vega Michel:** None.

Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.02/A23

Topic: A.06. Developmental Disorders

Support: JSPS KAKENHI 24K00510
the medical institute of Developmental Disabilities Research, Showa Medical University, MEXT Joint Usage/Research Center

Title: Alterations in auditory perception and speech motor control in adults with ASD, ADHD, and their comorbidity

Authors: *K. MATSUHASHI[1], T. ITAHASHI[2], R. AOKI[1,3], T. OKIMURA[2], M. NAKAMURA[2], H. OHTA[2], R.-I. HASHIMOTO[1,2];
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Abstract: Neurodevelopmental disorders, including autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), are often associated with difficulties in auditory perception. Speech fluency also varies across individuals, with ASD linked to increased disfluency under delayed auditory feedback (DAF) and an altered Lombard effect, suggesting atypical speech motor control. However, auditory perception and speech motor control have been studied separately, and no previous studies have assessed these difficulties using common sets of auditory perception and speech motor control tasks across multiple neurodevelopmental disorders. To address this gap, we explored group differences in auditory perception and speech motor control difficulties among ASD, ADHD, and their co-occurrence by recruiting 42 participants aged 18-35: typically developing (TD) individuals (n = 13; females = 5; age = 26.9±4.0 [mean±SD]), ASD (n = 11; females = 6; age = 26.7±5.1), ADHD (n = 7; females = 5; age = 28.0±4.2), and comorbid ASD+ADHD (n = 11; females = 4; age = 28.4±3.5). They completed multiple tasks assessing auditory perception and speech production. Auditory perception was tested with four tasks: Gap-In-Noise (GIN), Dichotic Listening (DL), AX-Continuous Performance Test (AX-CPT), and Speech-in-Noise (SiN) tasks, each of which evaluated distinct auditory functions. Speech motor control was assessed through a reading aloud task under DAF at delays of 50, 100, 200, and 400 ms, with background pink noise, which was compared to reading with unaltered auditory feedback.In the auditory perception tasks, GLM with group, sex and age revealed that participants with ADHD performed significantly worse than the TD group on SiN ($t = 2.61$, $p < .05$) and GIN ($t = 2.67$, $p < .05$) tasks, while the ASD+ADHD group showed no differences (SiN: $t = 0.03$, $p = .97$; GIN: $t = 0.95$, $p = .35$). Conversely, only the ASD+ADHD group demonstrated significantly poorer performance on DL ($t = -2.61$, $p < .05$) and AX-CPT ($t = 2.28$, $p < .05$), with the ASD group showing no significant difference from the TD group (DL: $t = -1.13$, $p = .27$; AX-CPT: $t = -0.27$, $p = .79$). In the speech production task, the ASD+ADHD group exhibited a significantly greater reduction in speech rate under DAF than TD ($t = 2.31$, $p < .05$), whereas the ASD group showed a marginally smaller reduction relative to TD ($t = -1.74$, $p = .08$). Despite the small sample, these results indicated that individuals with ADHD showed selective deficits in auditory perception, whereas the ASD+ADHD group exhibited broader impairments across tasks. These observations suggest that the comorbidity of ASD and ADHD shows distinct auditory and speech processing difficulties.

Disclosures: K. Matsuhashi: None. **T. Itahashi:** None. **R. Aoki:** None. **T. Okimura:** None. **M. Nakamura:** None. **H. Ohta:** None. **R. Hashimoto:** None.

Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.03/A24

Topic: A.06. Developmental Disorders

Support: NIH-NIMH P50 MH109429
CA Department of Health, grant to Nathan Klein Institute, Milham (PI)

Title: Developmental trajectory of language use and incidental behavior in ADHD and Autism: A large-scale analysis using AI

Authors: *A. SILVAN, L. C. PARRA, J. MADSEN;
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Abstract: Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) often co-occur and have overlapping symptoms. This suggests shared underlying neurological dimensions that have yet to be established. Matters are complicated by the traditional diagnostic approaches that rely on a complex combination of symptoms with subjective criteria that change with age. Here, we are interested in two dimensions of development that are affected by ADHD and ASD and can, in principle, be assessed objectively using modern computational tools, namely, language use and motor control.
Previous literature has analyzed these dimensions with subjective measures, and separately for ADHD and ASD populations, with mixed results. We leverage the Healthy Brain Network (HBN) data, which offers a unique, large-scale community sample of ~5000 children and adolescents (ages 5-22). This dataset includes rich psychiatric and behavioral data, such as clinical instrument scores (e.g., SWAN/CBCL for ADHD; ASSQ/SRS for Autism traits), clinician-confirmed DSM-5 diagnoses, and importantly, around 2,800 video-recorded scripted interviews where participants recounted a highly emotive cartoon movie “The Present”. Using modern AI methods (e.g., vision, speech, and language models), we automatically extracted quantitative metrics of body and face movement, speech patterns, and expressive language from these interviews.
We then modeled the effects of ADHD and ASD traits on these observed behaviors, accounting for co-morbidity, as well as developmental changes associated with age and sex. Our models revealed that while hyperactive traits were indeed associated with increased face and body movements, a substantial portion of this variance was also explained by developmental maturation with age. Similarly, objectively quantified communication deficits linked to ASD, such as reduced narrative abilities, disrupted manner of speech, and altered emotional (theory of mind) understanding, were also significantly moderated by age.
These findings demonstrate the feasibility of large-scale behavioral analysis using AI for neurodevelopmental research. But most importantly, they highlight the necessity of modeling developmental trajectories and potential confounders, like age and sex, to accurately identify disorder-specific behavioral markers.

Disclosures: A. Silvan: None. **L.C. Parra:** None. **J. Madsen:** None.

Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.04/A25

Topic: A.06. Developmental Disorders

Support: EU-AIMS Grant Agreement No. 115300

Title: Mapping the Development of Empathy in Autistic and Neurotypical Individuals: A Longitudinal Multimodal Study

Authors: *N. ALMUTAIRI;
Inst. of Psychiatry, Psychology, and Neuroscience, King's Col. London, London, United Kingdom

Abstract: Mapping the Development of Empathy in Autistic and Neurotypical Individuals:A Longitudinal Multimodal Study By Nouf Almutairi[1,2], Bethany Oakley[1], Luke Mason[1], Declan Murphy[1], Marija M. Petrinovic[1 1] Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, 16 De Crespigny Park, London, SE5 8AF, UK[2] Department of Psychology, Kuwait University, Sabah Al Salem University City, Kuwait **Background:**Empathy, the ability to understand and share emotions, is vital for social interaction. It is often reported to be lower in autistic individuals. While empathy encompasses emotional, cognitive, and behavioural aspects, few studies explore individual differences. This study compares empathy in autistic individuals and those with typical development (TD) using data from the EU-AIMS Longitudinal European Autism Project (LEAP), a significant multi-site research initiative. **Methods:**Participants aged 6 to 32, including 275 individuals with autism and 204 TD individuals, were drawn from the LEAP dataset based on empathy and behavioural measures. Empathy was assessed using the Empathy Quotient (EQ). Behavioural profiles were evaluated with the Social Responsiveness Questionnaire and the Strengths and Difficulties Questionnaire. Social attention was measured through eye-tracking tasks involving a dynamic scene. Analyses included ANOVA for group comparisons and Pearson and Spearman correlations to evaluate associations among empathy, behaviour, and visual attention. **Results:**TD participants scored higher on empathy measures than autistic participants ($p<.001$, effect size 0.714). Females had higher empathy scores than males in the TD group ($p<.001$). Empathy correlated positively with prosocial behaviour ($r=.4$, $p<.001$) and negatively with conduct problems ($r=-.3$, $p<.001$). More attention to faces during eye tracking was associated with higher empathy scores ($p<.01$). Principal Component Analysis (PCA) revealed multiple components of empathy, with cognitive empathy exhibiting significant group differences ($p<.001$). ROC analysis showed high classification performance for this component, with sensitivity and specificity over 80%. **Discussion:**Findings highlight the complexity of empathic functioning. Group differences were observed, while PCA revealed cognitive empathy's distinctive role. Its strong classification performance suggests that empathy differences in autism reflect specific component patterns. This supports a nuanced understanding of empathy and emphasises moving beyond generalised deficit models when studying neurodiverse populations.

Disclosures: N. Almutairi: None.

Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.05/A26

Topic: A.06. Developmental Disorders

Support: SECIHTI Scholarship 1181851

Title: Effects of Repeated Robotic Arm Manipulation on Facial Expressions in Children with Autism Spectrum Disorder

Authors: *H. M. LIBREROS JIMENEZ[1,2], G. A. CORIA-AVILA[3], R. TOLEDO-CARDENAS[4], M. HERNANDEZ[2], D. HERRERA-COVARRUBIAS[4], J. MANZO[5]; [1]Regenerative Neurobio. & Neuroelectronics Lab., Univ. of Arizona, Tucson, AZ; [2]Inst. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Mexico; [3]Inst. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Ver, Mexico; [5]Inst. for Brain Res., [4]Univ. Veracruzana, Xalapa, Mexico

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by early onset deficits in social interaction, including impairments in expressing and interpreting facial expressions. Precise facial muscle control is essential for non verbal communication and social engagement. This study aimed to promote the development of facial expression complexity in children with ASD as a long-term strategy to support social interaction. Over the course of 52 weeks, 11 children with ASD and 11 neurotypical controls (ages 6-19) participated in weekly sessions involving fine motor manipulation of a robotic arm to transfer objects, either alone or in the presence of a neurotypical peer acting as a social mirror. Facial expressions were recorded and analyzed using FaceReader software (Noldus IT, The Netherlands). The results showed that long-term engagement in fine motor tasks increased the complexity of facial expression (in basic emotions and action units) in children with ASD. Statistical analysis on multiple comparisons will be presented. This effect was amplified when tasks were performed with a peer, suggesting a modulatory role of observational learning. We hypothesize that these improvements may reflect sensorimotor reorganization involving adjacent hand and face representations in motor cortex, potentially supported by mirror neuron system engagement. These findings support the use of structured sensorimotor tasks as a tool to enhance socio-emotional development in children with ASD.

Disclosures: H.M. Libreros Jimenez: None. **G.A. Coria-Avila:** None. **R. Toledo-Cardenas:** None. **M. Hernandez:** None. **D. Herrera-Covarrubias:** None. **J. Manzo:** None.

Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

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Program #/Poster #: PSTR101.06/A27

Topic: A.06. Developmental Disorders

Support: Gatsby Charitable Foundation GAT3850
Israel Science Foundation 1731/24
European Research Council 833694

Title: Autistic individuals learn to exploit temporary regularities in simple but not complex contexts

Authors: *K. M. DÜSTERWALD[1], N. ZUK[2], V. SAMPATH[3], J. SLOBODSKOY-PLUSNIN[3], Y. WEISS[3], M. SAHANI[1], M. AHISSAR[4];
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Abstract: Autistic individuals (ASDs) learn some perceptual tasks as well as neurotypicals (NTs), yet update more slowly in others. We investigated whether context modulates update ability by asking ASDs to learn simple temporal regularities on their own as opposed to mixed with temporal irregularities. Participants completed reaction time (RT) tasks in which they were asked to respond as fast as possible to audiovisual stimuli, with paired EEG recordings. In the simple context experiment, stimuli were presented in identical blocks of fixed (2s) intervals (NT=32, ASD=25). In the complex context, stimuli were presented in blocks of fixed (2s) or irregular (uniform 1-3s) intervals, in a random, mixed order (as in Millin et al., 2018; NT=35, ASD=33). In the simple context, ASDs' and NTs' reaction times got faster across the experiment, suggesting adaptive learning to the regular rhythm ($p<0.05$). Both groups also developed significant contingent negative variation (CNV) components (cluster-based permutation tests in electrode Cz, $p<0.05$), indicative of neural entrainment to fixed stimuli.
We then tested whether autistics could perform as well in the fixed trials in a complex context, which included blocks of irregular-interval trials. Similar to the simple context, we found that NTs learned to react faster in fixed trials across the experiment ($p<0.01$). They were also faster in fixed trials than expected from near 2s interval irregular trials ($p<0.01$), meaning that a single central tendency effect across the entire experiment could not explain NTs' fast RTs in fixed trials. In contrast, ASDs did not learn during the block and their fixed trial performance could be explained by the same central tendency effect across both block types ($p=0.13$). ASDs also failed to show neural entrainment to fixed trials: NTs but not ASDs developed a CNV component, and it was significantly larger than ASDs' ($p<0.05$). Put together, these neural and behavioural findings show that while ASD individuals can learn simple temporal regularities on their own, they are unable to entrain to simple regularities in complex contexts. This suggests that perceptual models of autism should consider hierarchical context complexity in determining internal updates to task statistics.

Disclosures: K.M. Düsterwald: None. **N. Zuk:** None. **M. Sahani:** None. **M. Ahissar:** None.

Poster

PSTR101: Autism: Behavioral Analysis

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Program #/Poster #: PSTR101.07/A28

Topic: A.06. Developmental Disorders

Support: KAKENHI 25K03429

Title: A pilot study on a novel behavioral paradigm for assessing restricted interests in autism model mice

Authors: *Y. SHINODA, H. MATSUZAKI, K. YAMASHIRO, T. TAKAHASHI, Y. FUJIWARA;
Tokyo Univ. of Pharm & Life Sci., Hachioji, Tokyo, Japan

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interactions, communication challenges, and restricted, repetitive behaviors and interests. Behavioral testing in animal models is crucial for understanding neurodevelopmental and psychiatric disorders, including ASD. While numerous tests assess social behaviors, a core ASD phenotype, fewer tools exist for evaluating adherence to specific behaviors and interests. To address this gap, we tried to develop a behavioral assessment system focused on evaluating interest adherence in mice. Our method involves presenting four video stimuli on tablets in an open field: two videos feature periodically moving objects presented diagonally opposite, and the other two displays randomly moving or static objects. We then measure the time spent in areas associated with each video, aiming to identify conditions that increase engagement with the periodically moving stimuli. This report outlines the rationale behind our approach and details the video conditions explored in our experiments.

Disclosures: Y. Shinoda: None. **H. Matsuzaki:** None. **K. Yamashiro:** None. **T. Takahashi:** None. **Y. Fujiwara:** None.

Poster

PSTR101: Autism: Behavioral Analysis

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Topic: A.06. Developmental Disorders

Support: UNAM-PAPIT: IN216023
UNAM-PAPIT: IN218924
UNAM-PAPIT: IA205025
UNAM-PAPIME: PE304525

Title: Early Altered Ultrasonic Vocalizations in a Murine Model of Autism

Authors: *M. ARIAS-GARCÍA[1], N. CUÉLLAR[1], N. BRAVO[1], E. L. URBINA[3], E. RENDON-OCHOA[4], G. X. AYALA MENDEZ[5], D. TAPIA[6], V. CALDERON[7], M. PALOMERO RIVERO[6], A. LAVILLE[9], V. AVILÉS ROSAS[10], M. VERDEJO MANZANO[2], V. G. LOPEZ HUERTA[8], L. RAMOS-LANGUREN[11], E. GALARRAGA[12];
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Abstract: Communication is a critical cognitive function that emerges early in development. In rodent models, neonatal ultrasonic vocalizations (USVs) are key indicators of early social behavior and serve as translational tools for investigating the neurobiological underpinnings of neurodevelopmental disorders. Prenatal exposure to valproic acid (VPA) is a widely used preclinical model of autism spectrum disorder (ASD), replicating core behavioral and neurobiological features observed in human ASD.
C57BL/6J mouse pups prenatally exposed to VPA or vehicle (saline) were evaluated using a standardized brief maternal separation paradigm. USVs were recorded longitudinally from postnatal days 4 to 21, spanning critical windows of early development. Quantitative and qualitative analyses were conducted on multiple acoustic parameters, including call frequency, duration, and spectral features—as well as on the developmental trajectory of the vocal repertoire.
VPA-exposed pups demonstrated significant disruptions in USV production, including reduced call rates, altered spectral profiles, and delayed diversification of the vocal repertoire. These alterations suggest an atypical developmental trajectory of early social communication, consistent with phenotypes observed in ASD. Preliminary analyses also point to emerging sex differences in USV patterns, warranting further investigation.

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Poster

PSTR101: Autism: Behavioral Analysis

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Program #/Poster #: PSTR101.09/A30

Topic: A.06. Developmental Disorders

Support: This study was supported by Consejo Nacional de Ciencia y Tecnología, Mexico (CONACyT grant 243298 for NS
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CONACyT provided a Ph.D. scholarship to LJHS (grant 1009145).

Title: Melatonin prevents autistic signs in valproic acid-treated rats.

Authors: L. J. HERNÁNDEZ SIERRA, Sr., *R. C. SALGADO, N. SADERI;
Facultad de Ciencias, UASLP, San Luis Potosi, Mexico

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by deficient social interactions and repetitive behaviors, and is associated with several comorbidities such as anxiety, epilepsy, and circadian rhythm disruptions. Currently, there is limited evidence regarding preventive treatments during pregnancy that could reduce the risk of ASD in offspring. Melatonin is a hormone released by the pineal gland regulated by the circadian rhythm, which has been extensively investigated due to its antioxidant and neuroprotective properties. In ASD patients, melatonin blood levels have been reported to be lower than in non-ASD controls, suggesting that circadian rhythm might be impaired in ASD. Therefore, in this study, we evaluated the effects of melatonin administration during neurodevelopment in the offspring of rats prenatally exposed to valproic acid (VPA), a widely used experimental model of ASD. Pregnant rats (Rattus norvegicus) were injected with VPA or saline at embryonic day 12.5 (E12.5) and then treated with either melatonin or vehicle from E13 until weaning, allowing for the characterization of the differential effects between the sexes. The offspring (n=4-6 per sex per group) were evaluated for motor coordination, vestibular function, sociability, stress-related behaviors, and circadian variables, including locomotor activity and temperature. Additionally, we assessed morphological changes in the cerebellum, an area associated with motor control, attention, and social behavior, using Nissl staining. We also performed IBA1 immunohistochemistry to evaluate neuroinflammation levels in the hippocampus, which plays a crucial role in cognitive and emotional processes commonly impaired in ASD. The results suggest sex-dependent effects of VPA, with significant alterations primarily observed in males, while females showed fewer changes. For example, females exhibited greater immunoreactivity to IBA1 in the CA1 and dentate gyrus of the hippocampus, whereas males displayed behavioral and chronobiological alterations, particularly in locomotor activity. Both sexes showed reduced serum melatonin levels. Notably, chronic administration of melatonin during the perinatal period prevented the characteristic symptoms of autism observed in males, reduced neuroinflammation levels in females, and normalized serum melatonin concentrations in both sexes. These findings suggest that melatonin could represent a practical, affordable, and promising approach to preventing ASD-related symptoms and behaviors and highlight the differing vulnerabilities and therapeutic outcomes based on sex.

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Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

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Program #/Poster #: PSTR101.10/A31

Topic: A.06. Developmental Disorders

Title: Brain waste clearance deficits in autism: glymphatic system dysfunction revealed in a valproic acid-induced animal model

Authors: *C. LUDVIG GONÇALVES, S. JANUÁRIO BOLAN, V. LINDEN DE REZENDE, M. DA COSTA, G. LAPA VIANA, M. PEDRO EBS DE SOUZA, C. FALLER, A. KURSANCEW, S. ARAUJO, J. GENEROSO;
Univ. do Extremo Sul Catarinense (UNESC), Criciúma, Brazil

Abstract: Autism spectrum disorder (ASD) is characterized by impairments in social interaction and the presence of restricted and repetitive patterns of behavior and interests. Additionally, up to 80% of autistic children present with comorbidities, among which sleep disorders are particularly prevalent. The glymphatic system, responsible for clearing metabolic waste from the brain during sleep, has been implicated in the pathophysiology of several neurological disorders when dysfunctional. This study aimed to investigate alterations in the glymphatic system in a valproic acid (VPA)-induced animal model of ASD and to determine the time course of such dysfunction. All experimental procedures were previously approved by the Animal Ethics Committee of the University (91/2023). Animal care and handling followed the guidelines of the *Policies on the Use of Animals and Humans in Neuroscience Research*. To establish the model, pregnant Wistar rats received a single intraperitoneal injection of VPA (600 mg/kg) or 0.9% saline (SAL) on gestational day 12.5. Offspring were weighed on postnatal days (PND) 9, 17, and 25 and subjected to an olfactory discrimination test on PND 10. On PND 30, Evans blue dye combined with albumin (EBA) was injected into the cisterna magna. Animals were euthanized at 4 hours, 24 hours, 3 days, or 7 days post-injection for blood and brain collection. VPA-exposed animals exhibited significant delays in neurodevelopmental markers, including eye opening latency, nest-seeking behavior, and negative geotaxis. As expected, no significant differences in body weight were observed between groups. Animals exposed to VPA and euthanized at 4 hours, 24 hours, and 3 days post-injection showed significantly higher EBA concentrations in the brain compared to controls. In contrast, serum EBA concentrations were significantly lower in VPA-exposed animals at 4 hours, 24 hours, and 7 days, supporting impaired glymphatic clearance. Importantly, this study is the first to demonstrate glymphatic dysfunction in this model, suggesting impaired brain waste clearance. These findings open new avenues for exploring therapeutic strategies targeting the glymphatic system using the VPA-induced model of ASD.

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Poster

PSTR101: Autism: Behavioral Analysis

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Topic: A.06. Developmental Disorders

Support: Fapesc/Brazil Grant 2021TR1484
Capes Grant 88881.844954/2023-01

Title: Subanesthetic Intranasal Ketamine Modulates Conditioned Fear Expression Without Affecting Social or Anxiety-Like Behaviors in a Rodent Model of Autism

Authors: *E. PAVESI, B. SOARES ODORIZZI, A. GOUVÊA;
Morphology, Univ. Federal De Santa Catarina, Florianópolis, Brazil

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by impaired social interaction, restricted interests, and repetitive behaviors. Prenatal exposure to valproic acid (VPA), a teratogenic antiepileptic drug, is a widely used rodent model of ASD. This study evaluated the effects of subanesthetic intranasal ketamine, a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist, on behavioral and cognitive outcomes, as well as potential neuroplasticity changes, in adult Wistar rats prenatally exposed to VPA. The study was approved by the Institutional Animal Care and Use Committee (CEUA no. 9837230624). On gestational day 12.5, pregnant dams received a single intraperitoneal dose of VPA (600 mg/kg) or saline. VPA-exposed offspring exhibited neurodevelopmental delays, including impaired negative geotaxis. In adulthood, male and female animals (n = 6 per group) were randomly assigned to receive one of the following treatments: saline, aripiprazole (1.5 mg/kg, intraperitoneal), chronic ketamine (10 mg/kg, intranasal, once daily for 15 days), or acute ketamine (10 mg/kg, intranasal, single dose). Behavioral assessments were conducted one day after the final treatment and included the elevated plus maze (EPM), novel object recognition, three-chamber social interaction, and contextual fear conditioning. Acute ketamine administration did not significantly improve anxiety-like behavior in the EPM or sociability in the three-chamber test. In the novel object recognition task, a modest increase in the recognition index was observed in the acute ketamine group, although it did not reach statistical significance. Contextual fear conditioning revealed sex-dependent effects of ketamine, with reduced freezing behavior observed in females compared to males, suggesting a differential modulation of aversive associative memory. Data from the aripiprazole-treated group are still being processed and will be included in future analyses. These preliminary findings indicate limited efficacy of acute ketamine in rescuing ASD-like social deficits, but point to a potential benefit on cognitive function related to fear learning. Further analyses involving chronic treatment and neuroplasticity markers are ongoing to better elucidate ketamine's therapeutic potential for ASD-related comorbidities.

Disclosures: E. Pavesi: None. **B. Soares odorizzi:** None. **A. Gouvêa:** None.

Poster

PSTR101: Autism: Behavioral Analysis

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Program #/Poster #: PSTR101.12/A33

Topic: A.06. Developmental Disorders

Support: São Paulo Research Foundation (FAPESP) Grant 2024/09783-2
National Council for Scientific and Technological Development (CNPq) Grant 312009/2022-4

Title: Early Behavioral Markers and Medium Spiny Neuron Responsiveness to Cortical Inputs in a Rodent Model of Autism Spectrum Disorder

Authors: *F. E. PADOVAN-NETO, D. RIBEIRO;
Univ. of São Paulo, Ribeirao Preto, Brazil

Abstract: Autism Spectrum Disorder (ASD) is characterized by social deficits, restricted communication, and repetitive behaviors such as stereotypies. In rodents, grooming behavior is commonly used as a model of stereotypy relevant to ASD. Prenatal exposure to valproic acid (VPA) is a well-established model for investigating how early neurodevelopmental disruptions may contribute to ASD-related phenotypes. This study investigated whether early-life neurological assessments can predict the emergence of stereotyped grooming behavior in adolescent rats prenatally exposed to VPA. Pregnant Sprague-Dawley rats received an intraperitoneal injection of VPA (600 mg/kg) or saline (control) on gestational day 12.5. Offspring (males from both groups) underwent sensorimotor testing during the first postnatal week, including negative geotaxis (postnatal day [PND] 7) and nest-seeking behavior via olfactory discrimination (PND 9). Grooming behavior was evaluated in adolescence (PND 41). Linear regression was used to assess whether early-life sensorimotor performance predicted grooming behavior. To investigate underlying circuit mechanisms, in vivo single-unit extracellular recordings were performed between PND 30 and 41 to examine the responsiveness of putative striatal medium spiny neurons (MSNs) to electrical stimulation of the primary motor cortex. These recordings aimed to characterize potential alterations in corticostriatal connectivity in VPA-exposed animals. VPA-exposed animals exhibited a significant delay in negative geotaxis performance, and olfactory discrimination showed a trend toward group differences. Grooming behavior was also elevated in the VPA group. Regression analysis revealed a marginally significant negative association between negative geotaxis performance and grooming behavior. Taken together, the results suggest that early deficits in motor function may be predictive of later stereotyped behaviors, potentially linked to corticostriatal circuit dysfunction. These findings underscore the translational relevance of early developmental assessments and support further investigation into the neurobiological mechanisms underlying repetitive behaviors in ASD.

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Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.13/A34

Topic: A.06. Developmental Disorders

Title: An acute sleep deprivation during a critical neurodevelopmental window is sufficient to induce both short- and long- term behavioral deficits in C57BL/6 mice

Authors: N. COFSKY, *M. BINDER;
Trinity Univ., San Antonio, TX

Abstract: Sleep plays a vital role in neurodevelopment. Consequently, sleep deficits are among the most common comorbidities of various neurodevelopmental conditions such as autism spectrum disorder, fragile X syndrome, and attention-deficit/hyperactivity disorder. Despite their high prevalence, the behavioral consequences of early life sleep deficits are not well established. We addressed this problem by subjecting C57BL/6J mice to an intermittent sleep deficit from postnatal days (PD) 4 to 12. The sleep deficit paradigm was validated via the non-invasive PiezoSleep system. Next, we examined communication on PD12 and found that sleep deprived pups produced fewer ultrasonic vocalizations, a shorter call duration, and lower fundamental frequency as well as an increased peak frequency relative to control animals. After PD12, pups were returned to normal housing conditions. When the mice were 8 weeks old, we assessed various behaviors and found that the mice that were sleep deprived early in life exhibited heightened anxiety, reduced time displaying prosocial and aggressive behaviors, and had fewer total events of aggressive behaviors as an adult. No differences were found for locomotion, repetitive behaviors, or sensory preferences. Additionally, there were no differences in body weight between groups, indicating that these findings were not due to altered physical development. Overall, intermittent early life sleep deprivation during a critical window of neurodevelopment led to lasting impairments in communication, social behaviors, and anxiety levels in C57 mice, suggesting that a comorbid sleep deficit may play a critical role in the onset of behavioral deficits commonly associated with neurodevelopmental disorders.

Disclosures: N. Cofsky: None. **M. Binder:** None.

Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.14/A35

Topic: A.06. Developmental Disorders

Support: Autism Speaks Foundation (NY, NY).
DoD Grant W81XWH-19-1-0178

Title: Assessment of folate receptor autoantibodies in language impaired ASD children through behavior, inflammation, and blood brain barrier efficacy

Authors: *D. MISHAN[1], J. M. ALARCON[2], R. E. FRYE[4], H. HUBERMAN[3];
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disability, affecting approximately 1 in 31 individuals in the USA (Maenner 2025). Core symptoms of ASD include impairments in social communication and restrictive repetitive behaviors (RRBs) (APA 2013), leading to difficulties in daily functioning. Early diagnosis and intervention are critical for achieving optimal outcomes, yet the average age of diagnosis in the US remains around 54 months (Maenner 2023). Currently, behavioral and speech therapies are the mainstays of treatment, with no FDA-approved pharmacological interventions targeting core symptoms (LeClerc 2015). Prior research has shown a strong association between Folate Receptor Autoantibodies (FRAA) and ASD, with FRAAs blocking folate transport across the blood-brain barrier (BBB) and contributing to CNS folate deficiency (a.k.a. vitamin B9 deficiency) in a majority of ASD-diagnosed children (Rossignol 2021, Ramaekers 2017). Leucovorin, a derivative of vitamin B9, has shown promise in alleviating some core symptoms, particularly in language and restrictive repetitive behaviors in older children (3 to 15 years, median age 7.2yrs) with ASD (Frye 2018). Our current project encompasses a double-blinded placebo control clinical trial to assess the treatment efficacy of the biochemically active levo-leucovorin (l-leucovorin) compound in 60 language impaired 3-5 year old children with ASD through evaluations of development (Mullen Scale of Early Learning, MSEL), and social communication (Social Responsiveness Scale-2, SRS-2). Importantly, to explore whether FRAA status is predictive (i.e., a biomarker) of ASD clinical presentation, we collected blood serum samples from participants and determined the correlation between FRAA positivity and symptom severity at the baseline stage of the study. Additionally, to mechanistically test FRAA positivity in ASD as an autoantibody disorder, we carried out quantitative ELISAs in peripheral plasma of inflammatory markers TNF-a and IL-10 in association with FRAA positivity and symptom severity at baseline. Next, we expanded our investigation by testing for the connection between neuroinflammatory insult and BBB dysfunction. Using quantitative ELISAs, we determined the association of FRAA status and symptom severity with peripheral plasma concentrations of protein markers of BBB permeability S100B and sPECAM-1 (Hussain 2021, Wimmer 2019). This study is expected to pave the way for biomarker discovery and targeted pharmacological approaches to improve outcomes for affected children.

Disclosures: D. Mishan: None. **J.M. Alarcon:** None. **R.E. Frye:** None. **H. Huberman:** None.

Poster

PSTR101: Autism: Behavioral Analysis

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.15/A36

Topic: A.06. Developmental Disorders

Support: Nancy Lurie Marks Family Foundation
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ANR-22-CE14-0051-01 NewMic
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French National Ministry of Research and Higher Education

Title: Sex-dependent learning and memory deficits mediated by maternal immune activation and their reversal through inhibition of the colony-stimulating factor 1 receptor

Authors: *S. IKEZU[1,2], J. DELPECH[3,2], H. YEH[2], Y. YOU[1,2], Z. RUAN[2], N. TOUCH[2], P. MONGUILLON[3], A. RAU[4], C. MADORE[3], T. IKEZU[1,2];
[1]Mayo Clin. Florida, Jacksonville, FL; [2]Pharmacol. & Exptl. Therapeut., Boston Univ. Sch. of Med., Boston, MA; [3]Human Nutr., INRAE, Bordeaux cedex, France; [4]Univ. Paris-Saclay, INRAE, AgroParisTech, 78350 Jouy-en-Josas, France, Jouy en Josas, France

Abstract: We previously reported the pathological role of microglia in autism-like behavioral abnormality induced by maternal immune activation (MIA), via aberrant secretion of neuritogenic factors and subsequent altered neural network in developmental brains. Transient administration of colony stimulating factor 1 receptor (CSF1R) inhibitor between postnatal day (P)21-P42 depleted and replenished microglia in MIA offspring. This intervention ameliorated the social deficit, reversed elevated basal dendritic spine density and microglial transcriptomic changes at adulthood, P60. In the current study, we aimed to determine whether MIA induces sex-specific impairments in social behavior, and learning and memory, as well as transcriptome in brain tissues, and whether CSF1R inhibitor can rescue such deficits by performing battery of behavior tests and brain tissue bulk RNA-seq. We induced MIA by intraperitoneal injection of 10 mg/kg of Polyinosinic:polycytidylic acid {Poly (I:C)} with pregnant female mice, which were pre-selected based-on their immune response to lower dose of Poly (I:C) injection. MIA offspring exhibited impairments in sociability, spatial working and associative memories in both sexes, while only male offspring displayed social novelty deficit. Administration of CSF1R inhibitor, PLX5622, between P21-42 with MIA offspring rescued sociability deficit in males, spatial working and associative memories in both sexes although there was no therapeutic effect on social novelty impairments. Importantly, there was no adverse effect observed in both MIA and non-MIA offspring following PLX5622 treatment. Transcriptomic analysis of prefrontal cortex and hippocampal tissues revealed more profound MIA effect on transcriptomic changes in female compared to male offspring. Furthermore, pathway analysis of differentially expressed genes in MIA offspring compared to the rest of the groups showed enriched synaptogenesis related signaling in male offspring, which was corroborated with our previous finding, and enriched cholesterol biosynthesis related pathways in female offspring, highlighting the potential role of metabolic dysregulation in female MIA phenotype. Thus, our results underscore the potential of the sex-specific therapeutic applications of CSF1R inhibitor for MIA-related social and cognitive disorders.

Disclosures: S. Ikezu: None. **J. Delpech:** None. **H. Yeh:** None. **Y. You:** None. **Z. Ruan:** None. **N. Touch:** None. **P. Monguillon:** None. **A. Rau:** None. **C. Madore:** None. **T. Ikezu:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.01/A37

Topic: A.06. Developmental Disorders

Title: Neurogenetic Insights into Ocular Disorders in the Nepalese Population: Findings from Exome Sequencing

Authors: *S. THAPA;
Mol. Genet., Kathmandu Ctr. for Genomics and Res. Lab. (KCGRL), Lalitpur, Nepal

Abstract: Background:
Many ocular disorders are intrinsically linked to the nervous system, particularly the retina, optic nerve, and central visual pathways. These conditions not only impair vision but often reflect broader neurodevelopmental and neurodegenerative processes. This study explores the neurogenetic architecture of ocular disorders in the Nepalese population, leveraging exome sequencing to uncover mutations with implications for both visual and neural function.
Introduction:
The retina, as a direct extension of the central nervous system, serves as a window into neural health. Despite the neurobiological importance of vision, little is known about the genetic basis of neuro-ophthalmic disorders in Nepal. This study bridges this gap by examining how pathogenic variants in vision-related genes affect neural development, synaptic transmission, and neuroplasticity, thereby influencing ocular and neurological phenotypes.
Methods:
Patients with inherited ocular disorders, many with suspected neurodevelopmental associations, were recruited from ophthalmic and neurological clinics across Nepal. Detailed clinical, neurological, and neuroimaging assessments were paired with exome sequencing. Bioinformatic analysis focused on genes involved in retinal development, phototransduction, and neurogenesis.
Results:
Key variants were identified in genes with established roles in both ocular and neural pathways. These include:

- **RS1** (retinoschisin) and **RP1L1**: essential for synaptic integrity and visual signal transmission.

- **LCA5** and **CERKL**: linked to early-onset retinal dystrophies and implicated in ciliary neurodevelopment.

- **TUBGCP6**: associated with microcephaly and chorioretinal defects, reflecting impaired neuronal microtubule organization.

- **FOXL2**: traditionally linked to blepharophimosis, also plays a role in neuroendocrine signaling.

- **HEXB**: connected to neuronal lysosomal storage disorders, indicating neurodegenerative overlap.

Additionally, several cases lacked detectable variants, highlighting potential epigenetic or regulatory contributions to these complex neuro-ocular disorders.

Conclusion:

This investigation underscores the intertwined nature of ocular and neural development. By identifying mutations in neurogenetically relevant genes, we reveal a layered understanding of how visual disorders in the Nepalese population often reflect deeper neural pathologies. These insights advance prospects for neuro-ophthalmic diagnostics, early genetic counseling, and personalized therapeutics in neurogenetics and visual neuroscience.

Disclosures: S. Thapa: A. Employment/Salary (full or part-time): Kathmandu Center for Genomics and Research Laboratory (KCGRL).

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.02/A38

Topic: A.06. Developmental Disorders

Support: NIH Grant 1F31NS141557
NIH Grant 1R01NS113591
NIH Grant S10OD030322

Title: Glia regulate neuronal ciliation in tuberous sclerosis complex

Authors: *K. DONOVAN[1,3], K. D. WINDEN[2], A. D'AMORE[1], M. SAHIN[2];
[1]F.M Kirby Neurobio. Ctr., [2]Dept. of Neurol., Boston Children's Hosp., Boston, MA; [3]Harvard Univ., Cambridge, MA

Abstract: Tuberous sclerosis complex (TSC) is a genetic disorder caused by heterozygous inactivating variants in *TSC1* or *TSC2*. TSC is characterized by the growth of benign tumors in multiple organs, as well as neurological manifestations such as refractory epilepsy, autism spectrum disorder, and intellectual disability. TSC1 and TSC2 form a protein complex with TBC1D7 that acts as an upstream negative regulator of the mechanistic target of rapamycin complex 1 (mTORC1). Hyperactivation of mTORC1 is thought to be a key pathogenic driver of TSC. Treatments that inhibit mTORC1 cause arrest or regression of tumors in TSC but have shown limited efficacy in treating epilepsy and the neurocognitive symptoms of TSC, necessitating further research to enable new treatment development. Among the several downstream consequences of mTORC1 dysregulation, disruption of primary cilia has emerged as one potential candidate for mediating neuronal dysfunction in TSC. The primary cilium is a non-motile sensory organelle present on all cells which is necessary for cortical lamination and neuronal connectivity. We have found that TSC2-deficient cortical neurons are less likely to be

ciliated. Further, we observed that Heat shock protein 27 (HSP27) is significantly upregulated at both the transcript and protein level in TSC2-deficient cortical cultures and that knockdown of *Hsp27* increases ciliation of TSC2-deficient neurons, rescuing the phenotype. However, HSP27 is localized to astrocytes and not neurons in these cultures, suggesting a non-cell-autonomous mechanism. In addition, ablation of glia in TSC2-deficient cortical cultures restored neuronal ciliation. Notably, this cilia rescue did not change phosphorylation of mTORC1 targets, or the enlarged soma size observed in TSC2-deficient neurons, suggesting that HSP27 impacts ciliation independent of mTORC1. Overall, our study reveals that TSC2-deficient glia decreased neuronal ciliation, potentially impacting neuron function.

Disclosures: K. Donovan: None. **K.D. Winden:** None. **A. D'Amore:** None. **M. Sahin:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.03/A39

Topic: A.06. Developmental Disorders

Support: NIH Grant R01HD107722
NIH Grant R56HD102898

Title: Intergenerational neurocognitive disorder induced by the general anesthetic sevoflurane: underlying mechanisms and pharmacological prevention strategies

Authors: L.-S. JU[1], Z. KHAN[1], N. GRAVENSTEIN[1], B. SETLOW[2,3], ***A. MARTYNYUK**[1,3]; [1]Anesthesiol., [2]Psychiatry, [3]McKnight Brain Inst., Univ. of Florida, Gainesville, FL

Abstract: The postoperative neurocognitive disorder (PND), associated with general anesthesia and surgery, affects millions and may also accelerate other neurodegenerative diseases. Its mechanisms remain unclear, and no preventive pharmacological interventions exist. We hypothesized that (1) repeated exposure to the general anesthetic sevoflurane upregulates the hypothalamic-pituitary-adrenal (HPA) axis and inflammation via the excitatory NKCC1/GABA type A receptor ($GABA_AR$) pathway in hypothalamic arginine vasopressin (AVP)-producing neurons, creating a perpetuating feedback loop that sustains HPA axis activation, inflammation, and neurocognitive deficits in both exposed rats and their offspring; (2) the NKCC1 inhibitor bumetanide or the glucocorticoid receptor (GR) antagonist RU486 disrupt this loop, providing therapeutic benefits. Sprague Dawley male rats (F0) received 2.1% sevoflurane for 3 hours on postnatal days (P) 56, 58, and 60. Before each exposure, they were administered either vehicle (F0M_S), bumetanide (F0M_BS), or RU486 (F0M_RS). Rats were mated on P90 to generate offspring (F1). Both generations underwent behavioral testing, followed by mechanistic studies. The brain-gut microbiome (BGM) axis was analyzed via 16S rRNA gene sequencing of gut microbiota and hippocampal RNA sequencing. F0M_S, but not F0M_BS or F0M_RS, exhibited increased hypothalamic c-FOS and AVP (but not oxytocin) expression, increased *Nkcc1/Kcc2*

mRNA ratios, heightened HPA axis activity, and elevated inflammatory markers. Profound hippocampal transcriptome alterations, minor gut microbiota shifts, anxiety-like behavior, impaired sensorimotor gating, and spatial memory deficits were observed. F1 males sired by F0M_S, but not those sired by F0M_BS or F0M_RS, exhibited heightened corticosterone responses to stress, increased inflammatory markers, behavioral abnormalities, hippocampal transcriptomic alterations, gut microbiota dysbiosis, elevated serum low-density lipoprotein cholesterol and body weight. F1 females of F0M_S sires were less affected. These findings suggest a role for the hypothalamic NKCC1-$GABA_AR$-AVP pathway in sevoflurane-triggered intergenerational PND, with associated BGM axis abnormalities primarily in F1 males. NKCC1 and GRs may serve as potential targets for the pharmacological prevention of PND. Considering the feasibility of non-invasive gut microbiome sampling, gut microbiota changes have the potential to serve as biomarkers of intergenerational PND in humans.

Disclosures: L. Ju: None. **Z. Khan:** None. **N. gravenstein:** None. **B. Setlow:** None. **A. Martynyuk:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.04/A40

Topic: A.06. Developmental Disorders

Support: NIH 5-T32 GM141828-02
HA Innovator Award
The Shurl and Kay Curci Foundation

Title: Tracing the developmental and mechanistic origin of BAF induced congenital hydrocephalus

Authors: *A. RAJAN[1], R. HUMPHRIES[2], R. CHEN[3], L. LIU[2], R. M. FAME[2];
[1]Developmental Biol., [2]Neurosurg., Stanford Univ., Stanford, CA; [3]Sch. of Med., Meharry Med. Col., Nashville, TN

Abstract: Congenital hydrocephalus is a pediatric disease wherein inborn genetic mutations lead to excess cerebrospinal fluid (CSF) in the brain ventricles. There are more than 300,000 reported cases of congenital hydrocephalus every year, ranging between 2.2 to 18 cases per 10000 live births (Abebe et al., 2022). Congenital hydrocephalus has no cure, and treatment often requires shunting, a surgically invasive procedure to drain excess CSF. Multiple causes of congenital hydrocephalus have been implicated, including decreased CSF flow due to cilia impairment, aqueductal stenosis preventing CSF flow, or increased CSF secretion due to dysregulation in ion homeostasis. Recent whole-exome sequencing studies of 5 large independent pediatric cohorts have identified a handful of congenital hydrocephalus risk genes. Among them, BAF155 (Smarcc1) is a high-confidence congenital hydrocephalus risk gene that is associated with the

BAF (SWI/SNF) chromatin remodeling complex (OMIM: 620241). In human case of BAF155 associated congenital hydrocephalus, aqueductal stenosis has been detected as early as gestational week 17 (Hourvitz et al., 2023). Previous work has shown that in *Xenopus*, CRISPR/CAS9 knock-out or morpholino mediated knock down of BAF155 can cause hydrocephalus to emerge due to aqueductal stenosis (Singh et al., 2024). Studying BAF155 associated congenital hydrocephalus has proven challenging in mouse models, due to embryonic lethality of BAF155 mutants, and mice having a higher susceptibility for neural tube closure defects. It is critical to develop a mammalian model of BAF155 associated congenital hydrocephalus, to perform a developmental study of hydrocephalus formation. In this study, we have generated a conditional knockout mouse model of BAF155 in which mice heterozygous for BAF155 in neural progenitors. This genetic manipulation results in a 1/3 penetrance of hydrocephalus by P4 (N= 33). This model provides an excellent platform to investigate the mechanism through which congenital hydrocephalus arises and characterize the molecular changes that arise in early neural progenitors upon partial loss of BAF155. Taken together, this new model can inform basic development of early neural progenitors and how missteps in these processes can underlie neurodevelopmental disorders.

Disclosures: A. Rajan: None. **R. Humphries:** None. **R. Chen:** None. **L. Liu:** None. **R.M. Fame:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.05/A41

Topic: A.06. Developmental Disorders

Support: Shriners Hospitals for Children Research Grant (85111-PHI-23)

Title: Elucidating the role of Crb2 in ventricular system development and hydrocephalus pathogenesis

Authors: *A. DIMOU, S. KIM;
Temple Univ. Lewis Katz Sch. of Med., Philadelphia, PA

Abstract: Hydrocephalus is characterized by cerebrospinal fluid (CSF) accumulation and ventricular enlargement, affecting 1-3 per 1,000 live births globally. Mutations in Crb2 cause congenital hydrocephalus, ventriculomegaly, and aqueduct stenosis in humans. Crb2, an apical polarity complex protein, regulates epithelial polarity, ciliogenesis, adherens junction stability, and apical domain determination. Aqueduct stenosis, the narrowing of the passage between the third and fourth ventricles, disrupts CSF flow and often results from developmental abnormalities. However, Crb2's role in hydrocephalus pathogenesis remains poorly understood, especially in neural progenitors that generate the ependymal cells, which are critical for CSF dynamics. We hypothesized that Crb2 function in neural progenitors is required for ependymal

cell development. To test this, I examined Crb2 conditional knockout mice using various Cre drivers. Crb2 Nestin-Cre knockout mice (targeting most of neural progenitors) exhibited reduced ependymal and ciliated ventricular lining cells, suggesting an essential role in ependymal cell generation. In contrast, Crb2 Foxj1-Cre knockout mice, where Crb2 deletion occurs after lineage specification, showed only mild abnormalities, indicating a lesser role in maintenance. Because Crb2 Nestin-Cre mice developed aqueduct stenosis, I analyzed Crb2 Wnt1-Cre2 knockout mice (targeting the midbrain) to assess midbrain-specific loss of function. These data showed reduced rostral aqueduct ependymal cells, abnormal cilia, and fewer subcommissural organ (SCO) cells, indicating Crb2's role in aqueduct formation. Together, these findings highlight Crb2's essential role in progenitors for proper ependymal cell development and suggest a mechanism underlying hydrocephalus. Ongoing studies aim to further define Crb2's molecular role in this process.

Disclosures: A. Dimou: None. **S. Kim:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.06/A42

Topic: A.06. Developmental Disorders

Support: Division of Intramural Research, National Institute of Allergy and Infectious Disease (AI001102-11)

Title: Disease-associated mutations in the 20S proteasome cause dysregulated polyamine synthesis and altered neuronal development

Authors: *C. WINKLER[1], B. SCHWARZ[1], C. L. HAIGH[1], R. GOLDBACH-MANSKY[2], K. PETERSON[1];
[1]Natl. Inst. of Allergy and Infectious Dis., Hamilton, MT; [2]Natl. Inst. of Allergy and Infectious Dis., Bethesda, MD

Abstract: CANDLE syndrome (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) is a proteasome-associated autoinflammatory disease (PRAAS) caused by mutations that reduce the function of the 20S proteasome core. The resulting impaired protein degradation leads to over-production of type I interferons (IFNs) and induces multi-organ inflammation. Symptoms such as headaches, seizures, and cognitive delays have been reported with CANDLE, indicating that the syndrome may also impact the brain. Thus, we examined the effect of CANDLE mutations on neuronal development in patients and patient-derived tissues. Age-appropriate Wechsler Intelligence Scale testing of five CANDLE patients (between 10 and 24 years of age) showed lower IQ scores, indicating neurodevelopment is impaired. Cerebral organoids (COs) generated from 3 different CANDLE patient induced pluripotent stem cells (iPSCs) exhibited reduced labeling for neuronal progenitors and mature neurons compared to COs from 2 different healthy controls. To determine whether over-production of IFN resulting

from CANDLE the mutations contributed to this altered neuronal development, IFN and IFN-stimulated genes were analyzed in patient and control organoids with and without IFN-inducing viral infection. Surprisingly, IFN and IFN-stimulated gene expression was similar between CANDLE and control COs regardless of infection. Instead, the aberrant neuronal development in CANDLE COs was associated with increased production of polyamines, which were also elevated in the CSF of CANDLE patients. Consistent with these metabolic findings, the rate-limiting enzyme in polyamine synthesis, ornithine decarboxylase (ODC1), whose turnover is known to be proteasomal regulated, was elevated in CANDLE neurons. Inhibition of ODC1 with the small molecule difluoromethylornithine resulted in decreased putrescine levels and increased expression of mature neuron transcripts in CANDLE COs. These findings collectively suggest that CANDLE-causing mutations in the 20S proteasome impair ODC turnover, resulting in IFN-independent elevation of polyamine production in neurons and disrupted neuronal development. ODC1 inhibition restores polyamine homeostasis, partially reversing these defects and may represent a potential therapeutic strategy for treating CANDLE-associated neuronal development.

Disclosures: C. Winkler: None. **B. Schwarz:** None. **C.L. Haigh:** None. **R. Goldbach-Mansky:** None. **K. Peterson:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.07/A43

Topic: A.06. Developmental Disorders

Support: NIH Grant Simultaneous prenatal alcohol and cannabinoid exposure & offspring corticostriatal neurocircuitry: 5F32AA029866-03

Title: Prenatal alcohol and cannabinoid exposure impose distinct, sex specific changes in striatal epigenetic and proteomic cannabinoid signalling mechanisms.

Authors: *A. BOWRING[1], S. ROUZER[2], R. C. MIRANDA[3];
[1]Texas A&M Sch. of Med., College Station, TX; [2]Texas A&M Col. of Med., Bryan, TX;
[3]Neurosci. and Exptl. Therapeut., Texas A&M Univ., Bryan, TX

Abstract: Background:Prenatal exposure to alcohol or cannabinoids increases the risk of striatal dysfunction and, hence, reward-based conditions like substance use disorders. Both exposures are associated with changes in cannabinoid receptor 1 (CNR1)- associated function. We investigated whether simultaneous alcohol and cannabinoid exposure (SAC) produces distinct changes in CNR1 gene and protein networks.Method: Pregnant C57Bl/6J mice were assigned to one of four groups: drug-free control, alcohol-exposed, cannabinoid-exposed, or SAC-exposed. From Gestational Days 12-15, dams received cannabinoid agonist CP-55940 (750µg/kg) or saline via intraperitoneal injection. Dams were then immediately placed in vapor chambers for

30 minutes of inhalation of 95% ethanol or room air. Approximately one year after birth, offspring Dorsomedial Striatum (DS) tissues were collected for two purposes: a) bulk RNA-sequencing and transcript quantification, and b) western blot analyses to measure protein signals of preselected CNR1-associated genes. Results: Compared to sex-matched controls, prenatal SAC imposed a persistent decrease in CNR1 receptor-interacting protein (CNRip1) RNA expression, without affecting CNR1 expression. From a proteomic standpoint, SAC exposure had differing effects on CNR1 between sexes, maintaining expression in males and increasing expression in females. Similar to RNA effects, SAC decreased CNRip1 protein expression in both sexes. As CNRip1 negatively regulates presynaptic CNR1 activity, these genetic and proteomic expression levels suggest that the CNR1 signaling network may be disrupted by SAC exposure. This theory is further supported by observed SAC-induced increases in synaptic gene expression downstream of CNR1.Conclusion: Prenatal SAC exposure creates a distinct, sex-specific CNR1-associated striatal genomic-proteomic profile compared to control offspring, with changes detectable into late adulthood. Subsequent mPFC protein assessments within these same offspring will determine how mPFC activity corresponds with changes in DS signaling, fostering a network-level analysis of CNR1 activity.

Disclosures: A. Bowring: None. **S. Rouzer:** None. **R.C. Miranda:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.08/A44

Topic: A.06. Developmental Disorders

Support: National Natural Science Foundation of China 82204081

Title: Genetic Evidence for Estrogenic Effects of Benzophenone-2 on Zebrafish Neurodevelopment and its Signaling Mechanism

Authors: *W. SONG;
Xuzhou Med. Univ., Xuzhou, China

Abstract: Estrogens play a crucial role in regulating various biological responses during the early stage of neurodevelopment. Benzophenone-2 (BP2), a widely used organic ultraviolet (UV) filter, has been proven as an estrogenic compound whereas the estrogenic effects of BP2 on neurodevelopment remain largely unknown. Here, we investigated the neurodevelopmental toxicity of BP2 by exposing zebrafish embryos from 2 to 120 hours post-fertilization (hpf) at environmentally relevant concentrations. We demonstrated that early-life exposure to BP2 induced multiple concentration-dependent impairments in nervous system, including hypoactivity, abnormal brain morphology, impaired neurocyte proliferation, shortened *axon* and increased neurocyte apoptosis. Moreover, metabolomic profiling revealed a decrease of dopamine (DA) and its metabolites in BP2-treated larvae. Using E2 treatment and morpholino

knockdown assays, we provided strong genetic evidence that the BP2-induced behavioral disorders were associated with estrogen dependent signaling, especially estrogen receptor 2a and 2b (*esr2*). Subsequently, transcriptomic profiling indicated that activation of *esr2* further inhibited the expression of LIM homeobox transcription factor 1 beta a (*lmx1ba)* which is vital for normal neurodevelopment. Consistently, overexpression of *lmx1ba* and inhibition of *esr2* obviously alleviated BP2-caused neurotoxicity, uncovering a seminal role of *esr2b* and *lmx1ba* in BP2-induced neurodevelopmental toxicity. Our findings provide the first evidence in fish that BP2 can induce neurodevelopmental deficits and brain dysfunction and offer novel insights into the toxic mechanisms of BP2 as well as other emerging benzophenones.

Disclosures: W. Song: None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.09/A45

Topic: A.06. Developmental Disorders

Support: Eagles Autism Foundation
NIH Grant R01MH118827
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NIH Grant R01MH136152
NIH Grant R01NS138268
NIH Grant R01NS105200
NIH Grant P50HD105353

Title: Mbd1 regulation of neuronal maturation and autism

Authors: *Y. GAO;
Waisman Center, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Methyl-CpG binding proteins (MBDs) translate DNA methylation into gene expression changes. Alterations in human *MBD1* gene are associated with intellectual disabilities, including autism. We have shown that MBD1 deficiency in mice leads to autism-like behavioral deficits. However, the mechanism underlying MBD1 regulation of brain development and behaviors remains unclear. To identify genome-wide targets of MBD1 in the prefrontal cortex (PFC) during postnatal brain development, created a knock-in mouse line that has endogenous MBD1 tagged with a 3XFLAG tag and performed FLAG chromatin immunoprecipitation (ChIP-seq) . We found that MBD1 binds both actively transcribed and repressed genes and its binding profile exhibit dynamic changes throughout postnatal development. To further investigate how human MBD1 deficiency contributes to autism, we generated a human-equivalent MBD1 mutation mouse line, E339K, with a single amino acid change found in a subset of human autism patients. Our findings revealed that MBD1-E339K

mice exhibited autism-like behaviors and the MBD1-E339K protein had reduced binding to MBD1 target genes. Hence, our study unveils the function of MBD1 in brain development and how its deficiency contributes to autism.

Disclosures: Y. Gao: None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.10/A46

Topic: A.06. Developmental Disorders

Support: Gerber Foundation (MBB & CME)
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Title: Elemental micronutrients in very preterm infants and associations with brain development

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Abstract: Background: Little is known about associations between micronutrient blood content and brain development or the extent to which preterm infant micronutrient content differs from full-term infants. **Objective:** To 1) determine longitudinal changes in whole blood micronutrient content among hospitalized, very preterm infants, 2) compare to healthy, full-term infants at birth, and 3) determine associations of blood micronutrient content and brain size.
Design/Methods: We studied 43 very preterm infants (VPT, gestational age [GA] 24-30 weeks) and 15 full-term infants (FT, GA 37-39 weeks). Inductively coupled plasma-mass spectrometry was used to measure iron (Fe), zinc (Zn), copper (Cu), selenium (Se) and rubidium (Rb) content in whole blood samples from VPT at 4 time points (birth, 2 weeks, 1 month, discharge) and in cord blood from FT at birth. Content distributions were plotted at each time point and changes assessed using mixed effects modeling (MEM) and Sidak's multiple comparisons test. Differences between VPT at discharge and FT at birth were tested using Mann-Whitney U. VPT brain metrics at term equivalent were head circumference (HC) z-score and MRI-based measurements (interhemispheric distance; bifrontal, biparietal, and cerebellar diameters). The

associations of VPT brain metrics with mean micronutrient levels over time were analyzed using MEM. **Results:** VPT content for Se ($p<0.0001$), Fe ($p<0.0091$) and Rb ($p<0.0036$) all were decreased from birth to DOL30. Zn and Cu remained unchanged. Compared to FT cord blood, VPT at discharge had higher Cu ($p<0.0001$) but lower Se ($p<0.0001$), Fe ($p<0.0001$) and Rb ($p<0.0001$) content. VPT with biparietal diameter (BPD) in the top tertile had higher Se content over the course of the hospitalization compared to VPT with BPD in the bottom tertile ($p=0.0345$; MEM). We did not observe associations of HC z-score or other brain metrics with Cu, Zn, Fe, Se or Rb content. GA was similar in the top and bottom tertile groups. **Conclusions:** Se, Fe and Rb content in VPT at discharge were lower than in FT at birth raising concern for nutritional deficiency despite supplementation. Larger BPD was associated with higher selenium content during the hospitalization, a finding that aligns with our prior observation that higher selenium intake from milk was associated with white matter development (Bell et al., PAS 2024, 2140.3). Given the importance of selenoproteins in myelination, supplementation with selenium may be beneficial for brain development in VPT.

Disclosures: C.M. Elitt: None. **A. Cheng:** None. **J. Wang:** None. **S. Cherkerzian:** None. **M. Ross:** None. **K. Bell:** None. **B. Zhang:** None. **C. Cortina:** None. **Z. He:** None. **H. Christou:** None. **M. Belfort:** None. **P.A. Rosenberg:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.11/A47

Topic: A.06. Developmental Disorders

Support: CIRM Grant

Title: Elucidating Cortical Developmental Abnormalities in SATB2-Associated Syndrome Using Mouse Models with SATB2 Point Mutations

Authors: *Y. NIE, B. CHEN;
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Abstract: SATB2-associated syndrome (SAS) is a complex developmental disorder characterized by intellectual disability, developmental delay, craniofacial and dental anomalies, and behavioral issues. It is caused by de novo mutations in the SATB2 gene, including point mutations and intragenic rearrangements. As an autosomal dominant disorder, a single mutant allele is sufficient to produce clinical manifestations. Although SATB2 is known to encode a DNA-binding protein that regulates chromatin architecture and gene expression, the impact of SAS-associated mutations on brain development and the molecular mechanisms involved remain largely unclear, and no effective treatments are currently available. In mice brain, Satb2 is primarily expressed in cortical projection neurons and plays a critical role in the specification of both callosal and subcerebral neurons. Loss of Satb2 impairs the differentiation of both types of

neurons. Because mouse and human SATB2 proteins differ by only three amino acids, mouse models serve as excellent tools to study SAS. We selected five clinically relevant and severe SAS-associated point mutations (SATB2 p.R239*, p.E436V, p.R459*, p.G515S, and p.R389C) and generated corresponding transgenic mouse models using the improved Genome editing via Oviductal Nucleic Acids Delivery (iGONAD) method, which integrates CRISPR-Cas9 with oviductal electroporation. To date, I have successfully generated both F0 and F1 mice carrying the p.E436V variant, confirmed by sequencing. For the p.R459* mutation, a single-stranded oligodeoxynucleotide (ssODN) repair template was designed to include a 3xFLAG tag upstream of the stop codon, allowing for the detection of the truncated protein. F0 and F1 mice with the mutation and partial tag sequence have been obtained, and the F1 generation displays typical SAS-related phenotypes, such as abnormal tooth development. Additionally, candidate F0 mice carrying the p.G515S and p.R389C variants have also been produced. These transgenic mouse models represent valuable resources for investigating the developmental and molecular basis of SAS.

Disclosures: Y. Nie: None. **B. Chen:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR102.12/A48

Topic: A.06. Developmental Disorders

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CNPQ 403646/2021-9

Title: Nicotinamide can recover mitochondrial dysfunction, dendrites impairment and synapse disruption in a cellular model of primary cortical neurons treated with rotenone: relevance to neurodevelopmental disorders

Authors: *A. SIENA[1,2], L. E SILVA[2], V. ARAUJO[2], M. RIBEIRO[2], A. ORELLANA[2], D. Z. VIANA[2], L. S. LIMA[2], E. M. KAWAMOTO[2], P. SILVA JUNIOR[3], T. R. ROSENSTOCK[4], C. SCAVONE[2];
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Abstract: Previous studies from our group demonstrated that neonatal administration of rotenone (Rot), a mitochondrial complex I inhibitor, induces mitochondrial dysfunction during neurodevelopment, resulting in an animal model that exhibits schizophrenia(SCZ)-like phenotype. In the present study, we aimed to elucidate the cellular and molecular pathways disrupted by Rot exposure that contribute to the emergence of these behavioral alterations. For this, we exposed primary cortical neurons from rats (E19) to Rot 1.325nM for 24 hours—corresponding to levels detected in the cortex of the Rot animal model. We also co-treated the cells with Nicotinamide (NAM) 10μM for 42h, a mitochondrial metabolic modulator. Then, we analysed: i) superoxide production; ii) mitochondrial respiration; iii) mitochondrial dynamics; iv) dendrite arborization; and v) synapse formation. All data was normalized to Vehicle group (Veh=100%), expressed as mean±SEM and analysed by One Way ANOVA with Bonferoni pot-hoc. We found a decrease in superoxide production in Rot (84.9±4.5%; p=0.016 vs. Veh) that was reverted by NAM co-treatment (106.2±3.5%; p=0.001 vs. Rot). The mitochondrial respiration was impaired by Rot, in relation to Veh, at basal state (73.3±9%; p=0.007); ATP-linked respiration (73.1±8.2%; p=0.03), maximal respiration (71.6±7.6%; p=0.03) and spare capacity (76.4±7.8%; p=0.03). The co-treatment with NAM recovery the basal respiration (95.7±4.8%; p=0.04 vs. Rot) and ATP-linked respiration (94.9±4.4%; p=0.03 vs. Rot). Indeed, the levels of pDPR1 protein, related to mitochondrial fission, decreased in the Rot (58.51±3.6%; p=0.03 vs. Veh) and NAM co-treatment could not revert this feature. Moreover, the protein TOM40, that indicates mitochondrial mass, were increased on Rot (164.3±22.8%; p=0.03 vs. Veh) and NAM co-treatment returned the TOM40 levels to the same as Veh (92.4±8.2%; p=0.03 vs. Rot). We also verified that Rot impaired the dendrites number (Rot: 18.57±0.9; Veh: 26.9±1.92; p=0.002) and length (Rot:30.06±1.55μm; Veh: 37.18±1.6μm; p=0.01) and both aspects were improved by NAM co-treatment (number: 38.01±1.59μm; p=0.004 vs. Rot; length: 23.79±0.92; p=0.04 vs. Rot). Finally, the synapse occurrence (measured by PSD95 and Synaptophysin colocalization) was reduced on Rot group (0.16±0.02; p=0.01) in relation to Veh (0.27±0.02), and NAM co-treatment reverted this damage (0.33±0.03; p<0.0001 vs. Rot). Collectively, these findings strength the role of mitochondrial integrity in neuronal development and provide mechanistic insights into how mitochondrial dysfunction may contribute to the pathophysiology of neurodevelopmental disorders, such as SCZ.

Disclosures: A. Siena: None. **L. E Silva:** None. **V. Araujo:** None. **M. Ribeiro:** None. **A. Orellana:** None. **D.Z. Viana:** None. **L.S. lima:** None. **E.M. Kawamoto:** None. **P. Silva Junior:** None. **T.R. Rosenstock:** A. Employment/Salary (full or part-time): Sygnature Discovery. **C. Scavone:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.13/A49

Topic: A.06. Developmental Disorders

Support: NICHD intramural projects HD008962
NICHD Scientific Director's Award
NICHD Intramural Research Fellowship

Title: Multimodal transcriptomics reveal transcription dynamic alteration in a X-linked myoclonic epilepsy and Partington syndrome-like mice model

Authors: *J. LI, A. TANZILLO, V. GARG, Y. ZHANG, T. J. PETROS;
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Abstract: Arx (Aristaless-related homeobox) is an X-linked transcription factor that is expressed in inhibitory neurons within the ganglionic eminences as they exit the cell cycle. In humans, ARX variants are one of the leading causes of several distinct X-linked intellectual disabilities (XLID) and related syndromes. Notably, recent clinical evidence indicates that >50% of heterozygous female carriers of ARX variants also display mild to severe phenotypes. Loss of Arx results in aberrant interneuron differentiation & cell migration, with many models displaying infantile spasms and epilepsy. Here we generated *Nkx2.1-Cre;Arx*$^{F/Y}$ cKO males and *Nkx2.1-Cre;Arx*$^{F/+}$ heterozygous (Het) females to remove Arx in all MGE-derived neurons. The cKO male mice displayed severe phenotypes with spasms and epilepsy, likely recapitulating X-linked myoclonic seizures, spasticity and intellectual disability (XMESID) syndrome. Het female mice displayed mild to moderate anxiety and locomotor defect, mimicking symptoms of Partington syndrome. As expected, we observe significant reduction in PV+ and SST+ interneurons in these both cKO males and Het females, leading to increased seizure susceptibility. We performed single cell sequencing and spatial transcriptomics to identify genetic and cellular changes in embryonic and adult mice. In embryonic Arx cKO male mice, distinct cell clusters are completely lost and novel clusters appeared, whereas het females displayed both normal and novel cell clusters. In adult mice, we observed dysregulation of many neuropeptides in CA3 of cKO males, which likely modulates neuronal excitability and contributes to epileptogenesis. In addition, we identified non-cell autonomous transcriptional changes in excitatory cortical neurons in both sexes. Overall, we uncovered distinct dynamic transcription changes in Arx cKO males and Het females, likely underlying distinct phenotypes in patients.

Disclosures: J. Li: None. **A. Tanzillo:** None. **V. Garg:** None. **Y. Zhang:** None. **T.J. Petros:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.14/A50

Topic: A.06. Developmental Disorders

Support: 1ZIANS002994-21

Title: Neurodevelopmental disorder-associated variants affect NMDA receptor signaling and trafficking

Authors: *H. RYU[1], S. LEE[1], M. M. VIEIRA[1], S. LIU[2], K. W. ROCHE[1];
[1]NIH, Bethesda, MD; [2]GeneDx, Gaithersburg, MD

Abstract: Human rare variants in synaptic proteins are increasingly recognized as contributing factors to neurodevelopmental disorders (NDDs), including intellectual disability, epilepsy, and schizophrenia. Among these, mutations in *GRIN* genes, which encode subunits of NMDA receptors (NMDARs), are strongly implicated. In this study, we investigated the functional impact of two rare *GRIN2B* C-terminal domain (CTD) variants—GluN2B-1485 CextX1 and GluN2B-1485 CextX7—identified in human patients. These variants result in C-terminal extensions of 1 and 7 amino acids, respectively, and are located within the PDZ-binding motif critical for interaction with PSD-95 and stabilization of NMDARs at the synaptic membrane. Biochemical assays demonstrated that both variants exhibit impaired binding to PSD-95 and reduced surface expression of NMDARs. Further investigation revealed that these variants undergo selective endocytosis and degradation. A rescue assay using dominant-negative dynamin and degradation pathway inhibitors (MG-132 for proteasomal inhibition and chloroquine for lysosomal inhibition) indicated that the variants are primarily degraded via a dynamin-dependent, lysosomal pathway. Using primary cultured neurons, we observed reduced dendritic spine number and density in cells expressing the variants. Our findings identify a selective trafficking and degradation mechanism that governs GluN2B receptor stability, providing insight into how disruptions in this pathway may contribute to GRIN-associated NDDs. These results underscore the importance of post-translational regulation of NMDARs in maintaining synaptic integrity and function.

Disclosures: H. Ryu: None. **S. Lee:** None. **M.M. Vieira:** None. **S. Liu:** None. **K.W. Roche:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.15/A51

Topic: A.06. Developmental Disorders

Title: Transcriptome analysis of neuronal stem cell reveals critical role of neuromodulators in Haddad syndrome

Authors: *T. STOBDAN[1,2], I. DWIVEDI[2], V. VENTRAPRAGADA[3], D. LESSER[5], G. G. HADDAD[2,4,5];
[2]Pediatrics, [3]Biol. Sci., [4]Neurosciences, [1]Univ. of California San Diego, La Jolla, CA; [5]Rady Children's Hosp., San Diego, CA

Abstract: Background: Haddad syndrome (HS) is a rare genetic disorder where individuals have both congenital central hypoventilation syndrome (CCHS), a severe genetic disorder of neurodevelopment that controls breathing, and Hirschsprung's disease (HSCR), characterized by a lack of enteric nervous system ganglion cells (aganglionosis). Both CCHS and HSCR result from abnormal development of neural crest cells during embryonic development that lead to a broader structural and functional impairments of the autonomic nervous system (ANS). Only surgical or supportive therapies are currently available. At the molecular level mutations, especially poly-alanine repeat mutation (PARM), in PHOX2B, a transcription factor, known to have a role in ANS development, was identified as a diagnostic marker. However, the downstream implications of PARM are unknown.Method: In order to understand the underlying molecular mechanisms, we reprogrammed iPSCs from HS patients, both with PARMs, and family members and differentiated them into neuroepithelial stem cells . We tagged PHOX2B with eGFP, utilized fluorescence-activated cell sorting (FACS) to isolate $PHOX2B^{+}$ cells and performed transcriptomic analysis.
Result: PHOX2B antibody staining reveals that the $eGFP^{+}$ cells were also $PHOX2B^{+}$. Transcriptome analysis comparing $PHOX2B^{+}$ cells from patients (P2BM) with controls (P2BW) reveals 1281 differentially expressed genes (DEGs), a five time higher number than the comparison of background $PHOX2B^{-}$ cells from patients (NP2BM) with controls (NP2BW). Fold-Change-Specific Enrichment Analysis, which reveals a group of genes regulated in a specific and coordinated manner, reveal 'negative regulation of dopamine secretion', 'de novo Inosine monophosphate (IMP) biosynthetic process' and 'noradrenergic neuron development' among the top biological processes impacted by the PARM.
Conclusions: Given that both dopamine and noradrenaline overlap in multiple domains, we hypothesize that a coordinated dysregulation of these neuromodulators or their related biological process, plays a critical role in the pathogenesis of HS. The identification of downstream targets will be critical for the development of potential novel therapeutic targets.

Disclosures: T. Stobdan: None. **I. Dwivedi:** None. **V. Ventrapragada:** None. **D. Lesser:** None. **G.G. Haddad:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.16/A52

Topic: A.06. Developmental Disorders

Title: Single-cell-level dissection of neuronal lineages and transcriptomic alterations in DiGeorge syndrome

Authors: *J. LEE, M. CHOI;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: To better understand the complexity of mammalian brain development and the mechanism of pathogenesis, cell lineage tracing has emerged as a foundational technique in developmental neuroscience. This approach enables the reconstruction of origins and trajectories of diverse cells within the mammalian brain, which is essential for understanding the dynamics of cellular heterogeneity. Recent advances combining genetic barcoding and high-throughput single-cell RNA sequencing (scRNA-seq) have significantly improved the resolution of lineage tracing. DiGeorge syndrome (DGS) is a genetic disorder characterized by aberrations in neural crest cell-derived tissues, such as congenital heart defects, craniofacial defects, and immune dysfunction. Notably, patients also suffer from elevated risks for psychiatric and neurological conditions, the genetic mechanisms of which remain poorly understood. To investigate the mechanisms of abnormalities in brain development in DGS, we employed single-cell lineage tracing combined with transcriptomic profiling in a DGS mouse model (*LgDel+/-*). More specifically, we devised a barcode library modeled on the CellTag system and delivered it via a *piggybac*-mediated *in utero* gene transfer to developing mouse embryos at embryonic day (E) 12.5. The embryonic brains were harvested at E18.5 and subjected to scRNA-seq. We identified distinct transcriptional changes and neuronal lineages in the DGS model, with particularly notable alterations in medium spiny neurons and a subtype of layer 6 excitatory neurons that appeared to originate from the same lineages. Our approach provides unprecedented insights into the cellular and genetic mechanisms underlying development in DGS.

Disclosures: J. Lee: None. **M. Choi:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.17/A53

Topic: A.06. Developmental Disorders

Title: Paxalisib: Repurposing of PI3K pathway modulators for the treatment of PTEN hamartoma tumour syndrome.

Authors: C. PAPADOPOULOS[1], K. MÜLLER[1], P. FRIESS[1], F. TINARELLI[1], T. FIEBLINGER[1], M. MAJANDINOW[1], V. COSTANTINI[2], A. MERCURI[2], P. MARRESE[2], P. GERRARD[2], ***P. ELVIN**[3];
[1]Evotec SE, Hamburg, Germany; [2]Aptuit, an Evotec Co., Verona, Italy; [3]PTEN Res., Cheltenham, United Kingdom

Abstract: PTEN hamartoma tumour syndrome (PHTS) is a rare disease arising from germline mutations in PTEN. Approximately 25% patients with PHTS may develop symptoms of autism spectrum disorder (ASD) and ~2% patients with idiopathic ASD have been found to harbour PTEN mutations. PTEN mutations lead to an upregulation of PI3K-Akt-mTOR signalling that has been associated with macrocephaly and structural and functional change in hippocampal and cortical neurons in both human and murine CNS. Currently there are no approved treatments for

PHTS although a randomised placebo controlled trial of the mTOR inhibitor everolimus demonstrated a statistically significant improvement in the social domain. Drug repurposing studies in PTEN loss mouse primary neurons identified paxalisib, a dual pan PI3K-mTOR inhibitor, as a potential candidate for treatment of PHTS ASD. Adenovirus mediated delivery of PTEN shRNA resulted in enhanced neurite outgrowth and increased neuronal activity in mouse primary neuron cultures. Paxalisib inhibited the enhanced neurite outgrowth and neuronal activity in PTEN loss neurons at doses that were without cytotoxicity towards wild-type neurons. Inhibition of neurite outgrowth and neuronal activity was correlated with reduced levels of neuronal phospho-Akt and phospho-S6. Pharmacokinetic and pharmacodynamic studies suggest that paxalisib, at tested doses, crosses the blood brain barrier and inhibits PI3K pathway activity at exposures correlated with in vitro inhibition of aberrant PTEN loss neuronal change. Paxalisib is a promising candidate for assessment in a preclinical PHTS disease model and may be a potential candidate for clinical evaluation.

Disclosures: C. Papadopoulos: A. Employment/Salary (full or part-time): Evotec SE. **K. Müller:** A. Employment/Salary (full or part-time): Evotec SE. **P. Friess:** A. Employment/Salary (full or part-time): Evotec SE. **F. Tinarelli:** A. Employment/Salary (full or part-time): Evotec SE. **T. Fieblinger:** A. Employment/Salary (full or part-time): Evotec SE. **M. Majandinow:** A. Employment/Salary (full or part-time): Evotec SE. **V. Costantini:** A. Employment/Salary (full or part-time): Aptuit, an Evotec Company. **A. Mercuri:** A. Employment/Salary (full or part-time): Aptuit, an Evotec Company. **P. Marrese:** A. Employment/Salary (full or part-time): Aptuit, an Evotec Company. **P. Gerrard:** A. Employment/Salary (full or part-time): Aptuit, an Evotec Company. **P. Elvin:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

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Smith Family Foundation Odyssey Award
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NIH: R35NS116804
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USDA NIFA 2022-67018

Title: Acslx-mediated lipid homeostasis orchestrates synaptic and cognitive plasticity

Authors: *H.-S. LI[1], B. LIU[1], L. A. COLGAN[4], S. SUN[2], R. YASUDA[5], D. KONG[3]; [1]Harvard Med. School/Boston Children's Hosp., Boston, MA; [2]Harvard Med. School/Boston Children's Hosp., Brookline, MA; [3]Endo/Pediatrics, Harvard Med. School/Boston Children's

Hosp., Boston, MA; [4]Max Planck Florida Inst. for Neurosci., Jupiter, FL; [5]Max Planck Florida Inst., Jupiter, FL

Abstract: Mutations in the lipid-metabolizing enzyme acyl-coenzyme A (CoA) synthetase long-chain family member x (Acslx) are linked to intellectual disability, yet the underlying mechanisms remain unclear. Here, we generated neuronal Acslx knockout mice, which exhibited cognitive deficits, confirming a critical role for Acslx in neurodevelopment. Transcriptomic profiling of the hippocampus revealed downregulation of synapse-related genes upon Acslx deletion. We further identified that the brain-specific Acslx isoform, Acslx_B, is enriched in dendrites and dendritic spines. Loss of Acslx in the hippocampus significantly impaired dendritic spine maturation, neuronal intrinsic excitability, synaptic plasticity, and engram cell activation. Lipidomic analysis combined with two-photon fluorescence lifetime imaging microscopy (FLIM) demonstrated that Acslx modulates synaptic function through diacylglycerol-PKC signaling. Remarkably, *in vivo* administration of a clinically tested PKC activator fully rescued the synaptic deficits. Thus, this study defines the pathogenetic basis of Acslx-related ID and advances a promising therapeutic strategy.

Disclosures: H. Li: None. **B. Liu:** None. **L.A. Colgan:** None. **S. Sun:** None. **R. Yasuda:** None. **D. Kong:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

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Program #/Poster #: PSTR102.19/A55

Topic: A.06. Developmental Disorders

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Smith Family Foundation Odyssey Award
RSZ TNC Pilot Award
BCH-Feihe Pediatric Brain Development Fund
NIH: R35NS116804
NIH: R01MH080047
USDA NIFA 2022-67018

Title: Lipid Homeostasis Mediated by Acslx in Cognitive Development and Deficits

Authors: H.-S. LI[1], ***B. LIU**[2], L. A. COLGAN[3], S. SUN[4], R. YASUDA[5], D. KONG[6]; [1]Harvard Med. School/Boston Children's Hosp., Boston, MA; [2]Boston Children's Hosp. and Harvard Med. Sch., Boston, MA; [3]Max Planck Florida Inst. for Neurosci., Jupiter, FL; [4]Harvard Med. Sch., Brookline, MA; [5]Max Planck Florida Inst., Jupiter, FL; [6]Endo/Pediatrics, Harvard PhD Program In Neurosci., Boston, MA

Abstract: Neurodevelopment and cognitive disorders like intellectual disability (ID) affect the global population, yet effective therapies remain unavailable. Emerging evidence implicates

dysregulated lipid metabolism in the pathogenesis of ID, but the underlying mechanisms and therapeutic potentials are not fully understood. Our recent findings demonstrate that lipid homeostasis, regulated by a lipid-metabolizing enzyme long-chain acyl-coenzyme A (CoA) synthetase (Acslx), functions as a key modulator of synaptic and cognitive plasticity. Notably, mutations in Acslx have been linked to severe intellectual disability in humans. We further hypothesize that loss-of-function of Acslx plays a pathogenic role in the disease, and that restoring Acslx expression or restoring lipid signaling can prevent or reverse the cognitive deficits. To test this, we implemented a neuron-specific "deletion-then-re-expression" strategy in mice by using a brain-enriched AAV viral system and discovered a unique isoform of the enzyme that plays an essential role in neurodevelopment and cognition. Integrating "omics" studies, we have also identified a disrupted downstream signaling pathway following the dyslipidemia caused by the deletion of the Acslx. Importantly, we further screened and identified a small molecular compound, which effectively reactivated the pathway and restored the cognitive function. Together, our findings reveal an innovative mechanism in the brain behind intellectual disability and provide a promising therapeutic strategy.

Disclosures: H. Li: None. **B. Liu:** None. **L.A. Colgan:** None. **S. Sun:** None. **R. Yasuda:** None. **D. Kong:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.20/A56

Topic: A.06. Developmental Disorders

Support: KO1MH133970

Title: Investigating convergent effects of neuropsychiatric risk variants on bioenergetic function in human cortical organoids

Authors: *J. GUNDY[1], M. ROBINETTE[3], V. FAUNDEZ[3], G. J. BASSELL[4], R. PURCELL[2]; [1]Virginia Tech., Manassas, VA; [2]Fralin Biomed. Res. Inst., Virginia Tech., Roanoke, VA; [3]Cell Biol., Emory Univ., Atlanta, GA; [4]Emory Univ. Sch. of Med., Atlanta, GA

Abstract: The neurological basis of complex psychiatric conditions such as schizophrenia and autism spectrum disorder remains poorly understood. These disorders involve many different genetic factors, making it difficult to identify specific biological mechanisms. Recent advances in human genomics have led to the identification of several rare copy number variants (CNVs) that confer substantial risk for these disorders and may offer valuable insight into underlying disease pathways. Among these CNVs are the 3q29 deletion (3q29Del) and 22q11 deletion (22q11Del), which confer high risk for both schizophrenia and autism, but the underlying mechanisms that link these CNVs to disease remain unclear. An emerging question in the field is whether these CNVs act through distinct mechanisms specific to each variant or whether there

are shared biological pathways. To test if 3q29Del and 22q11Del similarly disrupt human neurobiology, we engineered either the 1.6Mb 3q29Del or the 2.5Mb 22q11Del into a neurotypical induced-pluripotent stem (iPS) cell line. We differentiated these lines into human dorsal cortical organoids and analyzed the impact of each CNV on developing neural proteomes from 50-150 days in culture. Quantitative proteomic analyses revealed that both 3q29Del and 22q11Del organoids exhibited dysregulation of proteins involved in bioenergetic processes, including mitochondrial translation, suggesting shared vulnerability in cellular energy metabolism. We hypothesized that challenging 3q29Del and 22q11Del organoids to solely rely on oxidative phosphorylation (OxPhos) for ATP production could reveal mitochondrial vulnerabilities. To test this hypothesis, we cultured 6-week organoids for 7 days in either standard glucose based medium, or equimolar galactose medium to induce metabolic stress. We determined the effects of this metabolic challenge on organoid transcriptomes and proteomes and found that both CNV lines exhibit altered responses to galactose induced metabolic stress when compared to controls. This altered response includes differential expression of genes and proteins associated with mitochondrial pathways, OxPhos, and overall cellular metabolic activity. Both 3q29Del and 22q11Del lines appear to show distinct patterns of dysregulation, which may suggest altered compensatory mechanisms. These findings help to support the role that mitochondrial dysfunction may play in the biological basis of neurodevelopmental disorders associated with rare CNVs. Both 3q29Del and 22q11Del organoids exhibited alterations in response to metabolic stress, with genotype specific patterns of dysregulation.

Disclosures: J. Gundy: None. **M. Robinette:** None. **V. Faundez:** None. **G.J. Bassell:** None. **R. Purcell:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.21/A57

Topic: A.06. Developmental Disorders

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NIH grant R01AA031319

Title: Neuroprotective role of DING protein in fetal alcohol spectrum disorders and depression

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Abstract: Introduction: An estimated 20% of women consume alcohol during pregnancy, and 10% of women receive antidepressants in pregnancy. Women with depression are more likely to use alcohol (EtOH) in early pregnancy and are more likely to have a child with fetal alcohol spectrum disorders (FASD). Previously, we provided evidence for neuroprotection against EtOH-mediated toxicity by DING phosphatase extracted from St. John's wort in rat and human fetal neurons *in vitro*. Now, we study the roles of the DING protein, serotonin transporter (SERT), and serotonin (5-HT) receptor in EtOH/Selective Serotonin Reuptake Inhibitor (SSRI)-mediated neurotoxicity. pDING (p38SJ), a member of the DING family of proteins, has been shown to have neuroprotective abilities under cellular stress and injury induced by alcohol. **Methods:** Fetal brain tissue was collected between 9 to 23 weeks' gestation. Primary neurons and neurospheres were prepared using a 16-week fetal brain. Exposure was assessed based on detailed EtOH and SSRI questionnaires. Neurotoxicity/apoptosis was assessed in synaptosome extracts with the Caspase-Glo 3/7 assay and Neurotoxicity array. Developmental expressions of DING, SERT, and 5-HT receptor protein levels were quantified in the brain, placenta, synaptosomes, serum, and fetal brain-derived exosomes (FB-Es) by quantitative western blot assay and ddPCR using the Odyssey® CLx Imaging System. Statistical testing included ANOVA. **Results:** Increased pDING, when added to cells or overexpressed, was associated with increased cell survival. Developmental expressions of pDING, in the presence of EtOH- or SSRI-exposure, were investigated in brain and placenta tissues. While HTR1A, 5-hydroxytryptamine serotonin receptor 1A (5-HT1A, 5HT1a, ADRB2RL1, ADRBRL1) was strongly inhibited under stress (EtOH or viral infection) conditions (>100 fold), pDING was not only able to reverse the negative effects of stress, as measured by the synaptic plasticity array) but also upregulate the 5-HT receptor (5-fold compared to untreated control) upon treatment of neurons. **Conclusions**: Maternal EtOH use is associated with decreased 5-HT receptor and pDING protein expression in the fetal brain and with increased neuronal apoptosis. Combined exposure to EtOH and SSRIs may have greater toxic effects than either one alone. pDING reversed the toxic effects of EtOH on serotonin receptors in neurons and neurospheres. Our findings provide potential mechanisms for the neuroprotective effects of pDING, which might suggest neuroprotective approaches to preventing FASD.

Disclosures: M.E. Selzer: None. **A. Darbinyan:** None. **N. Merabova:** None. **L. Goetzl:** None. **M.F. Morrison:** None. **S. Amini:** None. **N. Darbinian:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

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Program #/Poster #: PSTR102.22/A58

Topic: A.06. Developmental Disorders

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National Institute on Alcohol Abuse and Alcoholism (NIAAA) of NIH grant R01AA031319

Title: Myelin Basic Protein as a Potential Predictive Biomarker for Fetal Alcohol Spectrum Disorders

Authors: *J. HAMZE[1,2], U. BHARAI[2], E. C. SPARKS[3], N. MERABOVA[4], G. TATEVOSIAN[5], A. DARBINYAN[6], M. F. MORRISON[7], L. GOETZL[9], N. DARBINIAN[10], M. E. SELZER[8];
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Abstract: Introduction: Alcohol use is estimated to occur in 9.8% of pregnancies worldwide and can cause Fetal Alcohol Spectrum Disorders (FASD), the leading preventable cause of pediatric cognitive disability, affecting 5% of the US population. Globally, 1 in 67 alcohol-consuming women during pregnancy will deliver a child with the most severe form, Fetal Alcohol Syndrome (FAS). Worldwide, 119,000 children are born with FAS each year. Signs include small stature, unique facial appearance, small head circumference, small eyes, deficits in cognition and behavior, and destruction of neurons and oligodendrocytes (OL). Women who drink also suffer from depression, which may contribute to the genesis or severity of FASD. Maternal obesity (mObesity) also negatively impacts white matter development in the fetal brain. Children with FASD also are at risk for epilepsy. Effective non-invasive biomarkers for FASD might lead to improved prognosis and prevention. **Methods:** 255 women undergoing voluntary termination of pregnancy (n=95 non-alcohol users; n=160 alcohol users, based on an EtOH questionnaire) were stratified by gestational age (GA; first trimester 9-14 wks; 2nd trimester 14.1-22 wks), race, ethnicity, mObesity, and mDepression. 160 fetal eye tissues (9-22 wks) and matching maternal plasmas were collected. Fetal brain-derived exosomes (FB-E) were isolated from maternal plasma. Exosomal RNA was studied for expression of the OL marker myelin basic protein (MBP) by ddPCR. Protein levels were confirmed by ELISA. Eye diameter was measured in histological sections using a digital caliper. **Results:** Qualifying subjects were included in order of recruitment until we had 80 EtOH-exposed cases and 80 controls during the 1st and 2nd trimesters (the largest such study to date). EtOH exposure was associated with increased mObesity and with reduced FB-E MBP levels in both 1st and 2nd trimester FB-Es (↓ 2.3-fold, $p < 0.001$). Fetal eye diameter also was significantly reduced in EtOH-exposed fetuses

($p < 0.01$). Control levels of MBP rose dramatically in the 2nd trimester, whereas the MBP level in the EtOH group did not show this sudden jump. **Conclusions:** Alcohol use in pregnancy is associated with mObesity, and with reduced levels of MBP in the fetal brain. An outcomes study is underway to determine whether FB-E MBP or other molecular markers can predict which at-risk fetuses will be born with FASD.

Disclosures: J. Hamze: None. **U. Bharai:** None. **E.C. Sparks:** None. **N. Merabova:** None. **G. Tatevosian:** None. **A. Darbinyan:** None. **M.F. Morrison:** None. **L. Goetzl:** None. **N. Darbinian:** None. **M.E. Selzer:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.23/A59

Topic: A.06. Developmental Disorders

Support: Hartwell Foundation Individual Biomedical Research Award A23-2439

Title: Leveraging neural modeling of channelopathies to elucidate neural mechanisms underlying neurodevelopmental disorders

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Abstract: Neurodevelopmental disorders (NDDs), such as epilepsy, autism spectrum disorder, and developmental delays, present with considerable clinical variability and often impair social interactions, speech, and cognitive development. A key feature of these disorders is an imbalance in excitatory/inhibitory (E/I) input, which disrupts neuronal circuit function during development. Brain channelopathies, where neuronal ion channel activity is altered, provide an ideal model for studying E/I imbalance, as their effects can be directly linked to neuronal excitability. Ion channels are crucial in generating electrical activity in neurons, and disruptions to this activity are strongly associated with NDDs. Studying channelopathies at the single-cell level is well-established, however, investigating the impact of specific channel mutations on neuronal circuits requires more complex approaches. By utilizing a previously developed murine primary motor cortex (M1) model built using NetPyNE and NEURON, we employ large-scale, highly detailed biophysical neuronal simulations to examine how channel mutations influence individual and network neuronal activity. These simulations offer a mechanistic understanding of how channelopathies contribute to E/I imbalance and the pathology of NDDs. Through the M1 cortical column simulation, we measure the effects of biophysical changes in ion channels on network excitability and neuronal firing patterns, providing insights into the pathophysiology of

simulated channelopathies. We implement specific genetic mutations associated with NDDs to study channelopathies by modeling changes in cellular biophysical properties. Parameters for the simulated channelopathies were developed using biophysical properties that were experimentally obtained. Through altering neuronal activity through channelopathies, we are then able to model pharmacological interventions, such as GABA potentiators or AMPA inhibitors, to explore how these drugs may be able to restore activity back to baseline. This model not only serves as a tool for investigating specific channelopathy cases but also enables the exploration of pharmacological agents aimed at restoring E/I balance. Ultimately, this approach will enhance our understanding of targeted therapeutic strategies for alleviating disease symptoms and may uncover novel treatments with clinical potential.

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Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.24/A60

Topic: A.06. Developmental Disorders

Support: NIH Grant KO1 133970

Title: Investigating the impact of iron deficiency on neuronal development in 3q29 Deletion Syndrome

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Abstract: Abstract Decades of epidemiology and genomic studies have identified robust environmental and genetic risks factors for neuropsychiatric disorders such as schizophrenia (SCZ) and autism spectrum disorder (ASD). A copy number variant called 3q29 Deletion Syndrome (3q29Del) is a rare genetic condition affecting approximately 10,000 individuals in the United States, in which affected individuals are 40 times more likely to develop schizophrenia and 19 times more likely to be diagnosed with ASD, as well as having increased diagnostic rates of ADHD and anxiety. This broad and variable phenotypic spectrum of neuropsychiatric disorders, all attributed to the same variant, is suggestive of an environmental contribution. The 3q29Del results in hemizygosity of 22 protein-coding genes including *TFRC*, which encodes the primary cellular iron import receptor. Our analysis of the 3q29 Registry revealed that individuals with 3q29Del are 11 times more likely to report a history of anemia, which is commonly caused by iron deficiency (FeD). Our research aims to investigate the potential link between *TFRC* hemizygosity and 3q29Del FeD, and the impact this link may have on developing neurons. We hypothesize that iron deficiency is an environmental mediator of

3q29Del neuropsychiatric phenotypes. To test this hypothesis, we analyzed the frontal cortex and cerebellum tissue from mice with the homologous 3q29Del who were fed a standard iron replete chow diet. We found that compared to wild-type controls, 3q29Del mice had less iron in cortical and cerebellar tissue and displayed proteomic evidence of FeD. When exposed to the iron chelator deferoxamine (DFX), 3q29Del HEK cells and iPSC-derived neural progenitor cells had little to no TFRC regulatory response, while control cells showed significantly increased levels, suggesting that 3q29 cells are unable to compensate in FeD environments. We measured activity of mitochondrial Complex I (CI), which contains multiple necessary iron-sulfur clusters, and found that while control cells were unaffected by mild iron chelation, 3q29Del cells had significantly impaired CI function. These findings suggest that 3q29Del appears to increase vulnerability to FeD and our ongoing studies are aimed at the underlying mechanisms of this interaction.

Disclosures: A.R. Herriges: None. **Y. Du:** None. **J.G. Mulle:** None. **R.H. Purcell:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.25/A61

Topic: A.06. Developmental Disorders

Support: Northcott Devon Medical Foundation
Welcome trust TREE fund
Bristol Japanese Culture Society
British Society for Neuroendocrinology

Title: Exploring the Functions of JAKMIP1 in Neuronal IL-6/STAT3 Signaling and Its Relevance to Chromosome 15q-Duplication Syndrome

Authors: *A. OGURO-ANDO;
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Abstract: Autism spectrum disorder (ASD) and chromosome 15q-duplication syndrome (Dup15q) are neurodevelopmental disorders associated with synaptic dysfunction and neuroimmune alterations. JAKMIP1 (Janus Kinase and Microtubule Interacting Protein 1) is a neuronal protein with a putative role in regulating the JAK-STAT signaling pathway. Dysregulated JAKMIP1 expression has been reported in Dup15q, but its functional impact on neuronal and glial signaling remains unclear.
The IL-6/STAT3 pathway is a critical mediator of neuroinflammation and has been implicated in both neurodevelopment and neuroendocrine regulation. We hypothesize that JAKMIP1 modulates IL-6/STAT3 signaling in neurons, influencing neuroimmune interactions that may contribute to Dup15q pathology. In JAKMIP1 knockout (KO) models, we observed altered neuronal morphology and increased astrocyte and microglial densities in the somatosensory

cortex, suggesting a role for JAKMIP1 in regulating neuroinflammatory responses.
To further investigate this, we performed magnetic-activated cell sorting (MACS) to analyze JAKMIP1 expression across different brain cell populations, including neurons, astrocytes, microglia, and oligodendrocytes. Our findings indicate that JAKMIP1 is primarily expressed in neurons, whereas STAT3, a key downstream effector of IL-6 signaling, is highly enriched in microglia. Given the established role of STAT3 in neuroendocrine signaling, we are currently assessing how JAKMIP1 deficiency influences STAT3 activation and whether this impacts neuroendocrine pathways relevant to ASD and Dup15q.
By elucidating the molecular mechanisms linking JAKMIP1, IL-6/STAT3 signaling, and neurodevelopment, this study aims to provide insights into the interplay between neuroimmune regulation and neuroendocrine function. Understanding these interactions may contribute to identifying new therapeutic targets for neurodevelopmental disorders characterized by JAK-STAT pathway dysregulation.

Disclosures: A. Oguro-Ando: None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.26/A62

Topic: A.06. Developmental Disorders

Support: AB-Nexus Initiative MPI
R01 NS086933-05
NIDA T32 DA017637

Title: Akt1 regulation of endocannabinoid signaling in medial prefrontal cortical circuits in young adolescent mice

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Abstract: The endocannabinoid (eCB) signaling system mediates neuronal development and synaptic plasticity by activating downstream signaling pathways. One of these crucial pathways is the PI3K/AKT signaling pathway, which overlaps with synaptic functions. Interestingly, both the eCB system and AKT signaling, more specifically the AKT1 isoform, are dysfunctional within the frontal cortices of schizophrenic patients and are both crucial for proper medial prefrontal cortex (mPFC)-regulated behaviors. Therefore, we wanted to determine if AKT1

regulates mPFC function through eCB signaling and whether this is related to adolescent sensitivity to mPFC modulation by eCBs. To do this, we knocked out AKT1 and probed into a short-term retrograde eCB-mediated plasticity mechanism, depolarization-induced suppression of inhibition (DSI), and a long-term, non-retrograde eCB-mediated plasticity mechanism, slow self-inhibition (SSI), within layer 5 of the infralimbic (IL) mPFC. Here, we show that adolescent (P30) *Akt1* KO mice had reduced expression of cannabinoid 1 receptors at VGAT-positive IL mPFC terminals and reduced DSI responses. In addition, we report that SSI occurs within the IL mPFC in excitatory and CB1R-expressing interneurons. Interestingly, we observed no differences in *Akt1* KO versus SSI responses in WT mice regardless of age or neuronal subtype. Overall, this suggests that AKT1 regulates CB1R expression on CB1R-expressing GABAergic terminals in adolescent mice. These data suggest a critical period in which AKT1 and eCB signaling regulate each other for experience-dependent maturation of mPFC neural circuits.

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Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.27/B1

Topic: A.06. Developmental Disorders

Support: Grant and Support from DBT

Title: Kaptin mediated actin cytoskeleton remodelling in neuronal morphogenesis and seizure susceptibility

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Abstract: The proper functioning of the brain relies on efficient synaptic communication, which depends on cytoskeletal coordination by regulatory proteins. Kaptin, an actin-binding protein recently identified to possess actin filament capping activity, has been associated with neurodevelopmental delay and seizures in humans. In this study, we investigated Kaptin's role in neural circuit development using zebrafish as a model organism. Homozygous kaptin mutants were generated using CRISPR-Cas9, resulting in independent 14bp and 5bp deletions introducing premature stop codons, thereby producing null alleles. Whole-mount in situ hybridization at 1-cell, 24 hours post-fertilization (hpf), 48hpf, and 72hpf stages revealed maternal deposition of kaptin transcripts, followed by region-specific enrichment in the midbrain, hindbrain, and telencephalon. Early motor behaviours were evaluated via spontaneous tail coiling (STC) at 24hpf and touch-evoked escape response (TEER) at 48hpf. Compared to wild-type siblings, kaptin mutants exhibited significantly reduced coil amplitude and increased

frequency during STC, as well as decreased TEER velocity and maximum acceleration, indicating impaired motor circuitry, including possible defects in motor neurons, neuromuscular junctions, and muscle function. To assess motor neuron morphology, mutants were crossed with the Tg(*mnx1:GFP*) reporter line. Caudal primary (CaP) motor neurons in kaptin mutants displayed shorter axons and marked hyperbranching at both 26hpf and 60hpf. Rescue experiments with wild-type kaptin mRNA restored both axon length and branch density. In contrast, the actin-binding-deficient K55D variant restored axon length but not branch density, indicating that Kaptin's interaction with actin is specifically required for proper axonal branching. Given the hyperbranching phenotype and the association of kaptin mutation with increased seizure incidence in humans, seizure susceptibility was evaluated using pentylenetetrazol. This revealed kaptin mutants are more susceptible to seizures. Calcium imaging at 5dpf indicated hyperactivity in the hindbrain and optic tectum of mutants. This result prompts us to investigate kaptin mediated hyperbranching in the central nervous system causing increased seizure susceptibility. Collectively, these findings establish Kaptin as a critical regulator of actin cytoskeletal dynamics in neuronal development. Loss of kaptin causes disruption in actin cytoskeletal dynamics leading to hyperbranching, improper motor circuitry, and increased seizure susceptibility, underscoring its essential role in neural circuit development and function.

Disclosures: R. Banerjee: None. **A. Ghose:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

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Program #/Poster #: PSTR102.28/B2

Topic: A.06. Developmental Disorders

Support: NSFC Grant 82022018
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NSFC Grant 82161138025

Title: Fat2 cadherin dysfunction compromises synaptic integrity and motor function

Authors: *X. WANG[1,2], Y. PU[3], J. MIAO[3], L. GUAN[3], Y. CUI[2], J. WANG[2], L. QIN[3], Y. HAN[2], M. WÖHR[4], B. ZHANG[2];
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Abstract: Objective Motor ability is fundamental for animal survival, with dysfunction often causing life-threatening consequences. Digging—an instinctive murine behavior for foraging, nesting, and object-burying—requires precise limb coordination, serving as a key indicator of motor coordination. Vertebrate FAT cadherins (FAT1-4) are single-pass transmembrane

adhesion molecules. Each contains >30 extracellular cadherin repeats; FAT2 mutations in humans cause motor coordination deficits and cerebellar atrophy. Research into the functional mechanisms of this family has long lagged due to the immense molecular weight and complex structure of its proteins. Therefore, we try to elucidate the molecular mechanism by which FAT2 regulates motor behavior. **Methods** We engineered FAT2 transgenic mice and performed comprehensive behavioral assessments of motor/non-motor functions. Forelimb kinematics were quantified via high-speed videography. FAT2's synaptic mechanisms were dissected using: cell-surface binding assays, RNAscope hybridization, quantitative immunofluorescence, and patch-clamp recording. **Results** (1) FAT2 binds synaptic regulator Cbln1 via its first two cadherin repeat domains, with soluble Neurexin-1α competitively inhibiting this interaction; (2) Cerebellar granule cell-specific *Fat2* knockout reduced parallel fiber presynaptic vGluT1 density by 25% and excitatory current amplitude by 30%, while enhancing inhibitory currents, which phenocopied *Cbln1*-deficient mice; (3) FAT2 loss spared cerebellar macrostructure/axonal development, indicating functional rather than structural roles; (4) *Fat2*-deficient mice exhibited specific motor coordination impairments in the rotarod test, balance beam task, and marble burying behavior with intact basic locomotion and cognition. Stereotyped digging duration decreased 50%, implicating that FAT2 selectively regulates the execution of complex, cerebellum-dependent motor programs. **Conclusions** FAT2 is indispensable for motor behaviors, likely through Cbln1-dependent synaptic integrity. Given that motor dysfunction represents a core phenotype in multiple neuropsychiatric disorders, this discovery provides new directions for deciphering the molecular mechanisms of related diseases and developing targeted therapeutic strategies.

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Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.29/B3

Topic: A.06. Developmental Disorders

Support: NIH Grant RO1NS131223

Title: Defining disease mechanisms in a rare neurodevelopmental disorder caused by variants in TANC2.

Authors: *E. PATTIE, P. H. IFFLAND;
Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD

Abstract: TANC2-related disorder (TRD) is characterized by neurodevelopmental, neurological, and psychiatric conditions including intellectual disability, autism spectrum disorder, childhood speech and motor delays, repetitive behavior, and epilepsy. TRD is caused by haploinsufficiency

of TANC2 due to autosomal dominant loss-of-function variants in the *TANC2* gene. While TANC2 is expressed across many organ systems and cell types, it is most abundant in neuroglial progenitor cells in the developing neocortex. The mechanism underlying TRD is still poorly understood, but TANC2 is predicted to play a role in synaptic scaffolding, vesicle transport, and mTOR pathway regulation. As the mTOR pathway plays a crucial role in cell growth and cytoskeletal organization, and mTOR pathway hyperactivation has been shown to cause malformations of cortical development and epilepsy, we hypothesized that a loss of TANC2 would lead to dysregulation of cytoskeletal dynamics due to an increase in mTOR pathway activity. An *in vitro* approach was used to test this hypothesis. Patient-derived dermal fibroblasts and *TANC2* KO N2a cells were used. Changes in mTORC1 and mTORC2 activity were assessed with Western blotting by measuring phosphorylation levels of S6 (Ser 240/244), 4E-BP1 (Thr 37/46), and AKT (Ser 473), where we found no significant differences compared to wildtype and scramble controls. Using retinoic acid and low serum media, N2a cells were differentiated into neuron-like cells to assay morphological changes induced by *TANC2* KO. No differences were observed in soma size, primary process number, and primary process length between *Tanc2* KOs and to controls. In fibroblasts, live cell confocal microscopy was used to assay changes in cell migration. Using a wound healing assay, a significant reduction in directional variation in patient cells was observed compared to controls [$n = 90$ cells per group across 3 biological replicates); one-way ANOVA, $P < 0.05$]. These results suggest that TANC2 may not be necessary for mTOR pathway regulation, but that it does play a critical role in cell motility, potentially in an mTOR-independent manner. Further studies will investigate the underlying mechanisms for these migration changes. Cytoskeletal dynamics are a key driver of cell migration and dendrite morphology. Therefore, understanding how TANC2 impacts cytoskeletal regulation may provide key insights into the mechanisms underlying TRD.

Disclosures: E. Pattie: None. **P.H. Iffland:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.30/B4

Topic: A.06. Developmental Disorders

Support: NIH Grant U01DA058278

Title: Nicotine vapor conditioned place preference and genomic contributions in a heritable rodent model of dopamine dysregulation

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Abstract: Individuals diagnosed with psychiatric illnesses such as schizophrenia display significantly elevated rates of tobacco use compared to the general population. This comorbidity arises from reward hypersensitivity and self-medication against cognitive deficits. However, the neurobiological correlates and mechanisms that underlie this drug abuse vulnerability remain poorly understood. In the present study we use a transgenerational model of dopamine dysregulation to evaluate reward sensitivity to nicotine vapor and related molecular markers. The F1 generation offspring of animals neonatally treated with saline (MSxFS) or quinpirole (MQxFQ) have previously demonstrated enhanced dopamine D_2 receptor sensitivity. To assess alterations in nicotine reward response, animals underwent a six-day nicotine vapor conditioned place preference (CPP) paradigm. This experiment consisted of two preconditioning trials, three conditioning trials, and one post-test. During conditioning, rats were exposed to 10 min of either 30 mg/ml nicotine, 60 mg/ml nicotine, or vehicle vapor. Subjects received 1 puff per minute in the vapor chamber and the puffs persisted for 3s each. Results from the 60 mg/ml concentration show that both MSxFS and MQxFQ groups demonstrate robust nicotine CPP expression. The vapor MSxFS group demonstrated enhanced nicotine CPP compared to MSxFS animals injected with nicotine and tested on CPP. We hypothesize that MQxFQ rats will demonstrate an enhanced CPP vs. the MSxFS group at lower concentrations of nicotine vapor. To analyze plasticity changes in neurocircuitry that underlie these differences in CPP, we will quantify brain derived neurotrophic factor (BDNF) in the prelimbic cortex (PrL) and nucleus accumbens (NAc) via ELISA. We have previously shown enhanced BDNF in MQxFQ rats after i.p. injected nicotine CPP. The PrL and NAc are implicated in reward plasticity and context-associated cue preference, as well as the pathophysiology of psychosis. We will additionally present genetic differences between F1 generation MQxFQ and MSxFS rats via single-cell RNAseq. MQxFQ rats have previously demonstrated a 22-fold increase above the MSxFS group in the nicotine addiction KEGG pathway in the infralimbic cortex. The present study demonstrates the impact of transgenerational dopamine dysregulation on drug abuse vulnerability, with relevance towards psychosis. Behavioral testing will establish enhanced reward-seeking to nicotine vapor and increases in BDNF in mesocorticolombic regions. These findings will improve understanding of nicotine comorbidity in psychosis and inform future cessation strategies for this vulnerable population.

Disclosures: A.M. Cuozzo: None. **C.D. Ahmed:** None. **B.S. Schmeichel:** None. **W. Chen:** None. **Z. Chen:** None. **C. Wang:** None. **R.W. Brown:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.31/B5

Topic: A.06. Developmental Disorders

Title: Adolescent Nicotine Exposure Enhances Alcohol Use and Withdrawal in a Heritable Rat Model of Psychosis

Authors: *C. D. AHMED[1], A. M. CUOZZO[2], L. J. WILLS[5], H. J. ROSS[3], G. A. DEEHAN, Jr.[4], J. T. GASS[5], R. W. BROWN[6];
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Abstract: Schizophrenia (SZ) exhibits a remarkably high comorbidity with substance use disorders (SUDs), particularly nicotine and alcohol (EtOH) dependence. Rates of nicotine use in individuals with SZ approach 75%, and EtOH affects approximately 25%, exceeding the general population. Mechanisms underlying this intersection remain poorly understood. Subjects tested were the offspring of two founders neonatally treated with saline (SS) or quinpirole (QQ). We have shown previous work that the QQ group demonstrates enhanced dopamine D2 receptor sensitivity into adulthood. We employed two experimental paradigms to assess EtOH consumption patterns and motivation: 1) a two-bottle choice (2BC) test, where rats had continuous 24-h access to 10% EtOH and water, with acute drinking (3-, 6-, and 24-h post-nicotine injection time points) and 2) adolescent intermittent 10% EtOH self-administration, performed using lickometers in operant chambers where rats were trained on an FR schedule of reinforcement to measure EtOH seeking. On the 2BC test, male and female Sprague-Dawley rats (PND 28-48) received daily intraperitoneal (IP) nicotine (0.6 mg/kg, base) or saline. Following 21 days of EtOH/nicotine exposure, locomotor activity was measured on an open field test during withdrawal (Days 3, 5, 7, 10, and 14 post-exposure). To evaluate long-term effects, adult drinking relapse was assessed during adulthood (PND 63-76). Neurochemical analyses included lipid peroxidation using a thiobarbituric acid reactive substances (TBARS) assay in the prefrontal cortex (PFC), and Glutathione (GSH) levels. In the 2BC test, adolescent nicotine exposure significantly enhanced acute EtOH drinking in QQ rats at the 3- and 6-hour time points compared to control (SS) rats given nicotine or saline. QQ-Nicotine animals demonstrated significantly higher percentages of EtOH consumed at 3, 6, and 24 hours. After withdrawal there was a robust enhancement of acute EtOH consumption on PND 63 in QQ rats. Sex-dependent withdrawal symptomology was observed, with QQ females exposed to nicotine/EtOH exhibiting a lack of habituation and hyperactivity on locomotor testing. Neurochemical analyses revealed nicotine-driven increases in EtOH consumption were associated with elevated lipid peroxidation in the PFC. Our findings from the self-administration paradigm revealed that nicotine-treated rats in the QQ group self-administered significantly more EtOH than other groups, highlighting increased motivation for EtOH consumption. These findings revealed that adolescent nicotine exposure significantly exacerbates alcohol consumption and withdrawal in a heritable model of psychosis.

Disclosures: C.D. Ahmed: None. **A.M. Cuozzo:** None. **L.J. Wills:** None. **H.J. Ross:** None. **G.A. Deehan:** None. **J.T. Gass:** None. **R.W. Brown:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.32/B6

Topic: A.06. Developmental Disorders

Support: NIH Grant HD101680
Internal Grant Masonic Institute for the Developing Brian 2023 Seed Grant

Title: Gestational gut microbiota regulates embryonic microglia and neocortex development

Authors: *C. H. PUGLISI[1], H. VUONG[2], T. R. MONKO[1];
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Abstract: Recent clinical research reveals changes in gestational gut microbiome composition correlates with incidents of Autism Spectrum Disorder (ASD) in the offspring. Those diagnosed with ASD display altered gut microbial composition, increased microglial density, and increased microglial activity. Changes to host gut microbiome have been shown to impact microglia activity, development, and function. Further, changes to the gestational microbiome increase microglia number, disrupt microglia colonization pattern, and alter microglia transcriptome in the embryonic brain. Embryonic microglia can regulate dopaminergic axonogenesis. We show that a depleted (ABX) or deficient (GF) gestational microbiota reduces fetal thalamocortical axon (TCA) development. However, exactly how the gestational microbiome informs developing microglia to regulate TCA development remains unclear. We hypothesize the maternal gut microbiome regulates embryonic microglia morphology and function, and adolescent offspring behaviors. We will test how the gestational gut microbiota and associated metabolites can be used as a microbiome-mediated intervention to modify neurodevelopment.

Disclosures: C.H. Puglisi: None. **H. Vuong:** None. **T.R. Monko:** None.

Poster

PSTR102: Molecular Mechanisms Underlying Developmental Disorders I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.33/B7

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

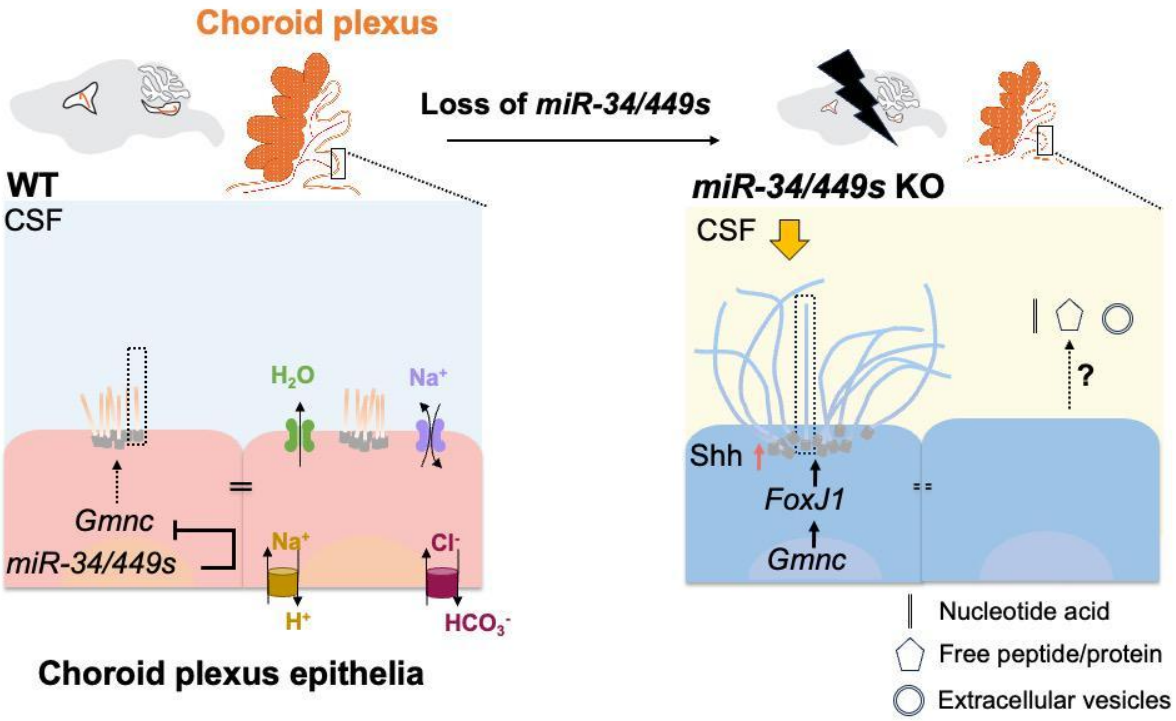
Support: NIH-N-R01NS12-LIN He

Title: Mir-34/449s regulate choroid plexus ciliogenesis to gate cerebrospinal fluid (csf) in and out

Authors: *S. MAO[1,2];
[1]UCSF, San Francisco, CA; [2]Mcb, UC Berkeley, Berkeley, CA

Abstract: Choroid plexus (ChP) epithelia contain multiple cilia per cells and its major function is to regulate cerebrospinal fluid (CSF) production to support neuronal development and

homeostasis. We previously observed that dynamic change of ChP cilia in length during normal development give rises to a decline of Shh signaling intensity and consequently an increase of CSF production. However, the mechanism of ChP cilia dynamic in choroid plexus development and CSF production is unknown. Here, we found that the complete loss of non-coding microRNA *miR-34/449s* leads to microcephaly and decreased CSF production which is characterized by impaired expression of ion channel and transporters in choroid plexus epithelia. We also uncovered that *miR-34/449s* deficiency disrupts the shortening of ChP cilia, and increases the number and length of choroid plexus cilia which dysregulate ciliary Shh signaling in choroid plexus epithelia. To investigate the molecular and cellular mechanism of *miR-34/449s* in ChP ciliagenesis and function, we develop an *in vitro* ChP cultures and identified that miR34/449s directly target essential multiciliagenesis pathway to restrain basal body assembly and ciliagenesis in ChP epithelia. Altogether, we uncover *miR-34/449s* as essential regulator in choroid plexus multi-cilia formation and dynamic which is essential for CSF regulation during development.



Disclosures: S. Mao: None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.01/B8

Topic: A.08. Adolescent Development

Support: R15DC020847

Title: Social housing alters learning strategies in a juvenile model system

Authors: *A. XANDERS[1], S. ELNAWAWI[1], A. PAPAROUSOPOULOS[1], R. ROY[1], A. CHAND[2], C. L. PYTTE[2,1];
[1]Queens College, CUNY, New York City, NY; [2]CUNY Grad. Ctr., Manhatten, NY

Abstract: Adverse childhood experiences (ACEs) are strong predictors of cognitive development, academic, and behavioral outcomes. While substantial research has explored outcomes of ACEs, more work is needed to understand how specific types of ACEs uniquely impact development. To begin addressing this, we created a model system using the highly social zebra finch which provides an opportunity to link specific types of social adversity to underlying changes in learning and feedback processing. Juvenile zebra finches (45-65 days old), roughly corresponding to human adolescence, were housed in two early life adversity conditions: "Neglect-Based" housing, in which they were socially isolated, or "Threat-Based" housing, in which they lived with a rotation of novel aggressive same-sex adults. We assessed effects of these social environments on juveniles' learning strategies and responses to reward and punishment using an operant Go/No-Go task in a song discrimination learning paradigm. The Go response required pecking a sensor to receive food reward, whereas the No-Go response required withholding pecking. Incorrect responses resulted in brief lights-out. The Threat-Based group performed more Go responses (correct and incorrect combined) than the Neglect-Based group, suggesting more impulsive or less risk-averse behavior regardless of the contingency. The Threat-Based group learned from all response types, including rewarded and non-rewarded behaviors, demonstrated by significant positive correlations between all responses and increasing accuracy across trials. The Neglect-Based birds, however, only learned from two contingencies: reward or punishment following a Go-stimulus. They did not learn from No-Go stimuli. This suggests that Neglect-Based housing may impair processing multiple stimulus-contingencies or result in attention specific to feedback from active behaviors (Go-response) and not from inhibiting behavior (No-Go response). Together, these findings provide insight into how distinct ACEs may alter neural systems for learning, decision-making, and behavioral regulation, with a goal of offering a foundation for tailored, developmentally informed interventions.

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Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.02/B9

Topic: A.08. Adolescent Development

Title: Sv2a modulator mitigates social isolation-induced binge eating in female rats

Authors: *A. M. WILLIAMS[1], V. WILLIAMS[2], A. RHEE[3], J. SIERRA[2], V. FUA[4], T. SIMON[2], T. LIMA[4], J. D. FIGUEROA[2];
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Abstract: Social deprivation, particularly during the critical developmental window of adolescence, has been shown to disrupt emotional regulation and increase vulnerability to binge eating behaviors. However, the precise neural mechanisms linking social deprivation stress to binge eating remain poorly understood. Emerging evidence suggests that social deprivation during adolescence disrupts synaptic maturation and the balance between excitatory and inhibitory (E/I) signaling in corticolimbic circuits involved in emotion and reward processing, thereby promoting binge-like eating. Synaptic Vesicle Protein 2A (SV2A), a key regulator of synaptic transmission and excitatory/inhibitory (E/I) homeostasis, is reduced in individuals with obesity and those exposed to traumatic stress. Yet, its role in stress-induced bingeing has not been defined. We hypothesized that E/I imbalance is a mechanistic link between social deprivation stress and binge eating and that the SV2A modulator, Levetiracetam (LEV, Keppra®), would attenuate binge-like behavior following adolescent social isolation (SI). Adolescent Lewis rats (n = 64; 50% female) were either pair-housed or subjected to social isolation and exposed to a three-week intermittent access model of high-fat diet-induced binge eating. In the third week, rats received either LEV (10 mg/kg) or vehicle before re-introduction to the high-fat diet (binge eating session). Behavioral tests and brain analyses were then conducted. SI led to increased weight gain, binge-like eating, heightened startle responses, and reduced sociability, with these effects being most pronounced in females. Notably, the administration of LEV significantly reduced binge-like eating in isolated female rats but not in males. Consistent with prior literature, females exhibiting binge-like behavior showed lower SV2A mRNA levels in the hippocampus, suggesting a potential molecular signature associated with stress-induced eating vulnerability. These findings identify SV2A as a potential mediator of isolation-related binge eating and support SV2A-targeting drugs as promising treatments for BED.

Disclosures: A.M. Williams: None. **V. Williams:** None. **A. Rhee:** None. **J. Sierra:** None. **V. Fua:** None. **T. Simon:** None. **T. Lima:** None. **J.D. Figueroa:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.03/B10

Topic: A.08. Adolescent Development

Support: NIH grant F31MH127805
NIH grant R01MH118297

Title: Aberrant social experience after juvenile social isolation drives sociability deficits

Authors: M. B. LEVENTHAL[1], K. OKAMURA[2], A. LIDOSKI[3], **A. KUNO**[3], V. FEDERICO[3], N. KAWAMURA[3], J. S. RICEBERG[3], L. WALTRIP[3], L. BICKS[3], M. JANIS[3], S. AKBARIAN[4], *H. MORISHITA[3];
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Abstract: Social experience is known to have a strong influence on adult brain function, behavior, and mental health, but little is known about the neurodevelopmental mechanisms by which social experience alters brain maturation. Previous studies suggest that, in male mice, there is a postnatal day (p) 21-35 juvenile critical period where social isolation causes long-lasting reductions in adult sociability and excitability of medial prefrontal cortex (mPFC) projecting to the posterior paraventricular thalamus (pPVT). However, the specific neurodevelopmental mechanisms that are disrupted by juvenile social isolation (JSI) are unknown. We unexpectedly found that JSI-induced deficits in sociability and mPFC->pPVT projection neurons are not present at the end of isolation. Instead, deficits emerge during the first two weeks of the adolescent rehousing period, when JSI mice display robust deficits in social interaction with their cagemates by accompanying an excessive activation of mPFC->pPVT projection neurons. Notably, chronically socially isolated mice (p21-50+) that were never returned to social housing, or chemogeneic suppression of mPFC->pPVT projection during rehousing period show reduced deficits compared to JSI mice. These results suggest that JSI may disrupt adult social behavior not only by impairing social development during the isolation period, but also by impairing subsequent development during the post-isolation developmental period. We propose that the prevailing “social deprivation model”, where adult social deficits are attributed to disruption of developmental processes occurring during the isolation period, should be supplemented by the “developmental mismatch model”, where social deficits are attributed to disruption of developmental processes occurring after the isolation period. Our study implicates mPFC->pPVT neuron and adolescent period as a promising circuit and a window for preventing post-isolation social deficits.

Disclosures: M.B. Leventhal: None. **K. Okamura:** None. **A. Lidoski:** None. **A. Kuno:** None. **V. Federico:** None. **N. Kawamura:** None. **J.S. Riceberg:** None. **L. Waltrip:** None. **L. Bicks:** None. **M. Janis:** None. **S. Akbarian:** None. **H. Morishita:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.04/B11

Topic: A.08. Adolescent Development

Support: NIH Grant HD109618-02

Title: Hormonal contraceptives during adolescence impact the developing prefrontal dopamine system in a rodent model

Authors: *E. DYBAS[1], R. A. GILFARB[2], D. HIRSH[3], K. M. LENZ[2], B. LEUNER[2];
[1]Neurosci. Grad. Program, [2]Dept. of Psychology, [3]The Ohio State Univ., Columbus, OH

Abstract: The development of the mesocorticolimbic dopamine (DA) system during adolescence is an important aspect of brain maturation necessary for the display of higher order executive functions such as decision making and working memory. Development of the DA system is characterized by increased DA innervation to the prefrontal cortex (PFC) and nucleus accumbens (NAc) from cell bodies originating in the ventral tegmental area (VTA) and refinement of DA receptor expression in DA target regions. In adolescent females, PFC development is in part mediated by ovarian hormones, estradiol and progesterone. Adolescence is also a time when many individuals begin using hormonal contraceptives (HCs), exogenous hormones that suppress endogenous ovarian hormone release and inhibit natural cycling. Despite the widespread use of HCs among adolescents, it is currently unknown if and how HCs may alter mesocortical DA maturation. To address this gap, we employed a model of adolescent hormonal contraceptive use where intact female Sprague Dawley rats were randomly assigned to receive daily subcutaneous injections of either vehicle (n = 13) or 10 µg ethinyl estradiol + 20 µg levonorgestrel (EE+LNG; n = 12) from postnatal day (PND) 35-56. On PND57, rats were sacrificed, and brains were processed for immunohistochemical staining of tyrosine hydroxylase (TH), the rate limiting enzyme in catecholaminergic synthesis and a commonly used marker for DA. Key regions of the mesocorticolimbic system were assessed: number of TH+ cell bodies in the VTA and coverage of DA fibers in the NAc and medial PFC (mPFC). EE+LNG treated rats showed increased TH+ fiber immunolabeling in the prelimbic and infralimbic cortices of the mPFC. However, coverage of TH+ fibers in the NAc and number of DA cell bodies in the VTA were unchanged by HC treatment in adolescence. In a separate cohort, rats were treated with vehicle (n = 6) or EE+LNG (n = 6), and RT-qPCR was performed on the mPFC for genes related to dopaminergic synthesis, clearance, and signaling. Several gene transcripts showed increased expression in EE+LNG treated rats relative to vehicle controls including those for dopamine receptors 1, 4 and 5. Taken together, these data show that HC treatment during adolescence may alter prefrontal dopamine signaling. Future work should aim to elucidate how and when these HC-induced alterations to mPFC DA arise as well as their persistence and impact on DA-mediated executive function.

Disclosures: E. Dybas: None. **R.A. Gilfarb:** None. **D. Hirsh:** None. **K.M. Lenz:** None. **B. Leuner:** None.

Poster

PSTR103: Early Life Stress and Development

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Program #/Poster #: PSTR103.05/B12

Topic: A.08. Adolescent Development

Support: UWRF USE Grant (AS, SS)
UWRF Faculty Research Grant (DGE)

Title: Adolescence as a sensitive period for the effect of social isolation stress on nicotine conditioned place preference and dendrite remodeling.

Authors: A. SCHAEFER, S. C. SYMALLA, A. N. OLSTAD, R. E. WYANT, E. R. ASHBACH, ***D. G. EHLINGER**;
Univ. of Wisconsin-River Falls, River Falls, WI

Abstract: Adolescence is a sensitive period in brain development marked by increased susceptibility to the effects of chronic stress, which may enhance vulnerability to substance use disorders. In this study, we examined the effect of adolescent social isolation on nicotine reward and dendrite remodeling. During adolescence (postnatal day P35-P49) or adulthood (P60-74), male and female C57BL/6J mice were exposed to either social isolation (SI) stress or standard rearing (SR) conditions and nicotine exposure (0.35mg/kg) during a modified nicotine conditioned place preference (CPP) procedure. On approximately P49 (adolescent) or P74 (adulthood) stress-coping behavior was examined during a 6-minute forced-swim test (FST), and brains were processed for Golgi-Cox staining and subsequent analysis of dendrite structure. Adolescent SI mice more rapidly developed nicotine CPP compared to both adolescent SR mice and adult mice and exhibit increased levels of immobility in the FST, Both adolescent SI and SR mice previously exposed to nicotine exhibit decreased immobility in the FST. Ongoing research is now examining nicotine and stress-induced structural plasticity (dendrite remodeling) of SI versus SR mice in the ventral striatum, hippocampus, amygdala, and medial frontal cortex. Collectively, our results suggest that adolescent social isolation stress enhances the rewarding effects of nicotine and negatively impacts stress-coping behavior. Ongoing analyses will help determine the long-lasting neurological correlates of these effects and inform our understanding of adolescent brain development and vulnerability.

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Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.06/B13

Topic: A.08. Adolescent Development

Support: NIH Grant R01-MH086507
NIH Grant R01-MH127850

Title: Early life adversity-mediated perturbation of mediodorsal thalamic development compromises prefrontal cortex maturation

Authors: *D. NEAL, K.-Y. TSENG;
Univ. of Illinois Chicago, Chicago, IL

Abstract: 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 during a discrete developmental window. At the center of cognitive and affective behaviors is the prefrontal cortex (PFC) which receives inputs from various brain regions, including the mediodorsal thalamus (MD), and undergoes a protracted maturation. Thus, it's conceivable that ELA exposure during a sensitive window of MD development may disrupt PFC maturation. To this end we used *in vivo* electrophysiology to assess the functionality of the MD-PFC pathway following ELA exposure during distinct MD developmental windows. We found that the pattern of PFC local field potential (LFP) responses to MD train stimulation is developmentally regulated through adolescence and is impacted by ELA exposure. Typically, the pattern of MD-evoked PFC LFP facilitation at 10Hz is dependent on local NMDAR whereas the LFP suppression at 20Hz and 40Hz is mediated by local GABA-AR. Following P2-20 maternal separation ELA, the facilitation pattern and suppression patterns were attenuated. Interestingly, rats exposed to P2-10 maternal separation ELA showed normal facilitation and suppression patterns. However, rats exposed to P11-20 maternal separation ELA reproduced the attenuated LFP facilitation and suppression patterns seen in the P2-20 maternal separation ELA rats. Collectively, these results reveal a distinct MD developmental window that is sensitive to disruption by ELA and compromise PFC maturation.

Disclosures: D. Neal: None. **K. Tseng:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.07/B14

Topic: A.08. Adolescent Development

Support: NIH Grant R15S088776

Title: The effects of early-life stress and status epilepticus on neonatal communication among C57BL/6J mice at a critical developmental timepoint

Authors: *T. R. BRADISH[1], C. LAU[1], S. PELL[1], K. BLANDIN[2], M. HEMMERSMEIER[1], J. J. THAYIL[1], C. KELLEY[1], K. LALLY[1], J. N. LUGO, Jr.[3];
[1]Baylor Univ., Waco, TX; [2]Psychology & neuroscience, Baylor Univ., Hewitt, TX; [3]Psychology and Neurosci., Baylor Univ., Mc Gregor, TX

Abstract: Epilepsy predisposes individuals to recurrent seizures. This disorder affects approximately 50 million people worldwide. Seizure activity varies in individuals with epilepsy, both in seizure type and duration. Status epilepticus (SE) refers to a neurological emergency where seizures last more than 5 minutes and can lead to neuronal cell death or injury. Stress has the potential to lower seizure thresholds, thus inducing seizures and exacerbating seizure activity in the brain. Early-life stress (ELS) can prompt epileptogenesis and increase the severity of epilepsy throughout development. Epilepsy and stress can result in autistic-like behavioral deficits in areas such as communication. In the present study, we characterized communication differences at a critical time point in early development as a result of ELS and SE. We simulated a stressful environment using a limited bedding and nesting paradigm on our C57BL/6J mice on postnatal days (PD) 2-9. On PD10, we induced a single episode of SE with an intraperitoneal kainic acid (KA) injection. The controls received a saline injection of similar volume. The pups were monitored for two hours, then were given a subcutaneous saline injection to rehydrate. On PD11, we recorded ultrasonic vocalizations (USVs) to evaluate communication variability. The two-minute recordings were later scored. An analysis of call type distribution found significant differences between the KA and saline injected pups in the control condition for chevron, upward, downward, flat, two-component, and frequency step calls ($p<.05$). Differences were also found between the KA induced pups in the control condition (non-stressed) and the KA induced pups in the ELS condition among chevron, complex, upward, downward, short, flat, two-component, and frequency step calls ($p<.05$). Sex differences were also noted in call-type distribution both within the control and ELS conditions. Examination of the USV spectral and temporal properties found significant differences in call duration, latency, and total call quantity, but none were present in fundamental frequency or power ($p<.05$). We expected to find differences between pups raised in the ELS paradigm and their non-stressed counterparts, with additional differences found in the SE pups. Our findings suggest that communication in early development is affected by SE regardless of environmental conditions. However, ELS only played a significant role when SE was involved. These differences were also sex dependent when evaluating call composition. This provides evidence that a single episode of SE can affect communication in early development, both in adverse and non-adverse environments.

Disclosures: T.R. Bradish: None. **C. Lau:** None. **S. Pell:** None. **K. Blandin:** None. **M. Hemmersmeier:** None. **J.J. Thayil:** None. **C. Kelley:** None. **K. Lally:** None. **J.N. Lugo:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.08/B15

Topic: A.08. Adolescent Development

Support: Research Council of Finland 356491

Title: Effects of early-life stress on sleep during adolescence.

Authors: *A. DONATI, H. ANTILA;
Univ. of Helsinki, Helsinki, Finland

Abstract: Early-life stress (ELS) such as maternal maltreatment, neglect, or abuse, predisposes individuals to develop mental disorders. The long-term effects of ELS include alterations in neuronal networks involved in emotion regulation, which persist into adolescence, when psychiatric symptoms often emerge. Sleep plays a key role in emotion regulation, and disrupted sleep is a common comorbidity in psychiatric disorders. We hypothesize that ELS induces changes in sleep structure and behavior during adolescence. To test this, we used an ELS mouse model combining the limited bedding and nesting (LBN) protocol from postnatal day (P) 4 to P14 with maternal separation for one hour at P8, P10, and P12. Twenty-four-hour EEG recordings were conducted weekly at key developmental stages (4-7 weeks of age). Additionally, behavioral tests were performed to assess the stress-induced phenotype during adolescence. ELS-exposed mice showed altered behavior in the marble burying test, elevated plus maze (EPM), and social preference test, indicating early-emerging phenotypes in both sexes. Compared to controls, stressed mice exhibited a general reduction in marble burying behavior, decreased exploration of the open arms, and diminished social interaction, patterns consistent with anxiety-like and depressive-like behaviors. Sleep analysis revealed differences between control and ELS mice, including alterations in both NREM and REM sleep, along with a blunted circadian rhythm in stressed mice only, during early adolescence. Furthermore, the data indicated sex-specific effects of ELS, with females showing more persistent alterations in sleep architecture and circadian regulation compared to males. We are also conducting more detailed analysis of the effects of ELS on sleep microarchitectural features, including microarousals, sleep spindles and the infraslow oscillation of EEG sigma power. Our findings demonstrate that ELS disrupts both behavioral and neurophysiological development during adolescence, with sex-specific patterns. Together, these results highlight sleep as a sensitive and early marker of stress-induced vulnerability, and a potential target for intervention.

Disclosures: A. Donati: None. **H. Antila:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.09/B16

Topic: A.08. Adolescent Development

Support: NIMH; 1 RO1 MH127850-01

Title: Exploring the Effects of Early-Life Adversity on CRHR1 Dynamics in the Developing Hypothalamus

Authors: *S. ROY[1], A. BALAKRISHNAN[2], H. C. BRENHOUSE[1];
[1]Psychology, [2]Northeastern Univ., Boston, MA

Abstract: Exposure to early-life adversity (ELA) increases the risk for long-term emotional and physiological dysregulation, including altered pubertal timing. In female rats, ELA has been shown to accelerate pubertal onset, yet the underlying neuroendocrine mechanisms remain unclear. Corticotropin-releasing hormone receptor 1 (CRHR1), acts in the hypothalamic anteroventral periventricular nucleus (AVPV) and arcuate nucleus (ARC) during typical development as a pre-adolescent inhibitor of early puberty, yet it is also a key mediator of stress signaling and is known to internalize upon ligand binding. Our preliminary data revealed that blocking CRHR1 during ELA prevented precocious puberty. Given the role of CRHR1 in both the regulation of pubertal development and stress responses, we investigated its subcellular distribution following ELA. Maternal separation (MS) is a rodent model for the study of ELA in which pups are separated from their mothers for 4 hours/day from postnatal day (PND) 2-20. Female Sprague-Dawley rats were assigned to either MS or control litters, and tissue from the AVPV and ARC was collected at PND20. Using subcellular fractionation and Western blot analysis, we analyzed CRHR1 levels in membrane and cytoplasmic fractions. MS animals showed a significant reduction in membrane-bound/total CRHR1 in the ARC ($p = 0.04$) but not the AVPV ($p = 0.5$), consistent with receptor internalization and reduced membrane signaling.These findings align with prior work in our lab, which show that MS leads to early expression of kisspeptin and gonadotropin-releasing hormone (GnRH) in the AVPV and ARC, two regions central to pubertal initiation. Together, these results suggest that CRHR1 internalization in response to early-life adversity may disrupt the balance of excitatory and inhibitory inputs within the hypothalamic-pituitary-gonadal (HPG) axis, potentially facilitating premature GnRH release and pubertal onset. CRHR1 internalization potentially influences the expression of genes regulating pubertal development. Ongoing qPCR analysis will offer deeper insight into how ELA impacts hypothalamic signaling by assessing the expression of these genes.

Disclosures: S. Roy: None. **A. Balakrishnan:** None. **H.C. Brenhouse:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.10/B17

Topic: H.05. Mood Disorders

Support: División de Investigación y Posgrado,
División de Estudios Sociales of the Universidad Iberoamericana Ciudad de México
SECIHTI SNII 219101
Programa de Ayudantias

Title: Impact of Maternal Separation on Palatable Food Preference, Weight Gain, and Cognitive Performance

Authors: N. ZAPATA-VALDEZ[1], ***M. H. BUENROSTRO-JAUREGUI**[2];
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Abstract: Early-life environment plays a crucial role in shaping behavior and metabolic health. Several studies have demonstrated that adverse developmental experiences, such as maternal separation, can disrupt stress regulation systems, feeding behavior, and cognitive functions. The present study aimed to evaluate the effects of early-life stress induced by maternal separation on weight gain, preference for highly palatable food, and cognitive performance in young Wistar rats. A 2x2 factorial experimental design was used to manipulate two independent variables: stress exposure (maternal separation vs. no separation) and diet type (palatable vs. standard). Maternal separation was applied daily for 3 hours from postnatal day (PND) 2 to 15. Subsequently, we assessed Oreo cookie consumption, body weight, and performance on cognitive tasks (Elevated Plus Maze, Passive Avoidance, and Novel Object Recognition). Results showed that rats exposed to maternal separation exhibited greater consumption of palatable food, increased weight gain, and poorer performance in specific cognitive tasks compared to control animals. These findings suggest that early-life stress may modulate feeding behavior and cognitive function, possibly through neurobiological mechanisms associated with the reward system and hunger-satiety signaling. Further research in this area is warranted.

Disclosures: N. Zapata-Valdez: None. **M.H. Buenrostro-jauregui:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.11/B18

Topic: A.08. Adolescent Development

Support: NIH Grant MH127850-01

Title: Investigating the role of puberty in mediating anxiety-like behaviors after Early life stress in rodents

Authors: *A. BALAKRISHNAN, S. ROY, H. C. BRENHOUSE;
Psychology, Northeastern Univ., Boston, MA

Abstract: Early-life stress (ELS) exerts profound and enduring effects on neuroendocrine development and emotional behavior. The maternal separation paradigm is a well-established model for studying ELS in rodents, facilitating investigation of its long-term neurobiological and behavioral consequences. We have observed that maternal separation from postnatal day 2 (P2) to P20 in female rats leads to earlier onset of puberty, which was correlated with an elevated acoustic startle response (ASR) in later life, findings that parallel observations in ELS-exposed humans. We hypothesized that alterations in pubertal timing directly impact changes in anxiety-like behavior emerging during adolescence and adulthood. We therefore investigated whether

delaying puberty could modulate anxiety-like responses after ELS. To do this, puberty was pharmacologically delayed using the gonadotropin releasing hormone (GnRH) agonist cetrorelix acetate (100 µg) administered daily from P21 to P28 in control-reared (CON) or maternally separated females. Anxiety-like behavior was assessed via baseline ASR at P40 and the light-enhanced ASR at P65. Notably, our treatment delayed puberty in both CON and ELA animals. Our results indicate that delaying puberty selectively increased ASR at P40 in MS animals, with no comparable effect in CON. By P65, MS animals exhibited a heightened baseline ASR relative to CONs and delaying puberty had no effect on the startle response. Exposure to bright light, a non-conditioned anxiogenic stimulus further potentiated the startle response in both rearing groups. These findings suggest that delaying pubertal onset may exacerbate specific anxiety-related phenotypes at particular ages. Experiments are ongoing to measure ASR-evoked cFos expression after manipulations to pubertal onset. This data will offer mechanistic insights and identify potential therapeutic targets for mitigating the long-term effects of ELA.

Disclosures: A. Balakrishnan: None. **S. Roy:** None. **H.C. Brenhouse:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.12/B19

Topic: A.08. Adolescent Development

Support: Western Washington University RSP office

Title: The rescue potential of cannabidiol and β-caryophyllene against the molecular changes induced by early life stress in mice.

Authors: *T. MCGILLIS[1], J. KAPLAN[4], Z. WILSON[2], O. DILLEMUTH[3];
[1]Western Washington Univ., Kent, WA; [2]Western Washington Univ., Lacey, WA; [3]Western Washington Univ., Bellingham, WA; [4]Dept. of Psychology, WESTERN WASHINGTON UNIVERSITY, BELLINGHAM, WA

Abstract: Cannabidiol (CBD) is a non-intoxicating phytocannabinoid with rapidly escalating popularity for the treatment of numerous off-label conditions in children and adults including anxiety and autismspectrum disorder (ASD). However, these benefits are often difficult to achieve in many users. Thischallenge likely results from the wide range of CBD's pharmacodynamic targets that are differentiallyimpacted with escalating doses; expanding the dose-efficacy range will improve CBD's medicinalutility. We've demonstrated that the addition of cannabis-inspired volatile organic compounds("terpenes") leads to more pronounced prosocial effects and higher reliability in the BTBR mousemodel of ASD. Therefore, we hypothesize that the addition of prominent cannabis terpenes canenhance CBD's therapeutic efficacy by expanding its dose-efficacy relationship, and elevations toGABAergic and anandamide signaling, which together, restore the brain's excitatory:inhibitory (E:I)balance, underlie these

effects. To test this hypothesis, we made stimulated local field potentialrecordings from hippocampal slices which revealed that BTBR mice are deficient in GABAergicsignaling compared to control C57BL/6J mice, and simulated seizure activity in a pro-epilepticsolution indicated that BTBR mice have a more pronounced E:I imbalance. Further, MALDI-TOFmass spectrometry confirmed that BTBR mice are also deficient in anandamide signaling, which wasrestored by acute passive inhalation of vaporized CBD oil. These effects are associated withreduced anxiety behavior on the elevated plus maze and improved social interaction in the 3-Chamber Test. We did not find that estrogen fluctuations across the estrus cycle, which oftenaccount for sex differences in phytocannabinoid effects, impacted anxiety or social behavior inC57BL/6J or BTBR mice. CBD exposure at different developmental stages may impact the decisionif or when to recommend CBD-based treatments in children with ASD or other conditions. Toaddress this concern, we tested the impact of CBD vapor exposure at three developmental stages:PND 7-21, PND 14-28, and PND 28-42. Vaporized CBD increased risk-taking behavior and impairedlearning and memory on the Barnes Maze, particularly in the PND 14-28 exposure group. Together,we find that CBD's therapeutic effects may be optimized by examining molecular and physiologicaltargets that correlate to behavioral outcomes, but our findings should be considered as cautionaryfor off-label CBD administration to children.

Disclosures: T. McGillis: None. **J. Kaplan:** None. **Z. Wilson:** None. **O. Dillemuth:** None.

Poster

PSTR103: Early Life Stress and Development

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Program #/Poster #: PSTR103.13/B20

Topic: A.08. Adolescent Development

Support: NCI – U54 GRANT - 5U54CA156734-12

Title: The cognitive and affective consequences of maternal separation co-occur with hippocampal and basolateral amygdala GABA/glutamate differences in adolescence

Authors: *A. T. C. ROPER[1], S. ROY[2], V. LEWIS[3], K. MVUDUDU[3], K. PARKHER[5], D. BRAVO TAPIA[3], T. DONALDSON[4];
[1]Psychology, Univ. of Massachusetts, Boston, Boston, MA; [2]Northeastern Univ., Boston, MA; [4]Psychology, [3]Univ. of Massachusetts Boston, Boston, MA; [5]Boston Univ., Boston, MA

Abstract: Studies have shown decreased cognitive performance and increased anxiety following Early Life Stress (ELS) in both clinical and preclinical models. These studies primarily test the effects of ELS in adult rodent models, leaving a gap in understanding the consequences of ELS in adolescence, a time of increased plasticity and vulnerability. A common form of ELS in rodents is Maternal Separation (MS), a model that produces cognitive and affective consequences later in life. In this study, we used six Long Evans dams (Charles River Breeding Lab, MA) and their offspring (N = 64). From PND 1-21, pups were separated from their dam for

two hours, five days a week, during the pre-weaning period. Offspring were tested in adolescence (female n = 36 (PND 32-34), male n = 28 (PND 45- 48)) for Anxiety-Like Behavior (ALB) on the Elevated Plus Maze (EPM), novelty seeking using the Hole Board (HB) test, and cognitive performance assessing learning and memory on the Novel Object Recognition (NOR) test. Immunohistochemistry (IHC) was conducted using Parvalbumin (PV) and Post-Synaptic Density (PSD-95), indicators of a subset of GABA interneurons and glutamate synaptic signaling, to examine the MS effects in brain areas involved in executive functioning, learning and memory, and emotional regulation. Significant anxiety differences were identified for the main effect of sex and MS. Females showed greater ALB, spending less time in the open arms and having fewer closed arm entries than males. The MS group showed greater ALB with more time spent in the junction and closed arms of the EPM. Additionally, there was an interaction with MS females having fewer open arm explorations than MS males. In the HB test, the MS group had increased ambulatory and stereotypic activity, driven by the MS male group. In the NOR, a sex effect was found with males spending more time with the novel object than females. A treatment effect was also found in the MS group; memory was impaired, with more time spent with the familiar object than the control group. IHC showed sex and MS differences in the hippocampus and basolateral amygdala (BLA). Males had more PV puncta in the CA3 compared to females. The MS group had more PV puncta and PSD puncta in the CA3 and BLA, respectively. These results highlight both sex and MS effects in ALB, novelty-seeking, and learning and memory assays. MS and female rodents displayed increased ALB and impaired learning and memory performance. The GABA/glutamate changes in the hippocampus and BLA implicate this mechanism in the observed behavioral deficits. Taken together, these findings confirm that MS impacts adolescents in a sex dependent manner and GABA/glutamate may be a potential target for treatment.

Disclosures: A.T.C. Roper: None. **S. Roy:** None. **V. Lewis:** None. **K. Mvududu:** None. **K. Parkher:** None. **D. Bravo Tapia:** None. **T. Donaldson:** None.

Poster

PSTR103: Early Life Stress and Development

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Program #/Poster #: PSTR103.14/B21

Topic: A.08. Adolescent Development

Support: R21MH121836
R01MH131053

Title: Synaptic Adhesion Molecule IgSF9b Supports Inhibitory Synaptic Maturation During Prefrontal Adolescent Development

Authors: *J. CLARIN[1], A. KEITH[3], C. ALEXANDROPOULOS[3], S. YANG[4], N. MACK[5], Y. LI[3], W.-J. GAO[2];
[2]Neurobio. and Anat., [1]Drexel Univ., Philadelphia, PA; [3]Drexel Univ. Col. of Med.,

Philadelphia, PA; [4]Neurosurg., Fudan Univ. Hushan Hosp., Shanghai, China; [5]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Across mammalian species, adolescence constitutes a period of considerable brain maturation that manifests both behaviorally and synaptically. The prefrontal cortex (PFC) is particularly plastic during this period, exhibiting marked changes in excitatory and inhibitory circuitry components. In terms of inhibition, previous studies in rodents have shown that inhibitory drive to prefrontal pyramidal neurons is enhanced throughout the adolescent period. However, the genetic factors contributing to this prefrontal inhibitory maturation are sparsely characterized. One such candidate is IgSF9b, a homophilic synaptic adhesion molecule important for the development of inhibitory synapses in the brain. Investigation of IgSF9b is further prioritized given its association with psychiatric disorders, such as schizophrenia. Given the prevalence of schizophrenia diagnoses during late adolescence, we hypothesized that IgSF9b contributes to inhibitory circuit maturation of the PFC during adolescence, and that its perturbation results in maladaptive cognition and affective behavior during adulthood. To study the expression dynamics of IgSF9b across prefrontal adolescent development, we tracked mRNA expression changes in discrete cortical cell types using hybridization chain reaction technology. Further, we applied a localized knockdown (KD) approach utilizing a viral construct encoding IgSF9b shRNAs. Viral infusion into the PFC took place took place at ~P40 in mice and behavioral and electrophysiological measures were assessed three weeks later, once mice matured to adulthood. Interestingly, adolescent KD of IgSF9b lead to deficits in working memory, social behavior, and approach-avoidance tasks, in a sex-dependent manner. To further investigate the underlying neural mechanisms governing these behavioral changes, we examined the effects of IgSF9b KD on synaptic and intrinsic properties of PFC pyramidal neurons in male and female mice. Physiologically, knockdown decreased frequency of inhibitory synaptic currents in young adulthood and altered pyramidal cell excitability. Our findings suggest that disruption of inhibitory synaptic development during critical periods such as adolescence can have outsized effects on prefrontal circuitry and behaviors in adulthood.

Disclosures: J. Clarin: None. **A. Keith:** None. **C. Alexandropoulos:** None. **S. Yang:** None. **N. Mack:** None. **Y. Li:** None. **W. Gao:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

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Program #/Poster #: PSTR103.15/B22

Topic: A.08. Adolescent Development

Title: Pubertal onset decreases neuron number and increases perineuronal net formation in the VTA of male and female Long Evans rats

Authors: *V. R. RIESGO[1], T. ZUMASKI[1], K. THOMPSON[2], J. WILLING[2];
[2]Psychology, [1]Bowling Green State Univ., Bowling Green, OH

Abstract: Adolescence is a critical window of neural development associated with numerous behavioral and neuroanatomical changes. Previous research has focused on the changes that the prefrontal cortex (PFC) undergoes during adolescence. Less is known about the developmental trajectory of other brain regions, like the ventral tegmental area (VTA). We have previously documented a reduction in total VTA neuron number between the juvenile period and adulthood, but when this occurs during adolescence remains unexplored. In the present study we collected tissue from male and female Long Evans rats prepubertal (P32 for females, P40 for males), one day post pubertal onset, five days post pubertal onset, and at young adulthood (P60) to elucidate any specific role of puberty in these neuroanatomical changes. We immunohistochemically stained tissue containing the VTA with tyrosine hydroxylase (TH) to visualize dopamine and wisteria floribunda to visualize perineuronal nets (PNNs), and nissl stained matching sections to assess total neurons. Employing stereological techniques, we determined the number of PNNs, the number of dopaminergic neurons and the number of total neurons in relation to pubertal onset. We found that the number of total neurons decreases between prepubertal subjects and subjects five days post pubertal onset, showing that there is a role for puberty in the development of optimal cell number for the VTA. We also found that PNNs increase between 5 days post pubertal onset and P60, suggesting that the hormones that accompany puberty could mediate the formation of PNNs in this region, improving synaptic function and stability while influencing dopamine-mediated behaviors and ending the plastic period of adolescence.

Disclosures: V.R. Riesgo: None. **T. Zumaski:** None. **K. Thompson:** None. **J. Willing:** None.

Poster

PSTR103: Early Life Stress and Development

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Program #/Poster #: PSTR103.16/B23

Topic: A.08. Adolescent Development

Support: NSF-2242771
BX005403

Title: Coordinated Spatial Transcriptomics and Super-Resolution Microscopy Reveals Subregion-Dependent Maturity States of the Tripartite Synapse Across Development

Authors: *M. JONES[1], A. WALLS[1], N. KUMAR[1], T. MUCK[1], F. MALONE[1], O. COULTER[2], H. SEXTON[1], S. AKTER[1], K. DENNING[3], M.-L. RISHER[4];
[1]Marshall Univ., Huntington, WV; [2]Marshall Univ., HUNTINGTON, WV; [3]Pathology, Joan C. Edwards Sch. of Medicine, Marshall Uni., Huntington, WV; [4]Biomed. Sci., Joan C. Edwards Sch. of Medicine, Marshall Uni, Huntington, WV

Abstract: Astrocytes are an integral part of the tripartite synapse. These non-neuronal glial cells are critical for the regulation and maintenance of synaptic structure and function. The ensheathment of synapses by peripheral astrocyte processes (PAPs) allows for close PAP-

synaptic proximity that facilitates astrocyte-neuronal crosstalk via contact-mediated and secreted signaling factors. We previously demonstrated that the proximity and maturation of the tripartite synapse occurs across unique developmental timeframes depending on the subregion of the brain. We and others have also shown that intermittent binge ethanol exposure during adolescence (AIE) disrupts PAP-synaptic proximity in a subregion-dependent manner. However, a full evaluation of tripartite synapse maturation across the adolescent period and how changes in PAP-synaptic proximity align with local changes in neuronal and astrocyte-specific gene expression are not well understood. We hypothesize that the varying subregion-specific maturation states of the tripartite synapse predict vulnerability to AIE-induced loss of PAP-synaptic proximity. Here, we focused on the subregions of the orbitofrontal cortex (OFC), a key brain region for higher order executive function that is significantly impacted by ethanol exposure. Since the ventral (vOFC) and lateral OFC (lOFC) differ in function and vulnerability to ethanol, we hypothesize that these subregions differ in tripartite maturation trajectory across adolescent development. To test our hypothesis, we collected brains from male and female C57BL/6 mice at postnatal days (PND) 30, 46, and 72. Brains were fixed, and slices were prepared for immunohistochemistry (IHC) followed by stimulated emission depletion (STED) microscopy to determine changes in PAP-synaptic proximity across development. Adjacent slices were prepared for spatial transcriptomics using Visium HD (10x Genomics), allowing for the alignment of spatially transcribed genetic information and PAP-synaptic structural characterization. Our data demonstrates that, following ethanol exposure, there is a loss of PAP-synaptic proximity in the vOFC while proximity remains unchanged in the lOFC. Spatial gene expression data is currently being analyzed to be presented in relation to the changes in PAP-synaptic proximity. These data fill a crucial need by providing a detailed characterization of the tripartite PAP-synaptic structural and associated gene expression changes that occur during a pivotal time of late-stage adolescent/young adult development—a period of time that has been shown to be highly vulnerable to the effects of stress, alcohol, and illicit drug use.

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Poster

PSTR103: Early Life Stress and Development

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Program #/Poster #: PSTR103.17/B24

Topic: A.08. Adolescent Development

Support: NIMH R01MH121829

Title: Molecular and developmental analysis of oxytocin neurons in California mice

Authors: *V. CEA SALAZAR, B. C. TRAINOR;
Univ. of California, Davis, Davis, CA

Abstract: Oxytocin neurons from the paraventricular nucleus (PVN) of the hypothalamus have historically been classified as magnocellular or parvocellular neurons. Recent studies in mice used morpho-electric properties of oxytocin neurons and discovered that this distinction may be more complex. It's unclear the extent to which results observed in Mus musculus generalize to other species. We used single nucleus sequencing to analyze PVN adult California mice (Peromyscus californicus) to study the molecular properties of oxytocin neurons in the PVN. We analyzed a total of 262 oxytocin neurons in males and 990 oxytocin neurons in females. A clustering analysis identified 4 distinct clusters of oxytocin neurons, one of which expressed Foxp1 (identified as a marker gene for magnocellular in Mus). This cluster expressed high levels of Ar but not Esr1 or Esr2. A second cluster expressed Adarb2 identified as a marker gene for parvocellular neurons). This cluster expressed high levels of Esr1 and Esr2 but not Ar. Intriguingly, the largest cluster of oxytocin neurons did not express Foxp1 or Adarb2. Expression of steroid receptors was also inconsistent across this cluster. This cluster resembles findings from morpho-electric analyses in mice that found many oxytocin cells that do not neatly fit into cells classified as magno- or parvocellular. Additional analyses are being done in developing mice to examine how oxytocin and Ar expressing neurons are distributed across the PVN at these developmental timepoints.

Disclosures: V. Cea Salazar: None. **B.C. Trainor:** None.

Poster

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Topic: A.08. Adolescent Development

Support: NIH Grant R01AG078758
NIH Grant 1F31MH138131

Title: Dim light at night during adolescence in mice induces persistent changes in anxiety-related physiology and behaviors

Authors: *K. BELL[1,2], C. GREGG[3], L. K. FONKEN[2,1];
[2]Div. of Pharmacol. and Toxicology, [1]Univ. of Texas at Austin, Austin, TX; [3]Natl. Inst. of Mental Hlth., Rockville, MD

Abstract: Modern environments allow for exposure to electric lighting throughout the day and night, which can disrupt the body's internal 24-hour timing system (i.e., circadian system). Lighting environment is increasingly recognized as a risk factor for mental health. Adolescent brains may be especially sensitive to environmental cues like nighttime light. Growing evidence links repeated nighttime light exposure during puberty to mood/anxiety disorders and long-term mental health outcomes. Thus, to assess the effects of dLAN during puberty, male and female C57BL/6J mice were randomly assigned to either control [12h:12h light (150 lux)/dark (0 lux)]

or dim light at night [dLAN; 12h:12h light (150 lux)/dim (15 lux) cycle] from postnatal day (PND) 30-44. On PND45 mice returned to dark nights until adulthood. Anxiety- and depressive-like behaviors were then assessed at the end of dLAN exposure during adolescence (PND43-44), or following placement back in dark nights during adulthood (PND60). Peripheral immune tissue, gonadal tissue, and brains were also collected at the two ages. During adolescence, mice exposed to dLAN exhibited decreased motivational-like behavior in a nest building test. Changes in anxiety-related behavior were test dependent: dLAN mice showed increased anxiety-like behavior with increased grooming time during a splash test but no differences were observed in the elevated plus maze between control and dLAN animals. Interestingly, although there were no changes in adrenal weight or CORT levels, dLAN animals had increased spleen size and perigonadal fat pad weight. During adulthood, dLAN mice continued to build worse nests and had a trending decrease in the time in open arms. These modest changes in behavior in mice previously exposed to dLAN were accompanied by elevated CORT concentrations and increased adrenal gland weights despite having returned to dark nights. Male dLAN mice also had increased spleen size and decreased perigonadal fat pad weight. Overall, developmental dLAN exposure in mice induces modest behavioral changes during puberty that can persist into adulthood. Additionally, developmental dLAN exposure also induced more substantial physiological changes that were more severe in adulthood. Further investigation into the mechanisms underlying the response to dLAN during puberty is needed to understand the broader implications and to explore potential interventions aimed at alleviating long-term consequences.

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Poster

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Program #/Poster #: PSTR103.19/B26

Topic: A.08. Adolescent Development

Support: NIH Grant DA047575

Title: Age-related development in prefrontal-subcortical resting-state functional connectivity in nonhuman primates

Authors: H. DESHPANDE[1], ***S. J. KOHUT**[2,1];
[1]McLean Hosp., Belmont, MA; [2]Harvard Med. Sch., Belmont, MA

Abstract: Understanding age-related changes in functional connectivity (FC) with regards to the maturation trajectories of cortical-subcortical circuits is critical for identifying biomarkers for disease vulnerability. The present study investigated resting-state FC in adolescent and adult nonhuman primates to characterize developmentally-sensitive functional brain circuits. Resting-state fMRI data were acquired in adolescent (33.3±1.59 months; n=22) and adult (117.29±2.86

months; n=15) squirrel monkeys and FC was compared in seven prefrontal and ten subcortical regions-of-interest (ROIs). The effect of subject age on FC between each pair of ROIs was evaluated to identify nodes with the most age-sensitive connections (hubs) which were then used in seed-to-whole-brain FC analyses. A subset of adolescents (n=7) was also assessed over 3 longitudinal scans to track changes in hub connectivity throughout adolescence. A significant effect of age on ROI-ROI FC was found for adolescent ($p<0.001$), but not adult, subjects ($p=0.8$). Evaluation of parameter estimates (β) for each ROI-ROI pair found three within-prefrontal (dorsolateral (dlPFC), dorsomedial (dmPFC), and medial orbitofrontal cortices), two within-subcortical (R amygdala and L hippocampus), and three between prefrontal-subcortical (dlPFC, dmPFC, L caudate) hubs with the highest number of age-related connections. Large-scale organizational differences were also observed between the adolescent and adult groups. Longitudinal scans found within-subject changes in FC consistent with group effect. The relationship between changes in FC and age during adolescence indicates dynamic maturation of several prefrontal-subcortical circuits in nonhuman primates. These findings provide specificity in our understanding of the development of functional brain circuits during and into late adolescence.

Disclosures: H. Deshpande: None. **S.J. Kohut:** None.

Poster

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Topic: A.08. Adolescent Development

Support: NIEHS Grant 1R01ES035686-01
NIH Grant P30 ES005605
NIH Grant T32-NS007421

Title: Investigation into ADHD-relevant behaviors following adolescent exposure to insecticides in male mice modeling farm work experience of teenage boys

Authors: *M. X. CHEN[1], J. AHN[1], R. TAYLOR[1], X. LI[1], M. GARCIA-MARES[1], J. A. DOORN[2], H.-J. LEHMLER[3], H. E. STEVENS[1];
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Abstract: Adolescence is a sensitive neurodevelopmental period when environmental exposures can impact neurobehavioral functioning. Our adolescent populations experience wide-ranging insecticide exposures through dietary consumption, while farm-working teenagers are at heightened risk due to additional spray drift and dermal exposures through direct handling of insecticides. Our epidemiological collaborators have ongoing studies of teenage boys who have occupational exposure to insecticides, particularly to chlorpyrifos and α-cypermethrin. These

boys demonstrate neurobehavioral problems, including cognitive difficulties during working memory tasks and higher attention-deficit/hyperactivity disorder (ADHD) symptoms, that correlate with measured pesticide exposure levels; problems persist months following completion of farm work. Whether these boys' problems are a result of insecticide exposure and whether combinations of insecticides modify effects remains unclear. Therefore, we developed a translational adolescent pesticide exposure model in male mice (n=12/group). Exposures and outcomes were timed during adolescence (between postnatal days 49 and 78). We used a dermal route of administration and dosage daily for seven days, comparable to exposures of teenage boys in epidemiological studies. Then, we investigated ADHD-relevant behaviors in a battery of behavioral tasks testing for exploratory behavior, impulsivity-like behavior, locomotion, and working and spatial memory following exposures to four conditions: corn oil vehicle, chlorpyrifos, α-cypermethrin, or combination of chlorpyrifos and α-cypermethrin, at two translationally relevant timepoints: towards the end of exposure period and weeks after exposures. ANOVA and appropriate posthoc tests were used for analysis. Towards the end of exposure period, we found hyperactivity in the α-cypermethrin exposed group (+20%; $p<0.05$) and hypoactivity (-20%; $p<0.05$) in the combination group. We also observed impulsivity-like behavior in the α-cypermethrin group (+44%; $p<0.05$). No working or spatial memory deficits were observed in any groups. These changes did not persist in the cohort tested after completion of exposures. Assessment of ADHD-relevant dopaminergic neurotransmitter systems and oxidative stress genes in ADHD-relevant brain regions is ongoing and will be presented. Ultimately, as we gain understanding of how environmental stressors impact the developing adolescent brain, we can better inform public health policy to protect our most at-risk young people and minimize overall disease burden.

Disclosures: M.X. Chen: None. **J. Ahn:** None. **R. Taylor:** None. **X. Li:** None. **M. Garcia-Mares:** None. **J.A. Doorn:** None. **H. Lehmler:** None. **H.E. Stevens:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.21/B28

Topic: A.07. Development of Neural Systems

Title: Necrotizing Enterocolitis Selectively Disrupts Pontine Development in the Preterm Brain

Authors: *G. SANIDAS[1], C. LOWE[3], C. BYRD[3], R. VIDVA[2], G. SIMONTI[1], T. CHANDERENG[3], V. GALLO[4], P. KRATIMENOS[5];
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Abstract: Background:
While survival among preterm infants with necrotizing enterocolitis (NEC) has improved, survivors face disproportionately high rates of neurodevelopmental impairment (NDI), independent of prematurity. The specific neurologic alterations in the human brain preceding these outcomes remain poorly defined. Despite extensive preclinical research, a comprehensive understanding of NEC-induced brain injury in humans and its contribution to adverse neurodevelopmental outcomes remains elusive. We hypothesized that NEC induces a distinct pattern of brain injury involving immune-mediated mechanisms and region-specific vulnerability. Methods:
We analyzed a cohort of preterm infants with (n=69) and without NEC (n=115) using a multimodal approach that included longitudinal neuroimaging, somatic growth tracking, and postmortem brain transcriptomic and neuropathologic analysis. Regional brain injury profiles and molecular signatures were correlated between NEC and non-NEC groups. Results:
NEC displayed a selective pattern of injury in the midline brain structures associated with exacerbation of the typical preterm brain injury pattern, with disproportionate injury to the pons (Figure 1). This unique phenotype in NEC neonates is characterized by pontosubicular necrosis and apoptotic neuronal profiles, correlated with arrested radiographic pontine growth independent from somatic growth trajectory impairment, indicating selective injury pattern (Figures 2 and 3). Pontine abnormal development was characterized molecularly with transcriptomic analysis showing altered neuronal differentiation pathways together with adaptive immune molecular dysregulation and T-lymphocytic activation mirroring the intestinal molecular and histological profile of the primary site of NEC injury (Figure 4). Conclusions:
NEC induces a unique, immune-mediated pattern of brainstem injury, selectively targeting the pons and disrupting neurodevelopment. These findings provide novel insights into the specific neuropathological consequences of NEC, highlighting the pons as a key region affected by NEC-related injury and providing a potential mechanistic explanation for the associated neurodevelopmental deficits.

Disclosures: G. Sanidas: None. **C. Lowe:** None. **C. Byrd:** None. **R. Vidva:** None. **G. Simonti:** None. **T. Chandereng:** None. **V. Gallo:** None. **P. Kratimenos:** None.

Poster

PSTR103: Early Life Stress and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.22/B29

Topic: A.08. Adolescent Development

Title: Effect of diet composition on memory, food preference and anxiety- and depressive-like behavior in adolescent C57BL/6 mice

Authors: *M. CHAVEZ HERNANDEZ[1], L. RODRIGUEZ-SERRANO[2];
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Abstract: Adolescent overweight and obesity represent a mayor public health problem for which long-term consumption of palatable food may constitute a risk. Dietary patterns have changed, and the availability of highly palatable foods (HPF) has increased. On the other hand, governments have increased efforts to reduce consumption of ultraprocessed foods by implementing campaigns informing of the risk of over consumption of foods high in sugar, fats and calories (e.g. front-of-pack warning labels implemented by the Mexican government). While these campaigns may help reduce the amount of HPF consumed by adolescents, it is possible that even a small amount may have an effect on anxiety, depression and cognitive performance, as well as the development of overweight and/or obesity. It has been reported that access to HPF during adolescence increases anxiety- and depressive-like behavior in male rats. However, this effect may be influenced by the amount of HPF consumed. In the present study we aimed to analyze the effect different diet compositions have on anxiety-like behavior, memory, depressive-like behavior and preference between palatable food (PF) and standard diet (SD). Male and female adolescent (30PND) C57BL/6 mice were divided into one of the following groups: control: 100% SD, diet 1: 25% PD-75% SD, diet 2: 50% PF-50% SD; or diet 3: 75% PF-25% SD. Mice were kept in the assigned diet for 5 weeks. On week five behavioral evaluation was conducted. Behavioral tasks were the following: elevated plus maze (EPM), open field task (OF), novel object recognition task (NORT), forced swim task (FST) and food preference task (FP). Results indicate male diet 3 mice show lower anxiety-like behavior in the OF task than male diet 2 mice, and that female diet 3 mice have better performance in short term memory NORT. No significant differences between diet compositions was found in EPM, FST, and acquisition and long-term memory NORT. These results indicate that different diets compositions during adolescence have an effect on anxiety and memory.

Disclosures: M. Chavez Hernandez: None. **L. Rodriguez-Serrano:** None.

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.01/B30

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

Support: Conahcyt-Mexico, grant number CF-I-2023-935 to Arturo Ortega

Title: Epigenetic Modulation of Glutamate Uptake in Bergmann Glia: A Synergistic Role of DNA Hypomethylation and AMPA Receptor Signaling

Authors: *B. O. OYETAYO[1], T. SUBAIR[2], L. C. HERNANDEZ[3], A. ORTEGA[3];
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Abstract: Bergmann glial cells (BGCs), specialized radial glia in the cerebellum, are key regulators of synaptic homeostasis through their role in glutamate clearance. These glial cells express high levels of Na^+-dependent glutamate transporters GLAST (EAAT1) and GLT-1 (EAAT2) which maintain neurotransmitter balance and protect against excitotoxicity. Glutamate receptors on BGCs, particularly ionotropic AMPA receptors, play an active role in sensing neuronal activity and modulating glial function through complex intracellular signaling cascades involving calcium influx and downstream effectors like Protein Kinase C (PKC) and transcription factor Ying Yang 1 (YY1). Recent research from our laboratory has uncovered a dynamic epigenetic layer of regulation over these glial glutamate transporters, particularly through DNA methylation. This mechanism, previously thought to be stable, is now recognized as flexible and responsive to extracellular cues. Specifically, we observed that glutamate exposure elevates 5-methylcytosine (5-mC) levels and modulates both expression and uptake activity of GLAST and GLT-1 in primary chick BGCs and human Müller glia (MIO-M1 cell line). In this study, we further examined how DNA hypomethylation interacts with AMPA receptor stimulation to regulate transporter activity. Using a primary chick BGC model, we found that hypomethylating conditions significantly increased glutamate uptake *via* GLAST. This effect is enhanced by AMPA receptor stimulation, indicating a synergistic mechanism. Kinetic analyses show an increased Vmax and Km, suggestive of elevated transporter density at the plasma membrane. Importantly, pharmacological inhibition of protein trafficking reduced this effect, pointing to active transporter mobilization. Furthermore, blocking the PI3K/Akt signaling pathway abolished AMPA-induced transporter potentiation, highlighting its crucial role in the regulatory cascade. Together, these findings reveal a novel short-term mechanism in which epigenetic flexibility and synaptic receptor activity converge to enhance glutamate uptake in glial cells. This synergy between DNA methylation states and AMPA receptor signaling could provide new insights into how glial cells dynamically adapt to excitatory neurotransmission and maintain neuroprotective functions under both physiological and potentially pathological conditions.

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

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.02/B31

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

Support: ZIA MH002946-13

Title: Identification of novel proteins that interact with a C-terminal motif in the glutamate transporter, EAAT3

Authors: S. GHODRATI[1,2], S. RADHAKRISHNAN[1], *S. G. AMARA[1];
[1]NIMH, Bethesda, MD; [2]Program in Biomed. Sci., Univ. of Michigan, Ann Arbor, MI

Abstract: Glutamate, the main excitatory neurotransmitter in the mammalian brain, is regulated by a class of membrane proteins called excitatory amino acid transporters (EAATs). EAAT3 is widely expressed in neurons in the brain and is crucial for glutamate clearance from the synapse and modulation of neuronal signaling. Mutations in EAAT3 are associated with neuropsychiatric disorders such as schizophrenia and obsessive-compulsive disorders. A C-terminal sorting motif, ^{504}VNGGF^{508}, has been shown to play an important role in regulating the intracellular trafficking and dendritic localization of EAAT3 in hippocampal neurons. We used a TurboID biotin ligase-based proximity labeling technique in a neuroblastoma cell line, Neuro2A to identify proteins that interact with and regulate trafficking of EAAT3. The TurboID biotin ligase was fused to the N-terminus of a wild type EAAT3 or a mutant with alanine substitutions at the VNGGF motif. Biotinylated proteins were identified in cells transfected with WT- and mutant EAAT3-transfected cells by mass spectrometry. In addition to identifying previously known interactors of EAAT3, these analyses revealed novel interacting partners of the ^{504}VNGGF^{508} domain, including both WASHC2 and SNX3, which are involved in early endosomal transport and play crucial roles in cargo sorting and recycling. WASHC2 interacts with the retromer complex and helps facilitate the endosome-plasma membrane recycling of other transporters such as the glucose carrier, GLUT1. SNX3 is a sorting nexin that is also a part of the retromer complex and is involved in retrograde trafficking of proteins. We used immunocytochemistry and proximity ligation assay (PLA) in combination with confocal imaging to study the cellular localization of EAAT3 and the C-terminal mutant and to validate the findings from the proteomic analyses. Image analysis revealed a significantly higher degree of colocalization and number of PLA interactions between EAAT3 WT compared to the C-terminal mutant with proteins such as SNX3, WASHC2 and Numb, a previously known EAAT3 interactor which served as a positive control. Characterization of the EAAT3 interactome will allow us to gain further insights into the trafficking and localization of glutamate transporters in neurons and to identify proteins that interact with the VNGGF domain and regulate EAAT3 activity.

Disclosures: S. Ghodrati: None. **S. Radhakrishnan:** None. **S.G. Amara:** None.

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.03/B32

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

Support: NIH intramural Research Program
ZIA MH002946-13

Title: Selective Deletion of EAAT3 in Dopaminergic Neurons Attenuates Amphetamine-Induced Behavioral Activation and Impairs Working Memory in Rats

Authors: *M. HU[1], C.-Y. SUN[2], S. G. AMARA[3];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]NIMH, NIH, Bethesda, MD; [3]Natl. Inst. of Mental Hlth., NIMH, Bethesda, MD

Abstract: The neuronal Excitatory Amino Acid Transporter 3 (EAAT3) mediates glutamate uptake and plays a crucial role in regulating glutamatergic signaling within dopaminergic circuits. To investigate the behavioral impact of EAAT3 deficiency in dopamine neurons, we crossed a DAT-cre expressing rat line with a novel cre-dependent conditional EAAT3 rat line to generate EAAT3 DAT-cre knockout rats (EAAT3 DAT KO). Male EAAT3 DAT KO rats exhibit a significantly attenuated locomotor response to amphetamine (2 mg/kg, i.p.) compared to control littermates ($p < 0.05$). In open field tests, amphetamine-induced increases in both the duration and distance traveled within the central zone are markedly blunted in EAAT3 DAT KO rats relative to controls ($p < 0.05$), suggesting diminished psychostimulant sensitivity and altered anxiety-like behavior. Moreover, EAAT3 DAT KO rats require significantly more time to complete the radial arm maze task ($p < 0.05$), suggesting an impairment in working memory. Together, these findings demonstrate that EAAT3 expression and the regulation of extracellular glutamate concentrations surrounding dopamine neurons are essential for normal amphetamine-induced behavioral activation and cognitive function.

Disclosures: M. Hu: None. **C. Sun:** None. **S.G. Amara:** None.

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.04/B33

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

Support: NIH Intramural Research Program
ZIA MH002946-13

Title: Mapping the EAAT3 Interactome and Identification of Novel Regulators of EAAT3 Trafficking Using Proximity Labeling

Authors: *S. RADHAKRISHNAN, S. GHODRATI, S. G. AMARA;
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Abstract: Plasma membrane neurotransmitter transporters play a crucial role in regulating neuronal signaling by clearing neurotransmitters from the extracellular space. The neuronal excitatory amino acid transporter 3 (EAAT3) is essential for glutamate clearance and modulation of glutamatergic tone. EAAT3 mutations are associated with several neuropsychiatric disorders such as schizophrenia and obsessive-compulsive disorders. The activity of plasma membrane transporters can be altered by changes in transport kinetics, expression levels and trafficking to and from the plasma membrane. A C-terminal motif in EAAT3, ^{504}VNGGF^{508}, is required for EAAT3 somatodendritic targeting in hippocampal neurons and for the endocytosis of EAAT3

activated by amphetamines. To identify endogenous transient interactors and constitutive binding partners of EAAT3, we used the proximity labeling technique, TurboID. In preliminary studies conducted in Neuro2A cell lines, we employed constructs expressing the TurboID tag fused to EAAT3 to label proteins associated with wild type EAAT3 and with an EAAT3 with alanine substitutions at the ^{504}VNGGF^{508} motif. Biotinylated proteins were identified by mass spectrometry. Over 100 significantly enriched proteins were identified as potential interactors of EAAT3. 26 proteins were identified only in the WT and not the C-terminal mutant. STRING analysis was performed on these proteins, and we identified functional enrichment in GO terms related to endosomal transport, retrograde transport, SNARE complex and protein serine/threonine phosphatase complex. We identified a novel C-terminal interactor SNX3, a sorting nexin that is involved in the retrograde trafficking of cargo. This interaction was confirmed by colocalization studies, proximity labelling and functional studies showing that SNX3 regulates EAAT3 trafficking in Neuro2A cells. We expanded this approach by expressing the TurboID-EAAT3 construct in primary cortical neurons and mapping the proteomes of intracellular compartments (endosomes, lysosomes, golgi, plasma membrane) to identify EAAT3 proximal proteins at specific subcellular locations. This approach allows us to spatially resolve the EAAT3 intracellular interaction network. SNX3 was found in proximity to EAAT3 in primary neurons as well and specifically at the endosomal compartments, suggesting that EAAT3 is likely recycled in neurons through its interaction with the SNX3 on early endosomal membranes. Proteomic profiling of the EAAT3 interactome will help us gain insight into the constitutive regulation of EAAT3 and a better understanding of the effects of amphetamines on EAAT3.

Disclosures: S. Radhakrishnan: None. **S. Ghodrati:** None. **S.G. Amara:** None.

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.05/B34

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

Support: NIMH Grant R01-MH126017

Title: Presynaptic trafficking of Glutamate Decarboxylase isoforms is dispensable for basal GABAergic neurotransmission

Authors: *O. BENNER[1], C. H. KARR[1], M. A. XU-FRIEDMAN[3], S. CHANDA[2];
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[3]Dept Biol. Sci., Univ. at Buffalo, SUNY, Buffalo, NY

Abstract: The two major glutamate decarboxylase isoforms (i.e., GAD65 and GAD67) together synthesize the majority of γ-aminobutyric acid (GABA) in our nervous system. However, the subcellular distribution of these enzymes and their relative impacts on synaptic GABA release

remain mostly unclear. To address this important question, here we monitored their synaptic trafficking in mouse brain and dissociated neuronal cultures. We noticed that, unlike the glutamate-synthesizing enzyme Glutaminase, which was primarily associated with perisomatic mitochondria, both GADs together were highly enriched at GABAergic presynapses. Nevertheless, when expressed separately in GAD-deficient human neurons, GAD65 exhibited preferential distribution at presynapses over GAD67. Despite these differences in subcellular localization, both GAD isoforms produced equivalent levels of intracellular GABA, which adequately diffused to axon terminals, and triggered robust GABAergic synaptic activities. These findings raised the question of whether the presynaptic recruitment of GADs is, after all, necessary for efficient GABAergic transmission. To examine this hypothesis, we further swapped or removed the trafficking signals from both GAD isoforms, and even artificially restricted them at non-synaptic regions, including the cell nuclei. Regardless of our attempts, these chimeric and mutant GAD variants continued to produce a sufficient amount of GABA for vesicular loading and synaptic release. These results indicate that GAD65 and GAD67 are functionally redundant in GABA production if equitably expressed in neurons; and irrespective of their intracellular trafficking profiles, diffusion of GABA from distant sources can effectively supply and replenish the synaptic terminals for functional activities.

Disclosures: O. Benner: None. **C.H. Karr:** None. **M.A. Xu-Friedman:** None. **S. Chanda:** None.

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.06/B35

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

Title: Beyond the Synapse: Investigating the Nuclear Membrane Localization and Function of the Serotonin Transporter

Authors: A. JOHNSON[1], A. ROBLES[2], L. DINAMARCA[2], M. QUIROZ[3], *G. E. TORRES[4]; [1]Mol. Pharmacol. and Neurosci., Loyola Univ. Chicago, Maywood, IL; [2]Organic Chem., Pontificia Univ. Catolica de Chile, Santiago, Chile; [3]Mol. Pharmacol. ans Neurosci., Loyola Univ., Maywood, IL; [4]Mol. Pharmacol. and Neurosci., Loyola Univ. Chicago Sch. of Med., Maywood, IL

Abstract: Serotonin (5-hydroxytryptamine, 5-HT) is a critical neurotransmitter in the brain, regulating cognitive functions such as mood, appetite, sleep, and stress responses. Its synaptic availability is regulated by the serotonin transporter (SERT), a protein located at the neuronal plasma membrane that facilitates serotonin reuptake into the presynaptic neuron, thereby modulating serotonergic signaling. Beyond its classical role in neurotransmission, recent research has shown that serotonin also participates in post-translational protein modifications, notably through a process known as serotonylation—the covalent attachment of serotonin to

target proteins. One such target is Histone 3, which lies within the nucleus of neurons, wrapped in DNA. Serotonylation of histone H3 enhances chromatin accessibility, thereby increasing gene transcription. Genes regulated by this modification are implicated in neuropsychiatric and neurodegenerative disorders, including Major Depressive Disorder, Schizophrenia, and Alzheimer's disease, and influence key neuronal processes such as axon myelination, axon guidance, and oligodendrocyte differentiation. However, the mechanism by which serotonin enters the nucleus, a highly regulated environment, remains unclear. To address this, we employed immunohistochemistry, western blotting, and functional uptake assays to investigate the localization and activity of SERT at the nuclear membrane. Preliminary data reveal SERT localization not only at the plasma membrane of SERT-transfected cells but also at the nuclear membrane. Furthermore, uptake of the fluorescent false neurotransmitter (FFN246) into the nuclei of transfected cells was observed, suggesting a potential role for nuclear SERT in serotonin transport. These findings suggest that nuclear-localized SERT may mediate serotonin entry into the nucleus, providing a mechanistic link to serotonylation-driven gene regulation and offering a novel therapeutic target for neurocognitive and neurodegenerative disorders.

Disclosures: A. Johnson: None. **A. Robles:** None. **L. Dinamarca:** None. **M. Quiroz:** None. **G.E. Torres:** None.

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.07/B36

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

Title: Understanding the MDMA-Induced Non-vesicular Serotonin Release through the SerotoninTransporter

Authors: *C. WOOD[1], L. DINAMARCA[3], M. QUIROZ[4], G. E. TORRES[2];
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Abstract: Neuropsychiatric disorders like anxiety and depression affect approximately 5% of the global population and contribute to over 800,000 suicide deaths annually, with serotonin (5-HT) playing a crucial role in mood regulation. Current antidepressant treatments, such as selective serotonin reuptake inhibitors (SSRIs) (e.g., Celexa, Lexapro, Prozac), aim to increase serotonin availability by inhibiting its reuptake via the serotonin transporter (SERT). However, these treatments fail to improve symptoms in nearly 30% of individuals affected. A promising approach involves serotonin releasers, which induce non-vesicular serotonin efflux through SERT, leading to an increase in extracellular serotonin. Despite their potential, there is a significant gap in the literature regarding the mechanisms by which these releasers promote serotonin release through SERT, representing a potential area for therapeutic innovation. 3,4-Methylenedioxymethamphetamine (MDMA), a potent serotonin-releasing agent and

amphetamine derivative, promotes non-vesicular serotonin release via reverse transport through SERT. MDMA-assisted therapy has demonstrated clinical efficacy in treatment-resistant PTSD and has been designated a breakthrough therapy by the FDA. However, MDMA is also known to be neurotoxic and addictive, which limits its therapeutic utility. In this study, we use MDMA as a pharmacological tool to understand the underlying mechanisms of serotonin release. Based on our previous work with the dopamine transporter, we examined the role of G protein βγ (Gβγ) in MDMA-induced serotonin release via SERT and aimed to establish Gβγ as a novel target for enhancing serotonin release. Ultimately, we aim to leverage this interaction for in silico molecular dynamic simulation studies to identify novel compounds that mimic MDMA's serotonin-releasing effects with higher specificity, lower toxicity, and reduced abuse potential.

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

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.08/B37

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

Support: NICHD Intramural Research Program

Title: Dat+ dopamine axons innervating superficial cortical layers arise from collateralized projections to the dorsomedial striatum

Authors: *D. VULLHORST[1], J. P. WELDAY[2], E. M. LEWIS[3], R. MURPHY[4], A. L. BUONANNO[5];
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Abstract: Dopamine (DA) projections to the cortex are thought to express low levels of the DA transporter DAT, and cortical extracellular DA is believed to be cleared by COMT-mediated degradation and NET-mediated uptake into norepinephrine fibers instead. However, we previously showed that stimulation of the Neuregulin/ErbB4 signaling pathway acutely increases extracellular DA levels by downregulating DAT activity, not only in the striatum but also in the mPFC, thus implicating DAT in regulating cortical DA (Skirzewski et al., 2018; PMID:28727685).The goal of this study was to reassess DAT expression and activity in the mouse cortex using immunohistology, retrograde tracing and fiber photometry approaches. We find that DAT is strongly expressed in highly tufted DA axons restricted to layers I-III of the prelimbic subdivision of the medial prefrontal cortex (mPFC) and the ventral anterior cingulate cortex (vACC). Retrograde tracing with an mCherry-expressing CAV-2 virus microinjected into superficial cortical layers of DAT-Cre mice labels DA neuron cell bodies located in an area

encompassing the medial substantia nigra (SN) and ventrolateral portions of the ventral tegmental area (VTA). Unexpectedly, we find that cortical CAV-2_DIO-mCherry injections not only label cortical DA projections but also projections to the dorsomedial striatum (DMS); conversely, injections into the DMS also label DAT+ DA projections to superficial mPFC / ACC layers. Whole brain light-sheet microscopy reveals that these DA axons first enter the striatum where they branch out into two or more collaterals, some of which project to the DMS where they form terminal branches while others traverse the corpus callosum to innervate superficial layers in the mPFC and vACC. Lastly, using fiber photometry in forebrain slices expressing the DA sensor GRAB-DA3m, we demonstrate that the DAT contributes significantly to DA clearance in superficial vACC layers.

Disclosures: D. Vullhorst: None. **J.P. Welday:** None. **E.M. Lewis:** None. **R. Murphy:** None. **A.L. Buonanno:** None.

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.09/B38

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

Support: R01DA058143
R01NS071122-07A1
R21NS133384

Title: Cytokines regulate dopamine transporter activity in human macrophages

Authors: *S. V. C. R. CAMPOS[1], A. GOPINATH[1], A. GRILLO[1], D. BOOTH[1], L. PHAN[1], E. J. MILLER[2], J. SEIBOLD[1], A. H. NEWMAN[4], H. KHOSHBOUEI[3];
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Abstract: The dopamine transporter (DAT), a membrane protein primarily expressed in dopamine neurons, plays a key role in controlling dopamine signaling by regulating the duration and magnitude of dopamine levels. DAT operates in two modes: (1) an outward-facing conformation, where it uptakes dopamine, and (2) an inward-facing conformation, promoting dopamine efflux. While DAT is traditionally associated with regulation of dopamine signaling in the brain, it is also expressed in immune cells, including human macrophages—critical components of the innate immune system responsible for detecting and eliminating pathogens. Previous research has shown that inhibiting DAT in macrophages increases lipopolysaccharide (LPS)-induced inflammatory responses, indicating that DAT plays an immunosuppressive role. LPS exposure does not alter DAT membrane expression levels but reduces dopamine uptake by shifting DAT to the efflux-promoting conformation via a CD14-dependent, but TLR4-independent, mechanism. LPS, while a potent inflammatory molecule, affects a multitude of intracellular immunological cascades. We sought to determine whether physiologically relevant

immune stimuli, such as inflammatory or immunosuppressive cytokines, modulate membrane DAT levels and function in human macrophages. Via membrane biotinylation followed by immunoblot, we discovered that immunosuppressive cytokines, TGF-β and IL-10, significantly increase DAT levels at the macrophage membrane, supporting DAT's role in modulating immune responses. Next, we employed JHC1-64, a fluorescent DAT ligand that selectively binds the outward-facing, dopamine-uptake conformation of DAT, to assess conformation of DAT during treatment with immunosuppressive or inflammatory cytokines. Via confocal microscopy, we determined that JHC1-64-bound DAT is significantly increased following TGF and IL10 treatment, indicating increased outward-facing membrane localized DAT. To determine whether this increased outward facing DAT conformation increases DAT-mediated dopamine uptake, we used IDT307, a fluorescent dopamine analog. Treatment with both TGF and IL10 significantly increased IDT307 uptake. These findings suggest that immunosuppressive cytokines increase membrane localized, outward-facing DAT that also increases DAT-mediated substrate uptake. In our ongoing work, we will evaluate the effects of immunosuppressive cytokines on DAT expression and function in Parkinson's Disease compared to healthy macrophages, to determine the clinical implications of membrane-localized DAT in disease states that affect dopamine transmission.

Disclosures: S.V.C.R. Campos: None. **A. Gopinath:** None. **A. Grillo:** None. **D. Booth:** None. **L. Phan:** None. **E.J. Miller:** None. **J. Seibold:** None. **A.H. Newman:** None. **H. Khoshbouei:** None.

Poster

PSTR104: Neurotransmitter Transport and Degradation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.10/B39

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

Support: ANR-PRC CEST-Focus

Title: High-resolution glutamate-weighted mapping of in vivo mouse brain across age with Chemical Exchange Saturation Transfert MRI

Authors: *R. GAUDIN, T. DELEBARRE, M. GLATIGNY, E. SELINGUE, L. CIOBANU, D. BOIDO;
NeuroSpin, CEA, Paris, France

Abstract: Glutamate concentration is subject to variations across healthy ageing and pathologies in the brain. Using Chemical Exchange Saturation Transfer (CEST) MRI at ultra-high magnetic field, it is possible to map glutamate in vivo with high resolution. We scanned a cohort of mice from 4 to 23 months of age.We scanned 19 healthy mice at 17.2T with a glutamate CEST (GluCEST) protocol (RARE sequence, 150x150x500 μm) sampling a vast portion of the mouse brain. The GluCEST was significantly lower in the Neocortex than Hippocampus and Thalamus

(p<0.05, 1-way ANOVA and post-hoc Tukey) and lower in CA3 with respect to the other hippocampal subregions (p<0.01). A linear regression of the mean GluCEST value vs age displayed a significant decrease in Hypothalamus, Thalamus (p<0.05) and in CA3 (p<0.01). We observed no significant differences across cortical functional sub-regions, nor across cortical layers. These results are consistent with recent literature reporting the highest neuronal loss with ageing in hypothalamic region (Jin et al., 2025). Our noninvasive study highlights the regional changes in glutamate over age and provides a reference for long-term investigations on mouse models of pathologies.

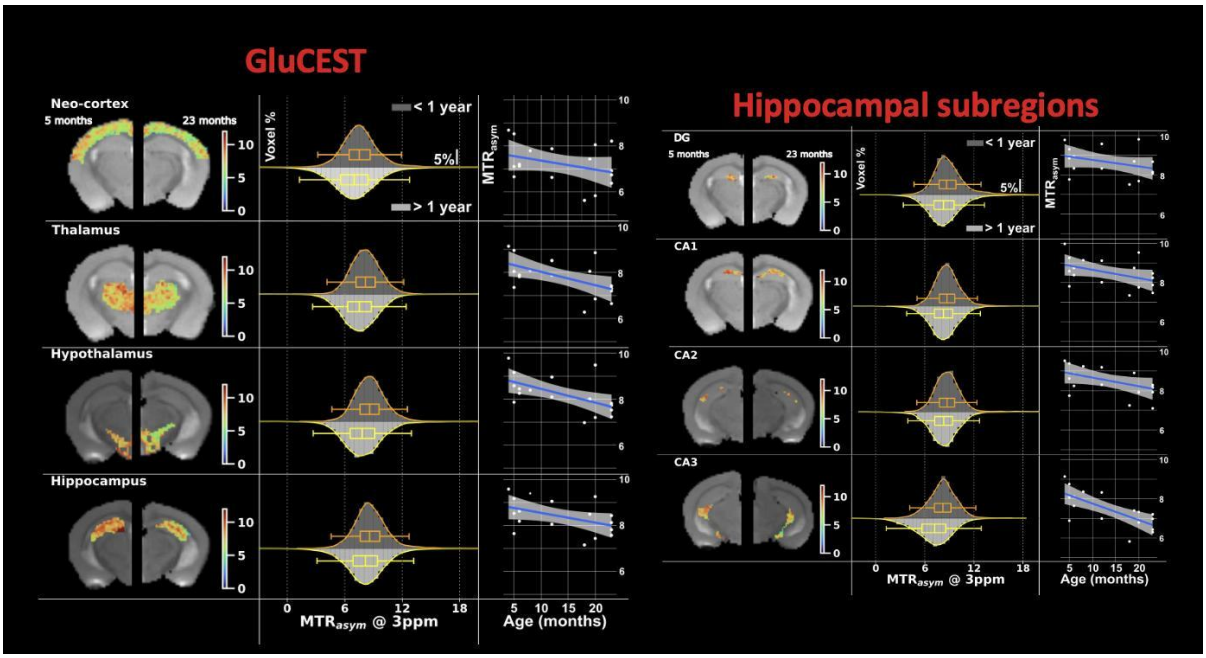


Figure: From left to right: example of GluCEST map in brain regions for a young mouse (5 months old, left side) and an old one (23 months old, right side). GluCEST values distributions in the same brain regions: top distributions are from young mice (<1 year) and bottom ones from old mice (>1 year). Mean GluCEST value of each mouse against its age, fitted with a line. The same evaluation was made in hippocampal subregions.

Disclosures: R. Gaudin: None. **T. Delebarre:** None. **M. Glatigny:** None. **E. Selingue:** None. **L. Ciobanu:** None. **D. Boido:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.01/B40

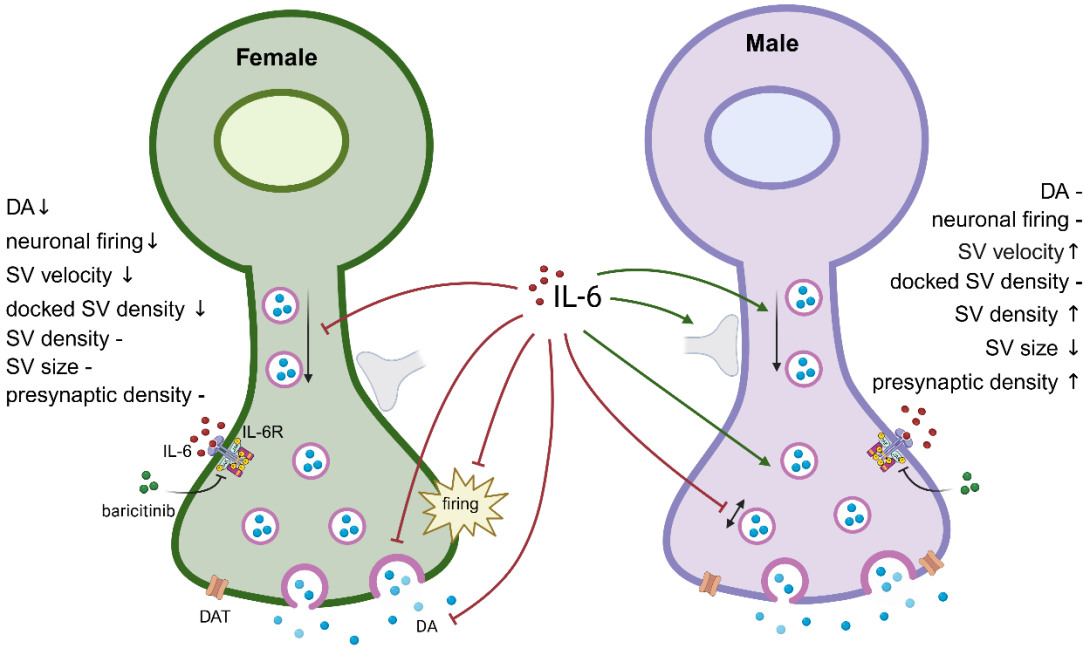
Topic: B.04. Synaptic Transmission

Support: NIH grant R21MH132012
NIH grant R01MH139822
NIH grant R01MH121102

Title: Effects of Inflammation on Human iPSC-derived Dopaminergic Neurons: Reversal by Baricitinib

Authors: *Y. HUANG[1], C. MICHALSKI[2], Y. ZHOU[2], C. XU[2], W. NIU[2], M. J. LUCIDO[2], J. WANG[2], Y. FENG[2], A. MILLER[2], Z. WEN[2];
[1]Laney Grad. Sch. Neurosci. Program, [2]Dept. of Psychiatry and Behavioral Sci., Emory Univ., Atlanta, GA

Abstract: Introduction: High inflammation is associated with motivational deficits in depression patients. Administration of inflammatory stimuli has led to depressive symptoms and reduced dopamine (DA) availability and release in the brain in humans and animal models. However, the underlying mechanisms are largely unknown. Furthermore, motivational deficits are more common in female depression patients with high levels of peripheral inflammatory markers, compared to males, while the role of inflammation in shaping this disparity remains unclear. In this study, we examined the effects of cytokine interleukin (IL)-6 on healthy female and male DA neurons and tested whether the anti-inflammatory drug baricitinib could reverse these effects. **Materials & Methods:** Eight-week-old female and male DA neurons derived from healthy control human induced pluripotent stem cells (iPSCs) were treated with vehicle or 5 ng/mL IL-6 or 5 ng/mL IL-6 + 200 nM baricitinib for 24 hrs. Extracellular DA concentration, network firing and burst activities, velocity of synaptic vesicles (SV), density, size, and docking of SVs at synaptic terminals, and density of presynaptic terminals were measured after treatment. **Results:** IL-6 treatment significantly reduced DA release, neuronal activity, velocity of SVs, and density of docked SVs in female DA neurons only. In contrast, IL-6 increased velocity and density of SVs as well as density of presynaptic terminals and decreased diameter of SVs in male DA neurons. Moreover, many inhibitory effects of IL-6 were reversed to baseline by baricitinib, especially in female DA neurons. **Conclusion:** IL-6 induces deficits in multiple aspects of DA function in female DA neurons and a compensatory phenotype in male DA neurons, which may be connected to female preponderance in depression. In addition, the efficacy of baricitinib in blocking the effects of IL-6 may reveal an important mechanistic impact of anti-inflammatory treatments for depressed patients with high inflammation.



Disclosures: Y. Huang: None. **C. Michalski:** None. **Y. Zhou:** None. **C. Xu:** None. **W. Niu:** None. **M.J. Lucido:** None. **J. Wang:** None. **Y. Feng:** None. **A. Miller:** None. **Z. Wen:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.02/B41

Topic: B.04. Synaptic Transmission

Support: German Research Foundation (DFG) - Project number 504371651
Alexander von Humboldt Foundation

Title: Synaptic nanotopology shapes readily-releasable pool size modulation of short-term plasticity

Authors: *A. ABRAHAMYAN[1], B. MUELLER[2], E. M. JORGENSEN[3], C. ROSENMUND[4], M. A. HERMAN[5];
[1]Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]The Univ. of Utah, Salt Lake City, UT; [3]Sch. of Biol. Sci., Univ. Utah, Salt Lake Cty, UT; [4]Inst. for Neurophysiol., Charite Med. Sch. Berlin, Berlin, Germany; [5]Inst. of Neurophysiol., Charité-Universitätsmedizin Berlin, Berlin, Germany

Abstract: The nanoscale organization of synaptic proteins — or synaptic nanotopology — plays a critical role in shaping neurotransmission and plasticity. In particular, the spatial relationship between voltage-gated calcium channels (VGCCs), docked vesicles, and release sites can influence how changes in the readily-releasable pool (RRP) affect neurotransmission. To investigate this, we used electrophysiological recordings and live imaging of neurotransmitter release combined with electron and super-resolution microscopy, to link the physiological behavior with underlying nanoscale architecture in excitatory and inhibitory synapses of primary cultured mouse and human iPSC-derived neurons. We manipulated synaptic strength by treatment with the adenylyl cyclase activator, forskolin, which potentiated postsynaptic current amplitudes and the RRP size in both glutamatergic and GABAergic synapses. Forskolin treatment had no effect on the paired-pulse ratio (PPR) in glutamatergic synapses, but significantly decreased PPR in GABAergic synapses. Based on the effect of open channel block of VGCCs in glutamatergic and GABAergic synapses, we hypothesize that the difference in effect of RRP potentiation on PPR is due to differences in synaptic nanotypology. Indeed, while high pressure freezing fixation of EM samples showed an increased number of docked vesicles with forskolin treatment in both synapse types, 3D STORM imaging revealed a forskolin-induced modulation of Munc13-1-VGCC distance only in GABAergic synapses. Specifically, the Munc13-1 and CaV2.1 nearest-neighbor distance was significantly decreased, suggesting reconfiguration of the channel-vesicle coupling nanotopology in mouse GABAergic synapses. No change in nanotopology in glutamatergic synapses was observed with forskolin treatment. These findings uncover distinct topological strategies used by excitatory and inhibitory synapses to regulate information flow and highlight differential coupling between calcium influx and vesicle release as a core mechanism underlying the diversity of short-term synaptic plasticity.

Disclosures: A. Abrahamyan: None. **B. Mueller:** None. **E.M. Jorgensen:** None. **C. Rosenmund:** None. **M.A. Herman:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.03/B42

Topic: B.04. Synaptic Transmission

Support: Rosenau Research Foundation 549774

Title: The impact of Lysosomal Storage Diseases on SNARE complex dynamics and presynaptic function

Authors: *D. S. ZELADA[1], N. SALDIVIA[1], S. SAMANO[1], R. REBIAI[3], P. A. SUTTER[4], Z. ZURAWSKI[2], D. SHIN[5], M. I. GIVOGRI[1], S. J. CROCKER[6], S. T. ALFORD[7], E. R. BONGARZONE[1];
[2]Anat. and Cell Biol., [1]Univ. of Illinois at Chicago, Chicago, IL; [3]Univ. of Illinois At Chicago (UIC), Chicago, IL; [4]Uconn Sch. of Med., Farmington, CT; [5]Biochem., SUNY Buffalo, Buffalo,

NY; [6]Dept Neurosci, Univ. of Connecticut Sch. of Medi Neurosci. Grad. Program, Farmington, CT; [7]Anat. and Cell Biol., Univ. of Illinois At Chicago Dept. of Anat. and Cell Biol., Chicago, IL

Abstract: Krabbe disease (KD) is a Lysosomal Storage Disorder (LSD) caused by loss-of-function of the lysosomal enzyme galactosylceramidase (GALC), resulting in the accumulation of the neurotoxic sphingolipid psychosine. While demyelination is a hallmark of KD, the mechanisms by which psychosine affects synaptic function are still unclear. Here, we demonstrate that GALC deficiency induces a cell-autonomous effect on synaptic function in hippocampal neurons. Using mouse models of KD (Twitcher mice and conditional GALC knockouts), we observed reduced excitatory postsynaptic potentials and impaired paired-pulse facilitation, indicative of defective synaptic vesicle (SV) exocytosis. Electron microscopy revealed a loss of SV pools and dendritic spines, alongside enlarged synaptic clefts and disrupted pre-/postsynaptic alignment. Remarkably, psychosine was found to accumulate predominantly in presynaptic compartments, altering SV cycling by inhibiting SV exocytosis and SNARE-dependent membrane fusion. Vesicle trafficking alterations were also triggered by other lipids mediating other LSDs, such as gangliosidoses, metachromatic leukodystrophy, Gaucher disease, and Niemann-Pick disease, respectively. Mechanistically, we identified increased levels of phosphorylated SNAP-25 (Ser187), inactivated GSK3-β, and activated PP2A in the hippocampus, which promoted aberrant accumulation of SNARE complexes. These alterations were specific to regions with high psychosine burden. Thus, our findings reveal that psychosine disrupts synaptic vesicle cycling by altering SNARE complex dynamics, highlighting synaptic dysfunction as a primary consequence of GALC deficiency. This study identifies presynaptic lipid accumulation as a potential shared pathological mechanism in other sphingolipidoses, offering novel insight into synaptic failure in LSDs.

Disclosures: D.S. Zelada: None. **N. Saldivia:** None. **S. Samano:** None. **R. Rebiai:** None. **P.A. Sutter:** None. **Z. Zurawski:** None. **D. Shin:** None. **M.I. Givogri:** None. **S.J. Crocker:** None. **S.T. Alford:** None. **E.R. Bongarzone:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.04/B43

Topic: B.04. Synaptic Transmission

Support: TLL core funding

Title: Mobilization of reserve pool synaptic vesicles by synapsin phosphorylation

Authors: S.-H. SONG, ***G. J. AUGUSTINE**;
Temasek Lifesciences Lab., Singapore, Singapore

Abstract: Synapsins cluster synaptic vesicles (SVs) in the presynaptic reserve pool via two mechanisms: by liquid-liquid phase separation (LLPS) at GABAergic synapses and by synapsin

oligomers cross-linking SVs at glutamatergic synapses (*Cell Reports* 42: 113004). How are SVs mobilized from the clusters formed via these different mechanisms? We have addressed the role of protein kinase A (PKA) in these processes. At inhibitory synapses, synapsin 2a mutants with either phospho-mimetic or phospho-null substitutions in their PKA phosphorylation site successfully rescued GABA release when expressed in synapsin triple knockout (TKO) neurons. This suggests that PKA does not regulate mobilization of GABAergic SVs. Consistent with these results, neither treatment with PKA nor mutation of its PKA phosphorylation sites affected the LLPS properties of synapsin 2a. In contrast, the synapsin 2a phosphorylation site mutants were unable to rescue synaptic depression evoked by train stimulation of glutamatergic TKO synapses. This suggests that PKA-mediated phosphorylation is essential for mobilization of glutamatergic SVs. Consistent with these results, PKA-dependent phosphorylation disrupted synapsin oligomerization and altered binding of synapsin 2a to SVs. These findings highlight that distinct kinase-dependent regulatory mechanisms differentially mobilize SVs from synapsin-dependent clusters at excitatory and inhibitory synapses.

Disclosures: S. Song: None. **G.J. Augustine:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.05/B44

Topic: B.04. Synaptic Transmission

Title: Rim-binding protein regulates P/Q-Ca^{2+}-channel coupling at central synapses

Authors: *M. LUBAS[1], E. TOULME[1], T. TRIMBUCH[1], B. MUELLER[2], E. M. JORGENSEN[2], C. ROSENMUND[1];
[1]Inst. of Neurophysiol., Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Univ. of Utah, Salt Lake City, UT

Abstract: In synaptic transmission, the fast, precise, and synchronous release of neurotransmitters relies on a tight coupling between the synaptic release machinery, the synaptic vesicles, and the voltage-gated Ca^{2+}-channels (P/Q-type). Scaffolding molecules, including Rab-Interacting molecules (RIM), RIM-Binding Protein (RBP), ELKS, Munc13, Bassoon/ Piccolo and Liprin-α are the main known regulators of this coupling. Specifically, RIM and RBP have been shown to uniquely regulate synaptic vesicle docking and fusion, since no synaptic activity remains in RIM/RBP-deficient neurons (Acuna et al, 2016). The purpose of our study is to investigate the involvement of the scaffold protein RBP in voltage-gated Ca^{2+}-channel function using an autaptic model of mouse hippocampal glutamatergic neurons with conditional genetic deletions of RIM1, RIM2, RBP1 and RBP2. Synaptic vesicles can be artificially recruited to the active zone by expressing the fusion protein Zn-β4, composed of the RIM1α zinc-finger domain and the β4 subunit of Ca^{2+} channels (Tan et al, 2020). In RIM/RBP-deficient neurons, Zn-β4 expression is sufficient to restore vesicle docking and fusion competence, but not Ca^{2+} synaptic

influx or Ca^{2+}-dependent neurotransmitter release. Our results show that co-expression of Zn-β4 with RBP rescues both Ca^{2+} influx and Ca^{2+}-evoked responses to wild-type levels. Importantly, our current recordings in HEK293T cells expressing functional Ca^{2+} channels and RBP demonstrate that Ca^{2+} channel membrane trafficking and gating remain unaffected, indicating that the observed synaptic deficits are not due to altered channel function but rather to impaired spatial coupling between Ca^{2+} channels and release sites. Collectively, these data indicate that RIM/RBP deficiency strongly impairs vesicle docking and fusion, and disrupts the coupling of Ca^{2+} channels to release sites. While Zn-β4 can render vesicles fusion-competent, our results, along with previous studies from our lab, suggest that RBP is necessary for proper clustering of Ca^{2+} channels near release sites. We propose the protein domains form a molecular "bridge" between synaptic vesicles and Ca^{2+} channels, thus ensuring efficient Ca^{2+}-triggered neurotransmitter release.

Disclosures: M. Lubas: None. **E. Toulme:** None. **T. Trimbuch:** None. **B. Mueller:** None. **E.M. Jorgensen:** None. **C. Rosenmund:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.06/B45

Topic: B.04. Synaptic Transmission

Support: 5R01NS134128
5R01MH070727
1T32GM152284

Title: Spatiotemporal regulation of asynchronous neurotransmission

Authors: *K. J. ZHANG, L. M. MONTEGGIA, E. T. KAVALALI;
Vanderbilt Brain Inst., VANDERBILT UNIVERSITY, Nashville, TN

Abstract: Neurons communicate through precisely timed bursts of neurotransmitter release, orchestrating the intricate signaling that underlies cognition, movement, and perception. The neuroscience community has largely focused on the study of synchronous neurotransmission, which occurs within milliseconds of an action potential. However, a compelling body of research supports the existence of an additional mode: asynchronous neurotransmission. Unlike its synchronous counterpart, asynchronous neurotransmitter release introduces a temporal delay by extending synaptic signaling beyond the initial spike. Emerging evidence suggests that asynchronous release impacts oscillatory activity in neural circuits, and that the desynchronization of synaptic vesicle fusion may underlie several neuropsychiatric disease-related conditions. Despite its physiological relevance, the molecular regulation and spatial dynamics of asynchronous release**,** particularly at the quantal level, remain poorly understood. Here, we apply high-resolution optical imaging and computational modeling to dissect the

physiological and molecular mechanisms driving this delayed form of neurotransmission at the single synapse level. We first find that loss of synaptotagmin-1 (Syt1) function significantly desynchronizes release at single synapses, increases the number of vesicles released in tandem, and elevates the frequency of quantal spontaneous events. Next, we observe that Syt1 loss of function paradoxically increases local postsynaptic signaling pathways. Notably, this effect is not observed in neurons with loss of synaptotagmin-7 (Syt7) function or in neurons with combined Syt1 and Syt7 loss of function. Finally, we observe that Syt1 loss of function increases the spatial dispersion of glutamatergic events across the active zone. Collectively, our results demonstrate that asynchronous neurotransmitter release constitutes a distinct neural signaling pathway, separate from other modes of release, with unique regulatory mechanisms and functional consequences.

Disclosures: K.J. Zhang: None. **L.M. Monteggia:** None. **E.T. Kavalali:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.07/B46

Topic: B.04. Synaptic Transmission

Title: Scamp5 coordinates AP-4-dependent sorting of ATG9A for presynaptic autophagy by recruiting PI4KIIIβ and generating PtdInsP4 at the trans-Golgi network

Authors: *J. LEE[1], S. RYU[2], K. KIM[3], S. CHANG[3];
[1]Seoul Natl. Univ., Jongno-gu, Seoul, Korea, Republic of; [2]Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Physiol. and Biomed. Sci., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Presynaptic autophagosome formation requires the trafficking of ATG9A, an autophagy transmembrane protein that serves as a specific cargo of the AP-4 complex at the trans-Golgi network (TGN). However, the molecular mechanisms governing ATG9A sorting at the TGN for presynaptic delivery remain poorly understood. Here, we identify SCAMP5, a synaptic vesicle protein critical for presynaptic plasticity, as highly enriched at the TGN and essential for presynaptic autophagosome formation. SCAMP5 knockdown significantly impaired autophagosome assembly at presynaptic boutons. Mechanistically, we demonstrate that SCAMP5 interacts with phosphatidylinositol 4-kinase IIIβ (PI4KIIIβ) to regulate its TGN recruitment, thereby controlling local phosphatidylinositol 4-phosphate (PtdIns4P) production. Since PtdIns4P is required for AP-4 recruitment to the TGN, SCAMP5 depletion disrupts this process, leading to abnormal ATG9A accumulation at the TGN and impaired axonal trafficking. Consequently, presynaptic autophagy is compromised, disrupting synaptic protein turnover and homeostasis. These findings establish SCAMP5 as a critical regulator of ATG9A-dependent presynaptic autophagy through its control of PI4KIIIβ recruitment and PtdIns4P synthesis at the

TGN, revealing a novel mechanism linking synaptic vesicle machinery to presynaptic protein quality control.

Disclosures: J. Lee: None. **S. Ryu:** None. **K. Kim:** None. **S. Chang:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.08/B47

Topic: B.04. Synaptic Transmission

Support: NIH Grant AG083078
NIH Grant R21NS131752

Title: Age induced weakness of mouse NMJs is associated with reduced active zone density, reduced vesicle replenishment rate, slowed synaptic event kinetics, and reduced presynaptic calcium entry

Authors: N. LI[1], E. CASE[2], C. BLANCHARD[2], A. MONTELEONE[2], M. GANDHI[2], A. JAIE[2], Y. BADAWI[1], ***S. D. MERINEY**[2];
[1]Neurosci., [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Aging has been shown to affect both the structure and function of the neuromuscular junction. In our previous study, we documented a biphasic change (first an increase followed by a decrease) in neurotransmission over the aging time course at male mouse neuromuscular junctions (NMJs). Here, we explored several potential mechanisms behind the reduction in presynaptic neurotransmitter release observed in the later stages of aging. At 30 months of age, NMJs had a quantal content (QC) of 56 as compared to 81 and 77 recorded from 4- and 26-month-old mice respectively. In 30-month-old mice, we found that the active zone (AZ) density was significantly reduced (1.39/μm^2) as compared to 4-month-old (2.04/μm^2) and 26-month-old (2.39/μm^2) mice. Further, end plate potential (EPP) and miniature EPP (mEPP) kinetics (rise and decay time) in 30-month-old mice was significantly slower than in 4- or 26-month-old mice (while mEPP amplitude and frequency were unchanged). 30-month-old NMJs also showed a significant reduction in the vesicle replenishment rate. Lastly, calcium entry into the presynaptic nerve terminal following a single presynaptic action potential was reduced by 34% in 30 to 33-month-old NMJs as compared to NMJs from 4-month-old mice. Taken together, these transmitter release site changes may explain age-induced reductions in neuromuscular neurotransmission in aged mice. These data may also lead to the identification of novel therapeutic targets or potential biomarkers for future research in this area.

Disclosures: N. Li: None. **E. case:** None. **C. Blanchard:** None. **A. Monteleone:** None. **M. Gandhi:** None. **A. Jaie:** None. **Y. Badawi:** None. **S.D. Meriney:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.09/B48

Topic: B.04. Synaptic Transmission

Support: NIH Grant NS091546

Title: The core active zone scaffold BRP selectively promotes neurotransmission and homeostatic plasticity at weak tonic inputs

Authors: *W. DONG[1,2], K. HE[2], C. CHIEN[2], E. TCHITCHKAN[2], S. PERRY[2], R. STARK[2], P. GOEL[2], D. K. DICKMAN[2];
[1]USC, Irvine, CA; [2]USC, Los Angeles, CA

Abstract: The active zone (AZ) scaffold Bruchpilot (BRP), the *Drosophila* homolog of mammalian ELKS, is generally considered a universal and core component of the presynaptic release machinery. BRP is thought to facilitate neurotransmitter release by organizing Cav2 calcium channels at AZs and by participating in synaptic vesicle recruitment. However, whether BRP functions uniformly across all synapse subtypes in *Drosophila* has not been directly tested. The fly larval neuromuscular junction (NMJ), where individual muscle fibers are co-innervated by two distinct motor neuron inputs—the weak, tonic “Ib” with low release probability and the strong, phasic “Is” with high release probability—provides an ideal model to investigate potential functional specialization of BRP. Surprisingly, by selectively silencing either Ib or Is inputs using a genetically encoded botulinum neurotoxin (BoNT-C), we discovered an unexpected dichotomy: BRP is essential for promoting neurotransmitter release at Ib synapses, while it is largely dispensable at Is release sites. Counterintuitively, calcium imaging at terminal boutons revealed that BRP loss does actually reduce calcium influx despite a reduction in the number of Cav2 channels at AZs of both input types. Instead, our preliminary data suggests a compensatory mechanism where an apparent increase in the number of AZs helps maintain overall calcium influx, despite reduced Cav2 channel abundance at individual release sites. These findings indicate that BRP loss leads to a redistribution, rather than depletion, of calcium channels across AZs in both Ib and Is inputs. Notably, we propose that intrinsic differences between Ib and Is synapses, such as the greater distance between vesicles and calcium channels at Ib AZs, render Ib synapses uniquely vulnerable to BRP loss. Finally, we observed a similarly selective requirement for BRP in chronic presynaptic homeostatic potentiation (PHP), where BRP is necessary for the long-term enhancement of neurotransmitter release specifically at the Ib synapse. Our findings challenge the prevailing assumption of a uniform and universal role for the core AZ scaffold protein BRP/ELKS. Instead, these results uncover unexpected input-specific functions, highlighting that even highly conserved AZ components can be differentially utilized to shape synaptic transmission and plasticity in a synapse-specific manner.

Disclosures: W. Dong: None. **K. He:** None. **C. Chien:** None. **E. Tchitchkan:** None. **S. Perry:** None. **R. Stark:** None. **P. Goel:** None. **D.K. Dickman:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.10/B49

Topic: B.04. Synaptic Transmission

Support: DFG SCHO 820/9-1
iBehave

Title: The absence of uniformly oriented molecular populations in central mammalian synapses revealed by two-photon polarization microscopy

Authors: *M. GALKOV[1], M. FUHRMANN[2], D. DIETRICH[1], S. SCHOCH[1];
[1]Univ. of Bonn, Inst. of Cell. Neurosciences II, Bonn, Germany; [2]German Ctr. for Neurodegenerative Dis. (DZNE), Neuroimmunology and Imaging Group, Bonn, Germany

Abstract: The structural organization of the presynaptic active zone (AZ) has been primarily investigated using super-resolution light microscopy and electron microscopy, which revealed high protein density and spatial segregation of AZ material. However, detailed information about the arrangement of individual AZ proteins within the AZ cytomatrix remains limited. In this study, we applied two-photon polarization microscopy (2PPolM) combined with advanced computational analysis to examine whether AZ proteins exhibit preferential alignment at the presynapse using the effect of linear dichroism (LD). To validate our approach, we used chemically fixed cells expressing cytoplasmic eGFP, its membrane-anchored variant or an actin reporter fused to eGFP. 2PPolM not only showed that eGFP molecules associated with the membrane or actin filaments exhibited pronounced spatial alignment, in contrast to the randomly oriented cytoplasmic eGFP, but also provided estimates of their orientation distribution. These results confirmed the high sensitivity and broad dynamic range of our technique making it suitable for detecting even low LD signals. We then applied 2PPolM to cultured primary neurons expressing key AZ members tagged with eGFP via non-structured linkers. A low LD signal similar to that measured for cytoplasmic eGFP was observed for the tested AZ proteins indicating a broad orientation distribution of their molecules. Next, we confirmed that the lack of LD was not due to signal contamination by a diffusible protein fraction or to the geometry of the presynaptic membrane. In conclusion, our findings suggest that AZ proteins in mammalian central synapses do not adopt a regular spatial orientation on the scale of 300-500 nm. However, finer structural regularities may exist but remain undetectable owing to geometric constraints or limitations in resolution.

Disclosures: M. Galkov: None. **M. Fuhrmann:** None. **D. Dietrich:** None. **S. Schoch:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.11/B50

Topic: B.04. Synaptic Transmission

Support: NIH Grant R01 139586
MDA Development Grant 964854

Title: Active zones at mouse neuromuscular junctions have very few presynaptic voltage-gated calcium channels and use nanodomain coupling for calcium-triggered transmitter release

Authors: *T. B. TARR, E. CASE, M. GRAVINA, B. RAMCOOBEER, S. RAO, Y. BADAWI, S. D. MERINEY;
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Abstract: At mouse neuromuscular junctions (NMJs) acetylcholine is released from hundreds of presynaptic active zones (AZs) that each dock two synaptic vesicles between two double rows of about 20 transmembrane proteins. It is hypothesized that voltage-gated calcium channels (VGCCs) make up some unknown number of these transmembrane proteins, and some unknown fraction of these VGCCs open following an action potential to trigger each synaptic vesicle fusion event. The precise makeup of these AZs and the contribution of VGCCs to transmitter release is critical to understanding the strength and reliability, plasticity, and disease pathophysiology at these synapses. We used DNA-PAINT super resolution light microscopy, calcium imaging, and intracellular recordings of transmitter release magnitude to address these unknowns. Using antibodies to piccolo (to identify AZs) and Cav2.1 (P/Q-type) VGCCs we performed single-molecule localization microscopy using the Abbelight SAFe 360 system on an Olympus microscope and identified VGCC localizations that were between the paired piccolo clusters of localizations that defined the AZ. Using this approach, we found that AZs most commonly contained between 1-3 (but rarely 4-6) clusters of localizations that we interpreted as single P/Q-type VGCCs, leading us to conclude that mouse NMJ AZs have very few presynaptic VGCCs (and this number seems to vary between AZs). To address how many of these VGCCs open and contribute calcium ions to each synaptic vesicle fusion event, we took advantage of the known non-linear (4^{th} order) relationship between calcium influx and transmitter release magnitude. In separate experiments we determined the effect of varying concentrations of ω-Agatoxin IVA on calcium influx (using the calcium sensitive dye Calbryte 520) and on the magnitude of transmitter release (using intracellular recordings of endplate potentials). We then plotted these data on a log-log scale and found that the data fell on a line that was close to a linear relationship (and did not display the known 4^{th} order relationship between calcium and transmitter release). This near-linear relationship leads us to conclude that as calcium channels in the AZ are blocked, rather than decrease the concentration of calcium in the AZ, individual AZs are being removed from participation. These data lead us to hypothesize that the calcium ions through predominately a single open VGCC, which is tightly coupled to docked vesicles in the AZ, trigger each vesicle fusion event (nanodomain coupling). Therefore, mouse NMJ AZs contain very few VGCCs and action potentials trigger synaptic vesicle fusion by, on average, only opening only one of these VGCCs.

Disclosures: T.B. Tarr: None. **E. case:** None. **M. Gravina:** None. **B. Ramcoobeer:** None. **S. Rao:** None. **Y. Badawi:** None. **S.D. Meriney:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.12/B51

Topic: B.04. Synaptic Transmission

Support: NSERC
CIHR
CIRC
CFI
ORS
CIAN

Title: Apoe isoforms differentially regulate presynaptic vesicles pool dynamics at hippocampal schaffer collateral-ca1 synapses

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Abstract: Apolipoprotein E (APOE) is a lipid-transport protein with alleles E2, E3, and E4 exert profound effects on Alzheimer's disease (AD) susceptibility and neuronal function. APOE4 increases AD susceptibility and associates with synaptic loss, altered potentiation, impaired glutamate receptor trafficking, and dendritic spine deficits, indicating postsynaptic dysfunction. In contrast, APOE2 preserves synaptic integrity and lowers AD risk, but its presynaptic versus postsynaptic roles are unclear.To elucidate isoform-specific presynaptic mechanisms, we evaluated synaptic efficacy and vesicle-pool dynamics at Schaffer collateral (SC)-CA1 synapses in acute hippocampal slices from male APOE2, APOE3, and APOE4 knock-in mice at young (9-15 weeks) and older (9-10 months) ages. In young adults, input-output curves (10-100 μA SC stimuli) revealed that APOE2 exhibited significantly attenuated field excitatory postsynaptic potential (fEPSP) slopes compared to APOE3 and APOE4 at 90-100 μA. Conversely, in older mice, APOE4 demonstrated enhanced fEPSP slopes at 100 μA relative to APOE3. Paired-pulse ratio (50-200 ms intervals) was comparable across genotypes in young adults, however older APOE4 mice displayed enhanced facilitation at 100 ms interval versus APOE3, reflecting altered presynaptic release probability.To probe the readily releasable pool (RRP), a 100 Hz train of 40 pulses was applied, and cumulative fEPSP depression was analyzed. In young mice, APOE2 exhibited a higher depletion rate constant (K) and shorter time constant (τ) than APOE3, signifying accelerated vesicle turnover. APOE3 displayed more gradual depletion than both APOE2 and APOE4. In older animals, APOE4 showed a lower steady-state plateau, elevated K, and reduced τ compared to APOE3, whereas APOE2 and APOE3 maintained kinetics comparable to young adults' values.Reserve vesicle pool (RVP) dynamics were assessed via a 14

Hz train of 300 pulses. In young adults, APOE2 demonstrated the slowest depletion kinetics (lowest K, highest τ) and the lowest steady-state plateau among all genotypes. APOE3 exhibited the most rapid depletion (highest K, shortest τ), with APOE4 intermediate. In older mice, APOE4 retained the lowest plateau and fastest depletion kinetics, whereas APOE2 and APOE3 were comparable to young group.Collectively, these data indicate that APOE2 knock-in mice couple rapid RRP recruitment with slower RVP replenishment, thereby maintaining synaptic transmission during sustained activity. In contrast, APOE4 impairs presynaptic vesicle-pool dynamics, a dysfunction that likely underlies increased synaptic vulnerability and heightened AD risk in aged individuals.

Disclosures: Z. Ghasemi: None. **K. Patel:** None. **S.A. Connor:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.13/B52

Topic: B.04. Synaptic Transmission

Support: NIH 5 R01 DC018691-05

Title: Enhancingultrasonic vocalizations in murine models via human derived neuronal progenitors

Authors: *N. DE SILVA[1], E. LUO[3], E. N. WAIDMANN[2], E. D. JARVIS[3];
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Abstract: Projections from the mouse primary motor cortex (M1) to brain stem vocal motor neurons are promising targets for modifications to enhance mouse vocal learning abilities. Previous studies have shown that mouse embryonic stem cells (mESCs), when introduced with mouse stromal supporter lines, integrate well into the mouse brain stem, making robust long-range projections from the mouse cortex to the spinal column - visible for as long as 21 days in vivo. Here, we hypothesize that human embryonic stem cells (hESCs) will also integrate into local circuits when introduced to the murine M1, and that this integration will enhance the production and flexible usage of ultrasonic vocalizations (USV) in mice. In this study, we differentiated male and female hESC lines to human derived neural progenitor cells (NPCs) and injected them into the motor cortex of P1/P2 mouse pups. In age-matched NPC-injected and saline-injected groups, we measured the rate of pup isolation USVs on postnatal day P15, and adult social USVs on postnatal days P30 and P45. Immunohistochemistry (IHC) was conducted in parallel to test human NPC integration at days P15, P30 and P45. IHC results showed that human NPCs integrated into the murine cortex at P15. Moreover, our behavior results at P15 showed sex-specific enhancement of USVs in NPC-injected mice relative to saline controls. By days P30-P45, hNPCs were no longer visible - possibly due neuroapoptosis, and USV production

did not differ from that of saline controls in either group. Overall, we will continue to explore the introduction of human ESCs into mouse cortex as a strategy to enhance ultrasonic vocalization behavior in mice and optimize NPC in-vivo lifespan, which will provide insight into both the capacity of the lab mouse as a model for vocal behavior, and the specific properties of human cortical neurons that support our own vocalization behaviors.

Disclosures: N. De Silva: None. **E. Luo:** None. **E.N. Waidmann:** None. **E.D. Jarvis:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.14/B53

Topic: B.04. Synaptic Transmission

Support: NIH NIDA K01 award K01DA050804

Title: Altered Excitatory and Inhibitory Synaptic Parameters in Complex Regional Pain Syndrome

Authors: *N. S. MALAN[1], R. GOPALAKRISHNAN[2], S. BAILLET[3], M. ROY[4];
[1]Ctr. for Neurolog. Restoration, Lerner Res. Institute, Cleveland Clin., Cleveland, OH; [2]Ctr. for Neurolog. Restoration, Cleveland Clin., Cleveland, OH; [3]Montreal Neurolog. Inst., [4]Psychology, McGill Univ., Montreal, QC, Canada

Abstract: Complex Regional Pain Syndrome (CRPS) is a chronic and debilitating condition characterized by persistent pain, sensory abnormalities, and motor dysfunction. Despite evidence of cortical alterations in CRPS, the synaptic and circuit-level mechanisms driving these changes remain poorly understood. Based on the hypothesis that disruptions in cortical excitatory-inhibitory (E-I) dynamics contribute to the pathophysiology of CRPS, we combined magnetoencephalography (MEG) with computational neural mass modeling to investigate synaptic mechanisms underlying altered brain activity in this disorder. Resting-state MEG data from 29 CRPS patients and 29 healthy controls were source reconstructed using minimum norm estimation and parcellated into 362 cortical regions of interest (ROIs) defined by the HCP-MMP1.0 atlas. Power spectral densities were computed for each ROI and using a spectral graph model (SGM) we estimated synaptic parameters, including excitatory and inhibitory gains (g_{ei}, g_{ii}) and time constants (τ_e, τ_i). Group comparisons revealed significantly reduced alpha (8-12 Hz) and beta (13-30 Hz) power in CRPS, particularly across sensorimotor, parietal, and prefrontal cortices. Neural mass modeling revealed that CRPS patients showed increased g_{ei} and τ_e, along with reduced g_{ii} and τ_i, indicating an imbalance favoring cortical excitation over inhibition. This pattern reflects heightened cortical excitability and diminished inhibitory control, potentially contributing to abnormal sensory and motor processing in CRPS. Regionally, increased g_{ei} and τ_e were observed in the precentral gyrus, ventral visual cortex, and right parietal regions, while reduced g_{ii} and τ_i were noted in frontal operculum, middle frontal gyrus, primary visual cortex,

and posterior parietal areas. The entorhinal cortex showed combined increases in τ_e and decreases in τ_i, suggesting disrupted synaptic balance in limbic circuits. Our preliminary findings suggest that CRPS is associated with widespread shifts in synaptic-level E-I dynamics, potentially contributing to aberrant sensory and affective processing. These results offer novel insight into the neurophysiological underpinnings of CRPS and may guide future neuromodulatory interventions aimed at restoring E-I balance. This project is funded through National Institute of Health (NIH) NIDA K01 award K01DA050804.

Disclosures: N.S. Malan: None. **R. Gopalakrishnan:** None. **S. Baillet:** None. **M. Roy:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

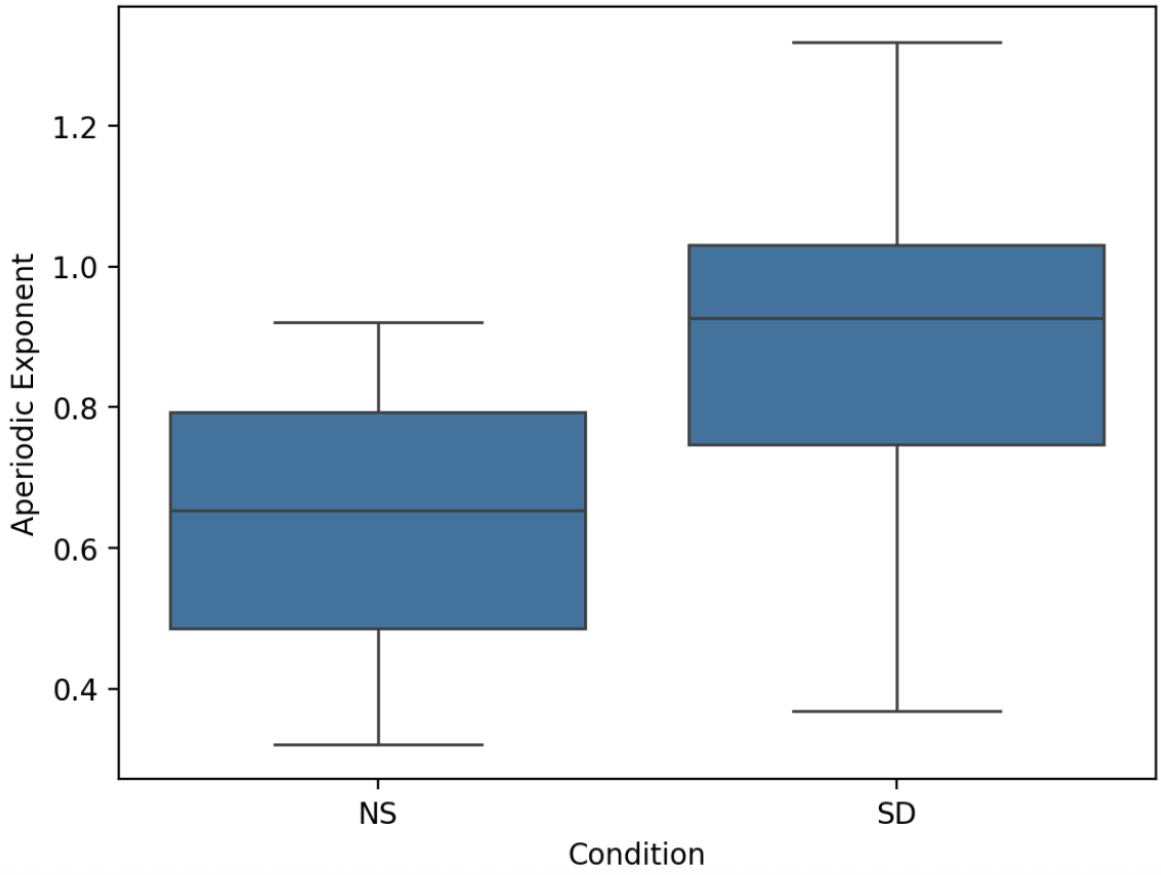
Program #/Poster #: PSTR105.15/B54

Topic: B.04. Synaptic Transmission

Title: Neural Signatures of Sleep Deprivation in Aperiodic EEG Activity

Authors: *E. SMITH[1], E. KAPLAN[2], B. VOYTEK[3];
[1]UC San Diego, San Diego, CA; [2]Cognitive Sci., UCSD, San Diego, CA; [3]Cognitive Sci., Univ. Of California, San Diego, La Jolla, CA

Abstract: EEG signals are composed of both periodic (oscillatory) and aperiodic (non-oscillatory) features, each reflecting different aspects of our cognition. Periodic activity shows a linkage to important cognitive functions such as memory consolidation, neural plasticity, and attention; while aperiodic activity reflects broader aspects of neural excitation and inhibition. Investigating the rate of aperiodic activity in sleep may elucidate its impact on neural signal composition and potential biomarkers associated with cognitive performance. In the present investigation, we analyze EEG recordings (N=71) following normal sleep (NS) and sleep deprivation (SD) conditions to investigate differences in aperiodic activity. Using time-resolved spectral parameterization, we find significant differences in aperiodic activity across the two conditions. Specifically, we identified higher rates of aperiodic activity in sleep deprivation conditions ($p=0.048$). These findings suggest that sleep deprivation may cause a shift in underlying neural balance of excitation and inhibition.



Disclosures: E. Smith: None. **E. Kaplan:** None. **B. Voytek:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.16/B55

Topic: B.04. Synaptic Transmission

Title: The effects of volatile general anesthetics on vesicular fusion in a lipid-only model membrane system: Implications of the Meyer-Overton Correlation

Authors: *R. J. POLAND[1], A. L. WHITEHEAD[2], T. M. BLOCKER[2], J. A. CASABLANCA[1], D. J. WOODBURY[2,1];
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Abstract: General anesthesia revolutionized medicine, yet its lipid-associated mechanisms remain poorly understood. About 125 years ago, Meyer (1899) and Overton (1901) demonstrated that anesthetic potency correlates with lipid solubility—now known as the Meyer-Overton

Correlation—implying a key role for the lipid membrane in mediating anesthetic action. One such lipid-based process is cellular exocytosis. Using a protein-free lipid membrane model, we measure how general anesthetics affect fusion of liposomes to the membrane. Previously, we found that short-chain alcohols modulate liposome fusion, with extracellular ethanol reducing fusion rates by 29% at 0.08% w/v (Paxman et al., 2017), the U.S. legal blood alcohol limit. This could be one factor in the depressant effects of drinking alcohol. Consequently, we hypothesize that volatile anesthetics alter vesicular fusion rates through a similar mechanism. To test this, we selected three agents of varying potencies—ethanol, diethyl ether, and chloroform—based on the Meyer-Overton Correlation. Clinical doses of ethanol, ether, and chloroform are delivered as vapor, and their effects on fusion rates are statistically analyzed. Experimental agent delivery is verified via gas chromatography. Ethanol vapor experiments (n=3) show inhibitory effects on fusion, consistent with our prior liquid-based alcohol findings. Ether vapor experiments (n=3) demonstrate similar inhibitory effects at a lower dosage, aligning with its higher lipid solubility. Based on this trend, we predict chloroform (with increased lipid solubility) will also inhibit vesicular fusion rates at an even lower dose. This research demonstrates that general anesthetics can modulate vesicle fusion to lipid membranes and offers insight into possible additional mechanisms whereby anesthetics may modulate neurotransmitter release from neurons. These findings may inform anesthetic protocol refinement, enhance procedural safety, and contribute to advancement of neuroscientific knowledge and medical care worldwide.
REFERENCE: Paxman, J. R., Hunt, B., Hallan, D., Zarbock, S. R., & Woodbury, D. J. (2017). Drunken membranes: Short-chain alcohols alter fusion of liposomes to planar lipid bilayers. *Biophysical Journal*, *112*(1), 121-132. https://doi.org/10.1016/j.bpj.2016.11.3205

Disclosures: R.J. Poland: None. **A.L. Whitehead:** None. **T.M. Blocker:** None. **J.A. Casablanca:** None. **D.J. Woodbury:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.17/B56

Topic: B.04. Synaptic Transmission

Support: : FONDECYT 1241173
ANID-MILENIO NCN2023_032
CIDI nº1 CENFI-UV, to MF

Title: Adolescent NMDAR Hypofunction Disrupts mPFC GABAergic Transmission and Synaptic Plasticity.

Authors: F. GUIFFA[1], S. VAN BUUREN[1], A. P. ESCOBAR[2], R. SOTOMAYOR-ZÁRATE[3], K. MORALES-WEIL[4], M. FUENZALIDA[5];
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Valparaiso, Chile; [4]Facultad de Ciencias de la Vida, Univ. Viña del Mar, Viña del mar, Chile; [5]Univ. De Valparaiso, Valparaiso, Chile

Abstract: Background: The medial prefrontal cortex (mPFC) is crucial for cognitive functions, including attention, decision-making, and working memory. During adolescence, GABAergic interneurons play a vital role in mPFC maturation. Disruptions in interneuron development during this period have been implicated in neuropsychiatric disorders, but their long-term impact on adult synaptic plasticity remains unclear.
Methods: We used subanesthetic doses of ketamine to investigate the effects of adolescent NMDAR hypofunction on adult mPFC synaptic plasticity. Electrophysiological and pharmacological techniques were employed to measure spontaneous and evoked inhibitory postsynaptic currents (IPSCs) and spike timing-dependent plasticity (STDP).
Results: In layer II/III pyramidal neurons of adult mPFC slices from ketamine-treated (Ket) mice, we observed: -A reduction in the frequency of spontaneous and miniature inhibitory postsynaptic currents (sIPSCs and mIPSCs) in Ket-treated mice. - An increased paired-pulse ratio of evoked IPSCs in Ket-treated slices, indicating altered GABA release. - Normal t-LTP induction, but reversed t-LTD (potentiation instead of depression) in Ket treated mice.
Conclusions: Adolescent NMDAR hypofunction impairs GABAergic interneuron maturation and function, reducing GABA release and disrupting the excitation/inhibition balance in the adult mPFC. This alteration reverses the temporal dependence of STDP-LTD, significantly impacting synaptic plasticity. These findings provide insight into the long-term consequences of adolescent NMDAR dysfunction on mPFC circuit development and may contribute to our understanding of neuropsychiatric disorders.

Disclosures: F. Guiffa: None. **S. van Buuren:** None. **A.P. Escobar:** None. **R. Sotomayor-Zárate:** None. **K. Morales-Weil:** None. **M. Fuenzalida:** None.

Poster

PSTR105: Presynaptic Mechanisms, Organization, and Structure II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.18/B57

Topic: B.04. Synaptic Transmission

Support: NIH Grant R01 NS128713

Title: Thalamic inputs to electrically coupled neurons

Authors: *M. VAUGHN[1], J. S. HAAS[2];
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Abstract: The thalamic reticular nucleus (TRN) inhibits thalamocortical relay and is a key regulator of sensory attention as well as sleep and wake states. The TRN communicates within itself primarily through a dense concentration of electrical synapses that form small, selective networks. The organizing principles behind network formation in the TRN are largely unknown,

and this gap constrains our understanding of the contribution of coupled networks to TRN and thalamocortical function. Our previous work using genetically labeled neurons revealed that electrical synapses join TRN neurons that are driven by same order of thalamic nuclei as well as neurons that are separately driven by first-order thalamus and higher-order thalamus. However, these findings are supported by indirect evidence and need to be directly functionally validated. Here, we investigated the patterns and sources of thalamic driver inputs to electrically coupled TRN neurons. We injected an AAV carrying a Cre-dependent soma-targeted opsin into the ventricles of P0 Vglut2-Cre mouse pups to induce opsin expression in most excitatory neurons. We prepared slices from P11-P15 animals and patched electrically coupled neurons from somatosensory TRN. We focally photostimualted individual thalamic nuclei using a digital mirror device. For thalamic nuclei that evoked EPSCs in the coupled neurons, we systematically photostimulated smaller regions within that nucleus to more precisely identify the source of the inputs to the coupled TRN neurons. With this method, we characterized the degree of convergence and divergence of thalamic inputs to coupled neurons. Our results allow us to reject the null hypothesis that coupled TRN neurons receive the same input. We show that input to coupled TRN neurons have a substantial degree of independence that indicates thalamic divergence, suggesting that electrical synapses in TRN are positioned to modulate spike timing of TRN neurons, and the inhibitory feedback provided to thalamic relay neurons, based on comparisons of distinct activity in thalamus.

Disclosures: M. Vaughn: None. **J.S. Haas:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.01/B58

Topic: B.05. Synaptic Plasticity

Support: JSPS KAKENHI 20H05916
JSPS KAKENHI 24K09541
JSPS KAKENHI 24K02213
The Naito Foundation

Title: Reopening the critical period of experience-dependent plasticity in the dorsal lateral geniculate nucleus.

Authors: *M. NARUSHIMA[1,2], C. JIN[3,2], J. NABEKURA[1];
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Abstract: Neural circuits in the sensory system undergo changes in synaptic connectivity patterns in response to individual experiences during a specific developmental window known as the critical period (CP). Understanding the mechanisms that regulate the CP, as well as developing methods to restore plasticity after its closure, not only contributes to our fundamental knowledge of neural circuit development but also holds clinical potential for enhancing recovery from trauma or rehabilitation after brain injury. In the mouse visual system, the retinogeniculate (RG) synapses in the dorsal lateral geniculate nucleus (dLGN) are a powerful model for studying experience-dependent circuit plasticity and critical period mechanisms during development. Disturbance in visual experience from postnatal day 20 (P20) for 1 week alters the number and the strength of retinal inputs projecting to a single thalamocortical (TC) neuron. Thus, this developmental period is defined as a CP for the experience-dependent plasticity in the RG synapses. In this study, we explored the effects of astrocyte manipulation on the restoration of neural circuit plasticity after the closure of the critical period, because they have been suggested to be involved in synaptic development and plasticity. A chemogenetic tool termed DREADDs (designer receptors exclusively activated by designer drugs), which can activate Gq protein (hM3D) in the presence of artificial ligand, CNO, was used to enhance astrocytic activity. After expression of hM3D in the dLGN astrocyte by AAV, mice were treated with CNO during one week of visual deprivation after the closure of CP. We investigated remodeling of the RG synapses with in vitro electrophysiology. We found that the stimulation of astrocytes caused an increase in the number of retinal inputs projecting to a single TC neuron in the dark-reared mice but not in those with light rearing, nor in mice that experienced dark rearing without astrocytic stimulation. RNA sequence of dLGN astrocyte was also performed to explore the underlying mechanisms of astrocyte-induced RG synaptic plasticity. These results indicate the ability of astrocytes to promote experience-dependent remodeling of RG synapses after the termination of CP.

Disclosures: M. Narushima: None. **C. jin:** None. **J. Nabekura:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.02/B59

Topic: B.05. Synaptic Plasticity

Title: Neuroplasticity resolution at the molecular and structural level in rodent brain

Authors: *T. R. ROSENSTOCK[1], P. PATNI[1], L. JAGGER[1], D. LEITE[1], P. GYASI-ANTWI[1], R. CANAVATE DEL PINO[1], G. ANSA[2], G. LINCEVICIUS[1], W. PIJACKA[1], N. MODY[1], I. JONES[1], A. CARTER[1], T. PHILLIPS[1], S. THOMSON[1], S. P. VICKERS[1], N. R. MIRZA[1]; [1]Sygnature Discovery, Nottingham, United Kingdom; [2]Dark Blue Therapeut., Oxford, United Kingdom

Abstract: Dysregulated neuroplasticity has been implicated in various neuropsychiatric and neurodegenerative conditions. Pharmacological interventions, such as serotonergic agents and NMDA receptor antagonists, modulate neuroplasticity. Notably, the basis for Esketamine's efficacy in depression and potential of psychedelics for treating affective disorders is proposed to be due to their propensity to enhance neuroplasticity. Neuroplasticity refers to the brain's ability to reorganize its structure and function in response to internal or external stimuli. At the molecular level, this involves gene expression and synaptic protein dynamics. Structurally, it includes dendritic branching and spine morphology, ultimately influencing behaviour and other phenotypes. In the present work, we used a multi-modal approach to assess molecular and structural markers of neuroplasticity in ex vivo brain tissue from rodent models. Tissues were snap-frozen for mRNA extraction or PFA 4% fixed for histology. Methods included RT-PCR, immunostaining of pre- and post-synaptic proteins, and [^{3}H]-UCB-J binding to SV2A. Neuronal outgrowth and spine morphology (mushroom, filopodia, long-thin) were visualized via Golgi-Cox staining and diolistic dye labelling. Imaging was quantified using IMARIS software and AI-supported tools. Statistical analysis and data visualization were performed in GraphPad Prism. For gene expression analysis, we detected and quantified BDNF in rat hippocampal samples (ΔCT 5.6±0.08, mean ± SEM). Synaptic protein expression was assessed through immunostaining and quantitative analysis using Imaris software. In rat hippocampal brain slices, Bassoon (presynaptic marker) puncta counts were 2591±841 and Homer-1 (postsynaptic marker) puncta counts were 2610±839 (mean ± SEM, n=3). Neuronal outgrowth and dendritic spine morphology were assessed by measuring total neurite length and classifying spines into stubby, mushroom, filopodia, and long-thin types. In rat cortex slices, the total soma count was 198.1 ± 15.8, with a normalized average dendritic length of 184.7 ± 16.3 mm (mean ± SEM). In a representative image, we observed 25 stubby, 1 mushroom, 3 long-thin, and 9 filopodia spines. By combining molecular and structural endpoints we present here an integrated and multiplexed platform for quantitative assessment of neuroplasticity. This platform can be utilised to support drug discovery projects and provide translational insights on compounds that modulate neuroplasticity.

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Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.03/B60

Topic: B.05. Synaptic Plasticity

Support: VA Merit Grant 1I01BX005367

Title: Breaking the Cycle: How Stress and Alcohol Hijack Fear Extinction Memory Through Infralimbic Cortex Engram Dysfunction

Authors: *L. J. WILLS[1,2], J. T. GASS[1,2];
[1]Quillen Col. of Med., Johnson City, TN; [2]James H. Quillen VAMC, Mountain Home, TN

Abstract: Background: Understanding extinction memories represents a critical therapeutic target for PTSD and alcohol use disorder comorbidity, yet the neural mechanisms underlying extinction recall failure remain unclear. Our lab has demonstrated that combined restraint stress and chronic intermittent ethanol (RS+CIE) exposure impairs extinction recall, with these animals exhibiting increased freezing behavior correlated with decreased infralimbic cortex activity (GCaMP6) compared to controls. This finding suggests that specific neural ensembles - memory engrams - may be selectively disrupted by combined stress and alcohol exposure. **Methods:** Adult Wistar rats underwent stereotaxic surgery for unilateral IfL injection of AAV-Fos::CreER^{T2} and AAV-Ef1a::DIO-GCaMP6f viruses, with fiber-optic cannula implantation. Following RS+CIE or control treatment, rats underwent contextual fear conditioning in Context A, then extinction training in Context B using the ABA design. Extinction engrams were tagged using 4-hydroxytamoxifen injection (10 mg/kg, i.p.) administered 2h post-final extinction session during peak cFos expression. After a 30-day expression period allowing for complete viral integration, remote fear extinction recall was assessed in Context B using simultaneous fiber photometry recordings of tagged IfL extinction engrams and behavioral analysis. **Results:** Our findings reveal that RS+CIE animals exhibit significantly reduced IfL extinction engram activity during remote recall compared to controls, directly corresponding with increased fear behavior and extinction recall failure. Real-time fiber photometry data showed ensemble activity patterns in tagged extinction engrams, with integrated TTL signals precisely time-locked to tone presentations. Raw fluorescence converted to ΔF/F demonstrates significant differences in GCaMP6 signals between experimental groups, revealing the cellular basis of extinction memory dysfunction. **Conclusion:** This innovative study provides the first direct evidence of how stress-alcohol interactions disrupt specific memory engrams, elucidating critical neural mechanisms underlying extinction failure in PTSD/AUD comorbidity and providing promising therapeutic targets for intervention.

Disclosures: L.J. Wills: None. **J.T. Gass:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.04/C1

Topic: B.05. Synaptic Plasticity

Title: High-content imaging platforms for assessing neuroplasticity in early-stage drug discovery

Authors: P. REGAN[1], E. GRAVEL[3], C. DESAULNIERS-LANGEVIN[3], ***Y. FERNANDEZ**[3], Y. MAMANE[3], T. R. ROSENSTOCK[1], T. PHILLIPS[1], S. THOMSON[1], N. MIRZA[2]; [2]Neurosci., [1]Sygnature Discovery, Nottingham, United Kingdom; [3]Sygnature Discovery North America, Montreal, QC, Canada

Abstract: Cellular and structural neuroplasticity, involving dendritic branching, neurite outgrowth, and synaptic reorganization, is central to cognitive function and likely therapeutic outcomes of some drugs. Marketed drugs like Esketamine and psychedelics in development are thought to exert clinical effects partly through neuroplastic remodelling. However, identification of novel neuroplasticity-enhancing compounds is constrained by the limited availability of scalable, predictive in vitro models. To address this, we developed automated high-content imaging assays using rat PC12 cells, human SH-SY5Y neuroblastoma cells, and primary rat cortical neurons to quantify neurite outgrowth as a proxy for structural plasticity. PC12 and SH-SY5Y cells were seeded in Cultrex-coated 96-well plates and differentiated using various neurotrophic factors. Neurite length and branching were quantified from βIII-tubulin-stained images using CellProfiler or Celleste, with statistical analysis performed in GraphPad Prism. Nerve Growth Factor (NGF) promoted neurite outgrowth in PC12 cells in a concentration-dependent manner (EC_{50} = 4.7 ± 1.0 ng/ml, N=11) and high/low concentrations of NGF were routinely used as assay plate controls, demonstrating a reproducible assay window (range 0.8 - 3) against which to compare putative neuroplasticity modulators. In SH-SY5Y cells (differentiated with RA and BDNF), combination of BDNF + the ROCK inhibitor Y27632 consistently increased neurite length compared to BDNF + control (neurite length change of 131 ± 14%, intra-plate CV < 15%, n > 16). Similarly, primary cortical neurons showed a consistent BDNF-induced enhancement in neurite outgrowth compared to vehicle-treated controls ($p < 0.0001$, $t = 6.3$, $df = 13$). Neurite outgrowth in PC12 and SH-SY5Y cells was also evaluated following treatment with compounds with distinct mechanisms of action (MoA). Similar to SH-SY5Y cells Y27632 (10 μM) increased neurite outgrowth 73 ± 22% in PC12 cells (n=4, N=4-6). Comparable effect sizes were observed with other test agents (ifenprodil, resveratrol, human EGF, and D159687) reproducibly, and consistent with their MoA. In conclusion, this platform provides a robust, flexible, and scalable tool for early-stage screening of neuroplasticity-modulating compounds, with clear relevance for neuropsychiatric and neurodegenerative drug discovery.

Disclosures: P. Regan: A. Employment/Salary (full or part-time): Sygnature Discovery. **E. Gravel:** A. Employment/Salary (full or part-time): Sygnature Discovery North America. **C. Desaulniers-Langevin:** A. Employment/Salary (full or part-time): Sygnature Discovery North America. **Y. Fernandez:** A. Employment/Salary (full or part-time): Sygnature Discovery North America. **Y. mamane:** A. Employment/Salary (full or part-time): Sygnature Discovery North America. **T.R. Rosenstock:** A. Employment/Salary (full or part-time): Sygnature Discovery. **T. Phillips:** A. Employment/Salary (full or part-time): Sygnature Discovery. **S. thomson:** A. Employment/Salary (full or part-time): Sygnature Discovery. **N. Mirza:** A. Employment/Salary (full or part-time): Sygnature Discovery.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.05/C2

Topic: B.05. Synaptic Plasticity

Title: Regional and developmental characterization of a LAMP5+ neurogliaform cell enhancer AAV across species

Authors: *N. MCLEAN[1], A. VLACHOS[2], A. CACCAVANO[3], L. T. HEWITT[4], B. AVERBECK[5], K. A. PELKEY[6], G. J. FISHELL[8], C. J. MCBAIN[7];
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Abstract: Subpopulations of cortical GABAergic interneurons (INs) are diverse, exhibiting distinct anatomical, molecular, and functional characteristics. While numerically sparse, these minority populations critically balance excitation to coordinate network activity. Lysosome-associated membrane protein-5 (LAMP5)- expressing neurogliaform cells (NGFCs) represent one cardinal class of INs found throughout the hippocampus, neocortex, and striatum. NGFCs uniquely provide slow volume transmission across their dense axonal arborizations at synaptic and extrasynaptic sites through activation of both inotropic $GABA_A$ and metabotropic $GABA_B$ receptors. These unusual transmission characteristics combined with their extensive electrical/chemical interconnectivity and propensity to barrage fire optimally position NGFCs to coordinate inhibitory network influence over circuit activity broadly across space and time. Indeed, NGFCs have been implicated in slow network rhythms such as up/down state transitions and theta oscillations as well as providing slow GABAergic trophic support for immature neuron circuit integration following adult neurogenesis. Efficient targeting of NGFCs is confounded by the need for time-consuming intersectional genetics that remain limited to mice. Recombinant adeno-associated viruses (rAAVs) with small DNA regulatory elements identified with ATAC-Seq (Enhancer-AAVs) provide a novel method for cell-type specific targeting, allowing the identification and manipulation of neurons across species. However, enhancer-AAV specificity for intended target cell populations varies across brain regions, delivery method, and development. We compared transgene expression driven by the novel LAMP5 IN enhancer BiLAMP5e3 in mouse hippocampus, cortex, and striatum delivered by intracranial stereotax injection (IC, focused) or retro-orbitally (RO, systemic) to adult mice and by intracerebroventricular injection (ICV, systemic) perinatally. Additionally, AAV-PHP.eB-BiLAMP5e3-dTom was IC delivered to the hippocampus of non-human primates (NHPs) for cross-species comparisons. We'll report on the specificity of AAV-PHP.eB-BiLAMP5e3-dTom for NGFCs across regions, species, and development based on combined immunohistochemical, morphological, and electrophysiological profiling of dTom expressing cells. Our findings reveal best practices to maintain AAV-PHP.eB-BiLAMP5e3-dTom specificity for NGFCs and highlight region and species divergence of NGFC electrical properties.

Disclosures: N. McLean: None. **A. Vlachos:** None. **A. Caccavano:** None. **L.T. Hewitt:** None. **B. Averbeck:** None. **K.A. Pelkey:** None. **G.J. Fishell:** None. **C.J. McBain:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.06/C3

Topic: B.05. Synaptic Plasticity

Support: IBS-R001-D3

Title: Npas4-expressing CA3 neurons dampen synaptic input to cFos-activated CA1 neurons during contextual fear memory formation

Authors: *B. TIMALSINA[1], J. KIM[1,2], B.-K. KAANG[1];
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[2]Interdisciplinary Program in Neurosci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Memory formation involves the coordinated activity of immediate early genes (IEGs), yet how different IEG-expressing neuronal populations interact during learning remains unclear. In this study, we investigated the correlates between Npas4 and c-Fos expression in the dorsal CA3 and CA1 regions in mice following contextual fear conditioning (CFC). Immunohistochemical analysis in the CA3 region revealed that a Npas4 - expressing neurons in the CA3 region also expressed c-Fos at a rate significantly higher than expected by chance, suggesting the existence of subpopulation co-expressing Npas4 and c-Fos in the CA3 region. To explore whether these molecularly defined populations exhibit differences in the level of synapse, we applied dual-eGRASP, a technique for visualizing synaptic connections. Specifically, we assessed synaptic density between CA3 Npas4+ neurons and CA1 c-Fos+ neurons following CFC. While previous studies reported enhanced synaptic connectivity between CA3 c-Fos+ and CA1 c-Fos+ neurons after learning, our results indicate that the synaptic density between CA3 Npas4+ neurons and CA1 c-Fos+ neurons rather decreases compared to the density of CA3 Npas4+ to CA1 c-Fos- synapses. These findings suggest that *Npas4*-expressing subpopulation of CA3 c-Fos+ neurons may play a distinct regulatory role in shaping hippocampal circuit dynamics during contextual memory formation. This work provides new insight into how different IEG-labeled neuronal populations contribute to learning-related synaptic remodeling.

Disclosures: B. Timalsina: None. **J. Kim:** None. **B. Kaang:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.07/C4

Topic: B.05. Synaptic Plasticity

Support: Italian Ministry of Health Grant GR-2021-12372496

Title: Reversible pain-associated perineuronal nets alterations in response to analgesic drugs

Authors: *A. CECCHERELLI[1], S. NOTARTOMASO[2], R. GINERETE[1,2], S. CASTALDI[1], T. IMBRIGLIO[2], G. BATTAGLIA[1,2], V. BRUNO[1,2], F. NICOLETTI[1,2], G. MASCIO[2];
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Abstract: Chronic pain is sustained by a maladaptive form of neuronal plasticity occurring in all stations of the pain neuraxis, including cortical regions of the pain matrix. Perineuronal nets (PNNs), which are condensed structures of the extracellular matrix surrounding GABAergic interneurons in the forebrain, contribute to mechanisms of maladaptive neuronal plasticity underlying chronic pain. Previously, we have found that chronic inflammatory and neuropathic pain were associated with an increased density of PNNs labelled by the lectin *Wisteria Floribunda Agglutinin* (WFA) in the somatosensory cortex (SSC), medial prefrontal cortex (mPFC), and reticular thalamic nuclei (RTNs), and enzymatic degradation of PNNs in these regions caused analgesia (Mascio et al., J. Neurosci., 2022; Mascio et al., Pain, 2025). These findings suggest that an increased formation and/or reduced degradation of PNNs is a key determinant of nociceptive sensitization in chronic pain and changes in PNN density represent a general phenomenon associated with the development of chronic pain. Here, we have evaluated whether different classes of analgesic drugs with established efficacy in models of neuropathic pain have a different impact on PNN density and composition in the selected regions of the pain matrix. We found that pain-associated PNN increased density and proteoglycan component alterations in the contralateral SSC, mPFC, RTN, and insular cortex of mice developing neuropathic pain are reverted in response to different classes of analgesic drugs administered in a therapeutic regimen, i.e., after PNNs were formed. These drugs included the conventional analgesics, gabapentin (100 mg/kg) and amitryptiline (10 mg/kg), the epigenetic drug, L-acetyl-carnitine (100 mg/kg), and the mGlu5 receptors antagonist 3-((2-Methyl-1,3-thiazol-4-yl)ethynyl)pyridine (MTEP, 10 mg/kg). mGlu5 antagonists were consistently found to relieve neuropathic pain acting in the same regions where PNN density increases in response to pain. These findings support the cause-to-effect relationship between PNNs and nociceptive sensitization underlying chronic pain.

Disclosures: A. Ceccherelli: None. **S. Notartomaso:** None. **R. ginerete:** None. **S. Castaldi:** None. **T. Imbriglio:** None. **G. Battaglia:** None. **V. Bruno:** None. **F. Nicoletti:** None. **G. Mascio:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.08/C5

Topic: B.05. Synaptic Plasticity

Support: HL166204
AG086136

Title: Motor Neuron Dendritic & Mitochondrial Degenerations in Aging

Authors: *M. J. FOGARTY[1], D. DASGUPTA[2], G. C. SIECK[3];
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Abstract: In the elderly, age-associated muscle weakness and atrophy (sarcopenia) is prevalent in both limb and respiratory muscles. In the tongue and aerodigestive muscles, dyscoordination and sarcopenia predisposes elderly individuals to dysphagia, dysphonia and a greater risk for aspiration pneumonias and obstructive sleep apnea. In humans and in the Fischer 344 rat model of aging, motor neuron (MN) death occurs in old age, and the selective vulnerability of fast-fatigable motor units to loss is consistent with behavioral deficits in airway defense (e.g., cough). However, whether the timing of MN loss is gradual across the lifespan or precipitous from late-middle-age is unknown. Recently, the concept of an age -related increase of systemic inflammatory cytokines has been implicated in the development of sarcopenia, although the mechanisms by which this occurs remain obscure. In other cell types, inflammation triggers an unfolded protein response and mitochondrial fragmentation - processes implicated in neuronal death and neurodegeneration. In this study of female and male Fischer 344 rats at 6- , 18- and 24-months-old, we evaluated serum inflammatory cytokines (TNFα, IL1β & IL6) via ELISA, medullary unfolded protein response (pIRE1a^{S724} & CDK5) and mitochondrial fragmentation (pDRP1^{S616}) via Western blot, hypoglossal MN mitochondrial volume density and mitochondrial fragmentation via serial blockface electron microscopy (SBFEM), hypoglossal MN survival via Nissl histology and stereological counting. Neurodegeneration was assessed by golgi-cox impregnation of hypoglossal and nucleus ambiguus MNs. Here, we show that a systemic inflammation-induced unfolded protein response in the medulla and hypoglossal MNs mitochondrial fragmentation is present at 18-months-old. This mitochondrial fragmentation is consistent with increased medullary expression of pDRP1^{S616}. At this age, we observed dendritic spine changes characteristic of neurodegeneration, but no evidence of hypoglossal MN death. At 24-months old, hypoglossal MN mitochondrial deficits remained readily observable using SBFEM, with hypoglossal MN death present at this age. Overall, we conclude that denervation-related sarcopenia is precipitous from late-middle-age to old age in Fischer 344 rats. This MN death is triggered (or at least preceded), by an unfolded protein response, mitochondrial fragmentation and neurodegeneration. Interventions ameliorating inflammation, the unfolded protein response and/or mitochondrial breakdown may preserve MNs and prevent or reduce age-associated sarcopenia. This work was supported by NIH grants: HL166204, AG086136 & AG44615

Disclosures: M.J. Fogarty: None. **D. Dasgupta:** None. **G.C. Sieck:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.09/C6

Topic: B.05. Synaptic Plasticity

Support: Ovarian Cancer Institute
McCallum Family Foundation
Deborah Nash Endowment

Title: Neuronal reprogramming by ovarian cancer

Authors: *N. HOUSLEY, Z. ARSHAD, **J. ZHANG**;
Georgia Inst. of Technol., Atlanta, GA

Abstract: From growth, homeostasis, and regeneration, the nervous system is responsible for orchestrating and maintaining complex biologic processes. It is therefore no surprise that the nervous system is emerging as a critical regulator of cancer. Recent data demonstrates that brain cancers depend on paracrine and bioelectrical interactions with local neurons. These data highlight an underappreciated aspect of cancer biology and emphasize that neuron-malignant cell interactions are pivotal. Yet, whether peripheral cancer cell types possess the ability to similarly interact with their local and systemic neural networks and the consequences of such potential interactions remains understudied. Using ovarian cancer, we study the reciprocal interactions among peripheral tumors and the distributed peripheral nervous system networks by mapping the structural and molecular consequences of tumorigenesis. To molecularly characterize ovarian- and ovarian cancer-innervating neurons, we employ retrograde tracing of axons from tissues to their spatially distributed ganglia followed by transcriptomic analysis. By characterizing sympathetic and sensory neurons that innervate healthy and tumor bearing ovaries, we reveal unique molecular signatures and their spatial distribution driven by ovarian tumorigenesis. We further characterize the structural changes in local neuronal circuitry. Collectively, our multi-dimensional data reveal new insights into how malignancy structurally and molecularly reprograms the distributed network of ovarian innervating neurons.

Disclosures: N. Housley: None. **Z. Arshad:** None. **J. Zhang:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.10/C7

Topic: B.05. Synaptic Plasticity

Title: Mapping the sonication parameter space to characterise neuromodulation by ultrasound stimulation in the hippocampus

Authors: *R. CUTHELL, W. W. WATTS, D. J. WHITCOMB;
Univ. of Bristol, Bristol, United Kingdom

Abstract: Transcranial focused ultrasound (tFUS) is a promising tool for non-invasive neuromodulation, targeting neural activity in a highly focal manner. However, the influence of acoustic parameters on neural excitability and circuit-level function remains poorly defined. We investigated how variations in duty cycle (DC) and spatial peak pulse average intensity (ISPPA) affect network function in acute hippocampal slices prepared from male and female Han Wistar rats aged P21-28 (n=15) following brief ultrasound stimulation. A pulse repetition frequency (PRF) of 5Hz and sonication duration of 40 seconds were kept constant across all conditions, based on previous work demonstrating reliable modulation of excitability using this protocol. By fixing PRF and duration, we aimed to isolate the specific contributions of DC and ISPPA to post-sonication neuromodulation. We tested nine ultrasound conditions combining three DCs (10, 30, and 50%) and three intensities (0.5, 1, and 2 W/cm^2), these parameters were selected to remain within established safety thresholds whilst providing a range of profiles. For each condition a sham stimulation was included to control for non-acoustic effects. Changes in neuronal function were assessed using extracellular field recording electrophysiology to evaluate input-output (I/O) responses to increasing stimulation strength (0-20V in 1V increments). Field excitatory postsynaptic potentials (fEPSPs) and presynaptic fibre volleys (FVs) recorded from the CA1 stratum radiatum with increasing stimulation strength of the Schaffer collaterals were measured. Preliminary results indicate that both DC and ISPPA influence network function post-sonication. Notably this increase in neuromodulation is more pronounced in the fEPSP slope, suggestive of enhanced synaptic transmission. It is also indicated that ISPPA may play a more prominent role in affecting neural function where FV amplitude appears to increase within each DC. By identifying the relationship between DC and ISPPA under otherwise matched conditions, it informs the selection of ultrasound paradigms for future therapeutic applications. These findings highlight the need for systematic parameter mapping to move towards becoming more consistent and scalable, which will be important to reliably interpret outcomes of tFUS neuromodulation.

Disclosures: R. Cuthell: None. **W.W. Watts:** None. **D.J. Whitcomb:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.11/C8

Topic: B.05. Synaptic Plasticity

Support: A Roadmap from Neurogenetics to Neurobiology (024.004.012), the ERC under the European Union's Horizon 2020 research innovation program (grant agreement 804089; ReCoDE)
NWO VIDI grant 203.102

Title: Stress attenuates the excitability of accumbal neurons projecting to the lateral hypothalamus: potential consequences for binge eating

Authors: *D. WENJIE[1,2], R. A. ADAN[1], F. MEYE[1,2];
[1]UMC Utrecht, Utrecht, Netherlands; [2]UMCU, Utrecht, Netherlands

Abstract: Feeding can be largely perturbed by external experiences, like stress which reshapes food choices to diets that are high in sugar and fat, independent of metabolic needs. The neurobiology underlying this effect is not clear. Nucleus accumbens (NAc) projections to the lateral hypothalamus (LHA) have been shown to authorize feeding when inhibited, but whether stress causes plasticity in this pathway that affects feeding remains elusive. We hypothesized that, in mice, a stressor causing food overconsumption would reduce excitability in the NAc-LHA pathway. We observed, using ex vivo patch-clamp electrophysiology, that stress downregulates the excitability of the NAc-LHA pathway. We also observed that stress enhanced GABAB receptor signaling onto these neurons, as a possible expression mechanism. We also demonstrated that, despite stress-driven changes in this pathway, it retained its ability to strongly suppress palatable food intake upon in vivo optogenetic stimulation. Overall, our data reveal an important role for stress-induced plasticity in the NAc-LHA pathway, which might underlie uncontrollable overeating after experiencing stress.

Disclosures: D. Wenjie: None. **R.A. Adan:** None. **F. Meye:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.12/C9

Topic: B.05. Synaptic Plasticity

Support: Cody Wenthur Start Up Funding

Title: Serotonergic Psychedelic Induced Altered States of Consciousness: From Mechanism to Behavior

Authors: *Z. ZAHID[1], D. YADEN[1], C. J. WENTHUR[2], M. I. BANKS[3];
[1]Ctr. for Psychedelics and Consciousness Res., Johns Hopkins Univ., Baltimore, MD; [2]Pharm., Univ. of Wisconsin - Madison. Psychoactive Pharmaceut. Investigation Program, Madison, WI; [3]Dept. of Anesthesiol., Univ. of Wisconsin, Madison, WI

Abstract: The neuroplastic hypothesis of psychedelic action asserts that these drugs may affect therapeutic benefit through their action as psychoplastogens [2]. Psychoplastogens are drugs that increase the growth, pruning, and reorganization of the brain in a way that is efficient, a mechanism referred to as neuroplasticity. This psychedelic induced plasticity has been assessed in many *ex vivo* and *in vitro* experiments in different regions of the brain; however, no one study has examined these changes at the circuit level. A circuit of relevance is the one that exists between the ventral hippocampus to the medial prefrontal cortex. This circuit is highly involved in working memory and emotion-based cognitions and plays a large role in the etiology of anxiety-like behaviors both in humans and in rodents [3]. I examined changes in plasticity in this pathway in vivo in mice using electrophysiology at 4 hours and 24 hours following psychedelic drug administration. I also assessed plasticity at 24 hours in the dorsal hippocampus alone using an ex vivo slice model. I found evidence for plasticity in the medial prefrontal cortex and the dorsal hippocampus at 24 hours after drug administration *in vivo* and *ex vivo*, respectively. To contextualize these results in terms of psychopathology, I assessed changes in an assay of anxiety-like behaviors. The novelty suppressed feeding task measures approach and avoidance behaviors that are highly dependent on the action of the ventral hippocampal to prefrontal cortex circuit. Interestingly, no reliable behavioral result was found. This prompted interest in characterizing the time course of the effects of the psychedelic state. Literature suggests that there are acute changes in various domains of biological and physiological responding following psychedelic administration. One such domain is brain oscillatory power, a valuable tool in measuring brain network dynamics. We found that psychedelics caused broadband changes in the hours following psychedelic administration, the peak effect of these changes occurring around 1-2 hours with the effect decaying back to baseline in the 3-4 hours following. These data underscore the importance of fully characterizing acute and post-acute psychedelic-induced effects to work to unravel their effects.

Disclosures: Z. Zahid: None. **D. Yaden:** None. **C.J. Wenthur:** None. **M.I. Banks:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.13/C10

Topic: B.05. Synaptic Plasticity

Support: NSF DBI 2119968

Title: Differential impact of HHV-6A versus HHV-6B infection on differentiated human neural stem cell signaling in neuron-glia co-cultures.

Authors: *Y. YANG[1], E. BAHRAMIAN[2], R. M. CEBALLOS[3];
[1]Sch. of Natural Sci., [2]Mol. and Cell Biol., Univ. of California, Merced, Merced, CA; [3]Mol. and Cell Biol., Univ. of California Merced, Merced, CA

Abstract: Human herpesvirus-6A and -6B (HHV-6A and HHV-6B) are reported to be neurotropic viruses associated with a variety of neurologic disorders, including: multiple sclerosis, epilepsy, chronic fatigue and neuro-encephalitis. Studying neurons in co-culture with glial cells provides a more interpretable model for studying neuronal action potential generation and neuro-neuronal signaling. Since glial cells play important roles in neurotransmitter reuptake and myelination, neuron-glia co-cultures provide a more realistic model for studying the impacts of herpesvirus infection on nerve cell signaling. Previous studies have shown that HHV-6A causes more severe cytopathic effects than HHV-6B on differentiated human neural stem cells (dHNSCs), which suggests that HHV-6A is more virulent than HHV-6B on dHNSCs. Thus, we test the hypothesis that HHV-6A will have a more significant impact on perturbing individual neuronal firing as well as neuron-neuron signaling than HHV-6B in experimental infections using virus inocula at equivalent multiplicity of infection (MOI). More specifically, in this study, we culture dHNSCs on multi-electrode array (MEA) plates and record: firing rates and inter-burst frequencies for individual neurons and network interburst intervals - for uninfected and HHV-6A versus HHV-6B infected cultures. Parallel cultures are produced to determine neuronal neurotransmitter chemotype distribution at select time points of infection using immunofluorescence technique. The electrophysiological data alongside immunofluorescence profiles provides an indication of relative virulence of HHV-6A versus HHV-6B on dHNSCs and suggests potential difference in cell tropism between each of these roseoloviruses on specific neuronal neurotransmitter chemotypes. In turn, these data will forward our understanding of specific mechanisms by which roseolovirus infection leads to specific disorders (e.g., epilepsy) within the central nervous system.

Disclosures: Y. Yang: None. **E. Bahramian:** None. **R.M. Ceballos:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.14/C11

Topic: B.05. Synaptic Plasticity

Support: PlantEXT LTD
Israel Science Foundation
David R. Bloom Center for Pharmacy at the Hebrew University of Jerusalem
IMRIC Hub for Addiction Research

Title: N-oleoyl Glycine and N-oleoyl Alanine Attenuate Alcohol Self-Administration and Preference in Mice

Authors: *S. SHAHEN-ZOABI[1], R. YAKA[2];
[1]Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Abstract Background: Alcohol use disorder is a chronic relapsing disorder characterized by cycles of intoxication, withdrawal, and relapse. The endocannabinoid system (ECS) plays a significant role in the neurobiological mechanisms underlying drug addiction and may present a therapeutic target. The current study evaluated the impact of chronic alcohol self-administration (SA) on endocannabinoids (eCBs) and eCB-like molecules (eCB-Ls) levels and explored the role of N-oleoyl glycine (OlGly) and N-oleoyl alanine (OlAla) in regulating alcohol consumption and preference. Methods: Alcohol intake and preference were assessed in male and female mice using a chronic intermittent access 2-bottle choice paradigm. eCBs and eCB-Ls levels in specific brain regions were quantified via liquid chromatography-mass spectrometry. Additionally, mRNA expression of ECS-related enzymes and receptors was assessed using quantitative real-time PCR (qPCR). Results: We found that following EtOH SA there were no significant sex differences in the levels of the eCBs and eCB-Ls that were tested. However, following chronic EtOH consumption, we found that the main changes in eCB-Ls were found in both OlGly and OlAla in the PFC and PFC, NAc, and VTA, three major brain areas that composed the reward system, respectively. Systemic administration of either OlGly or OlAla significantly reduced EtOH consumption and preference in male mice, without affecting total fluid intake. Furthermore, OlGly treatment induced a shift in the brain lipidomic profile, and qPCR analysis revealed alterations in ECS-related gene expression. Conclusions: Our study has directly evaluated EtOH-induced alterations in eCBs and eCB-L s levels in female and male mice. Our findings suggest that OlGly negatively regulates EtOH consumption, and exogenous administration of selective eCB-Ls shows potential as a therapeutic approach for alcohol addiction and relapse prevention.

Disclosures: S. Shahen-Zoabi: None. **R. Yaka:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.15/C12

Topic: B.05. Synaptic Plasticity

Support: JSPS KAKENHI 25H00434
AMED Brain/MIND2 JP24wm0625101
JST CREST JPMJCR21E2
JST FOREST JPMJFR231T
JSPS KAKEN 23K14285

Title: Dendritic spine enlargement is required for awake cognitive functions in mice : Insights from the novel synaptic chemogenetics SYNCit-C

Authors: S. ZHOU[1], T. SAWADA[2], T. ARIMA[1], H. OKAZAKI[1], S. PANEZAI[1], M. OHTSUKA[1], T. HASHIMOTO[2], S.-I. TERADA[2], S. TAKARAMOTO[1], M. KONDO[2], N. KITAJIMA[2], T. YAMAMORI[3], K. OHKI[2,1], M. MATSUZAKI[2,1], S. YAGISHITA[2,1], *H. KASAI[1];
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Abstract: Awake brain states in animals are typically characterized by distinct patterns of electroencephalography (EEG), electromyography (EMG), and locomotor activity, reflecting coordinated neural network dynamics mediated by action potentials and synaptic transmission across broad cortical areas. Although cognitive processes during wakefulness typically involve memory formation, the precise role of associative synaptic plasticity—particularly dendritic spine enlargement—in maintaining awake cortical functions remains unclear, largely due to the absence of selective inhibitory methods. Here, building upon our previously developed synaptic chemogenetic tool SYNCit-K, which induces spine enlargement via Rac1-GEF (GDP exchange factor; Sawada et al., Science 2024), we established SYNCit-C (SynC), a new variant that selectively abolishes dendritic spine enlargement via Rac1-GAP (GTPase activating protein) for approximately 1 hour following administration of an A/C heterodimerizer (A/C). SynC did not affect neuronal excitability or synaptic transmission, including NMDA receptor function, and its effects were abolished in a GAP-dead mutant variant (SynC-dGAP). Consistent with selective effects, SynC expression in the visual cortex did not impair visual sensation after intraperitoneal A/C administration, whereas identical treatment targeting the motor cortex completely prevented rotarod learning, an effect not observed with SynC-dGAP. Notably, broad SynC expression in the frontoparietal cortex followed by A/C administration profoundly impaired behavioral performance, reducing locomotion velocity, center exploration, laser-dot chasing, and food-pellet feeding, despite intact EEG γ waves. This treatment also intermittently induced behavioral arrests and an unawake state (State-C), characterized by sleep spindles without a marked increase in δ waves, mirroring the δ wave sleep induction previously reported with SynK. Importantly, all behavioral impairments fully resolved within 1 hour and were not observed with SynC-dGAP. Together, our findings suggest a critical role for dendritic spine enlargement, alongside intact γ wave activity, in supporting awake cortical functions and wakefulness.

Disclosures: S. Zhou: None. **T. Sawada:** None. **T. Arima:** None. **H. Okazaki:** None. **S. Panezai:** None. **M. ohtsuka:** None. **T. Hashimoto:** None. **S. Terada:** None. **S. Takaramoto:** None. **M. Kondo:** None. **N. Kitajima:** None. **T. Yamamori:** None. **K. Ohki:** None. **M. Matsuzaki:** None. **S. Yagishita:** None. **H. Kasai:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.16/C13

Topic: B.05. Synaptic Plasticity

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

Title: Rapid dynamics of spine enlargement and presynaptic mechanical effect in pyramidal neurons

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

Abstract: Associative pre- and postsynaptic stimulation induces spine enlargement, whose long-term component accompanies an increase in postsynaptic glutamate sensitivity (LTP). Recently, we discovered that the short-term phase of spine enlargement mechanically facilitates presynaptic neurotransmitter release (Ucar et al., Nature 2021). However, the rapid onset of spine enlargement and associated presynaptic effects have not yet been fully characterized. Here, we stimulated single dendritic spines via two-photon uncaging of caged glutamate and elicited action potentials in postsynaptic neurons using CsChrimsonR to prevent washout effects from whole-cell recordings in rat hippocampal slice culture preparations. We observed rapid spine enlargement with an average onset of 2.5 s at room temperature, accelerating to subsecond values at 37°C (mean ~0.8 s; range 0-1.5 s), following associative stimulation (20 Hz, 20 pulses). This rapid enlargement was abolished by inhibitors of NMDAR, CaMKII, Rac1, and Arp2/3, indicating mediation via the molecular cascade. Rapid structural changes were subsequently followed by an increase in glutamate sensitivity only after a delay of approximately 2 min. Currently, we are employing two-color optogenetic associative stimulation of pre- and postsynaptic neurons to monitor presynaptic function using the glutamate sensor iGluSnFR.Associative stimuli resulted in an approximately 10% increase in spine volume and appeared to rapidly (within < 5 s) enhance presynaptic release probability (Pr) by up to ~70%. Thus, substantial mechanical amplification arises from the difference in the scale between the postsynaptic spine (0.2-1 μm) and the presynaptic active zone (20 nm): a modest ~10% spine volume increase can lead to an approximately ~10 nm distortion of presynaptic terminals, markedly facilitating SNARE assembly. Note that visualizing such subtle spine enlargement *in vivo* is challenging due to imaging noise; nevertheless, robust functional outcomes observed with SYNCit-C strongly suggest frequent occurrence of rapid structural plasticity in the neocortex. We are currently further investigating the detailed kinetics of this associative pre- and postsynaptic plasticity *in vitro* and *in vivo*.

Disclosures: H. Okazaki: None. **H. Kume:** None. **F. Eto:** None. **S. Takaramoto:** None. **Y. Morimoto:** None. **H. Kasai:** None.

Poster

PSTR106: Mechanisms and Modulation of Neuroplasticity: From Memory and Sensory Circuits to Therapeutic Targets

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.17/C14

Topic: A.06. Developmental Disorders

Support: NIH Grant 2T32HD007149-46
Kavli Foundation
No. RS-2024-00359456
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Simons Foundation
NOMIS Foundation
Manton Foundation

Title: Kiaa0319 controls cortical neurodevelopment through adhesion protein organization

Authors: *M. SCANDURA, C. LO, I.-H. PARK, J. R. GRUEN;
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Abstract: *KIAA0319* is a transmembrane protein associated with dyslexia through clinical studies. However, its function in human neurodevelopment remains poorly understood. Using human cortical organoids (hCOs) derived from *KIAA0319* knockout (KO) and wild type (WT) human embryonic stem cells (hESCs), we demonstrate that *KIAA0319* regulates a transcriptional network of dyslexia-associated genes, including *DCDC2*, *DNAAF4*, and *ROBO1*. *KIAA0319* knockout organoids exhibit dysregulation of radial glia cells and reduced expression of genes involved in ciliogenesis, including *ARL13B*, *IFT88*, *PKD1*, and *CEP290*. *KIAA0319* knockout organoids also have a 55% reduction in total primary cilia as visualized by immunohistochemistry. This defect in cilia production is correlated with impaired neural progenitor proliferation, reduced progression to M-phase, and dysregulation of key cell cycle genes. Single-cell transcriptomics reveals weakened synaptic gene expression and connectivity in mature neuron populations, with reduced cell-cell interactions and downregulation of synapse-enriched GO terms. Functional analysis using calcium imaging further shows reduced spontaneous depolarization events and wavelet coherence synchrony in *KIAA0319* KO hCOs. Additionally, immunostaining for β-catenin reveals abnormal localization and reduced organization at the apical surface of the ventricular zone, implicating disrupted adhesion protein trafficking or degradation. Together, these findings suggest *KIAA0319* is a key regulator of adhesion protein organization, which has downstream effects in primary cilia development, neural progenitor cell cycle dynamics, and synaptic connectivity. This sheds light on *KIAA0319*'s broader role in neurodevelopment and the molecular underpinnings of dyslexia.

Disclosures: M. Scandura: None. **I. Park:** None. **J.R. Gruen:** None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.01/C15

Topic: C.01. Brain Wellness and Aging

Title: Redefining DNA Repair Pathways through Homologous Recombination to Support Neuronal Differentiation and Genomic Stability

Authors: *G. KIM[1,2,3], Y. LEE[1,2,3], Y. HWANG[1,2], J. YOON[1,2], H. YUN[1,2], S. KIM[1,2], H. KANG[1,2,4,3];
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Abstract: Neuronal genomes are particularly vulnerable to DNA damage due to the long lifespan of neurons, high metabolic demands, and sustained transcriptional activity. Accumulated genomic damage has been implicated in bothneurodevelopmental and neurodegenerative disorders. Notably, neuronal activity itself can induce DNA double-strand breaks (DSBs), especially at promoters of actively transcribed genes, to facilitate transcriptional regulation. Althoughnon-homologous end joining (NHEJ) is the predominant DSB repair mechanism in neurons, it's error-prone nature poses risks of mutagenesis. In contrast, Homologous recombination (HR) ensures high-fidelity repair but has long been presumed inactive in post-mitotic neurons due to the absence of sister chromatids. However, recent evidence suggests that HR may still play a crucial role in neuronal DSB repair. Here, Here, we provide compelling evidence that HR is not only active but also essential in post-mitotic neurons. We demonstrated that HR factors, including RAD51, are recruited to DSB sites in neurons, and that HR deficiency results in pronounced neuronal cell death, suggesting that HR contributes to maintaining neuronal genomic stability and protecting from DNA damage. Furthermore, we observed that DNA breaks act as a signal for initiating neuroanl differentiation and are accompanied by the robust recruitment of HR machinery to the damage sites. These findings provide that HR may function in parallel with, or as a complement to, NHEJ, offering a more accurate mechanism for DSB repair in non-dividing neurons. Thus, our study reveals a previously underappreciated role for HR in promoting neuronal differentiation and safeguarding against neurodegeneration.

Disclosures: G. Kim: None. **Y. Lee:** None. **Y. Hwang:** None. **J. Yoon:** None. **H. Yun:** None. **S. Kim:** None. **H. Kang:** None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.02/C16

Topic: C.01. Brain Wellness and Aging

Title: Investigating systems that underpin healthy aging: examining properties of cells that are surviving neurotoxicity.

Authors: *O. J. OGUNGBEMI;
Sch. of Psychology and Neuroscience., Univ. of St Andrews. United Kingdom, St Andrews., United Kingdom

Abstract: Neurodegenerative diseases (NDD) such as Alzheimer's disease (AD) are characterised by the progressive loss of specific neuronal populations. However, in every population of neurons that is afflicted in neurodegenerative conditions not all cells die. There remains a subset of survivor neurons. My aim is to elucidate the underlying mechanisms contributing to this differential cellular resilience in neurodegeneration using cell models that are used to model AD such as the hippocampal cell line, HT-22. To create a controlled neurotoxic environment that mimics conditions seen in aging brains and NDD, I used homocysteine (HCy) and its metabolites as my neurotoxicant. One of the known prospective risk factors for AD is elevated levels of the sulphur-containing amino acid homocysteine (HCy) which is produced as part of the methionine cycle. Its metabolites homocysteine thiolactone (HCT) and homocysteic acid (HCA) are also known to be neurotoxic. I used HCy, HCA, HCT at 25 µM, 50 µM, 100 µM and 200 µM treatment concentrations (All of which are within the physiological concentration that would be seen in NDD condition). At these levels, cells die. Using a combination of cell viability (crystal violet, lactate dehydrogenase assay (LDH), MTT) and biochemical assays, I have modelled neuronal vulnerability *in vitro*. Using graph prism, a One-way ANOVA and Turkey HSD post-hoc test were used to analyse data. Preliminary data (N= 4 biological repeats) suggests the following may be occurring: Interestingly, HCy-treated group showed a significant decrease in cell number and an increase in release of LDH suggesting an increase in cell death. However, there was no significant change seen in the mitochondria activity. Further experiments looking at the mitochondria membrane potential showed the surviving population following HCy treatment clearly have a healthier mitochondrion compared to the control. Data from HCA and HCT showed a significant increase in cell death. However, there is a decrease in levels of reactive oxygen species suggesting that there may be some antioxidant defenses in place. There was also a difference with HCA-treated population, with an increase in NO level which was not seen in HCT. Elevated levels of nitric oxide levels suggest neuronal oxidative stress occurring (excitotoxicity). To sum it up, there was a difference in response to all three treatments. These preliminary results have established a protocol to further investigate pathways to neuronal vulnerability and resilience in cellular models of AD.

Disclosures: O.J. Ogungbemi: None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.03/C17

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 EY028284
NIH R01 EY035353
Research to Prevent Blindness
EyeSight Foundation of Alabama
Heidelberg Engineering

Title: Acute intraocular pressure elevation induces region-specific microglial, oxidative stress, and senescence-associated responses in the human retina

Authors: *M. SOMERVILLE[1], R. G. STRICKLAND[3], S. LIN[2], M. GARNER[1], A. BLAKE[4], G. H. GROSSMAN[5], C. A. GIRKIN[6], A. K. GROSS[3];
[2]Neurobio., [1]Univ. of Alabama, Birmingham, Birmingham, AL; [3]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; [5]Innovation, [4]Advancing Sight Network, Birmingham, AL; [6]UCSD, San Diego, CA

Abstract: Glaucoma is a neurodegenerative disease characterized by progressive retinal ganglion cell (RGC) loss and is driven in part by elevated intraocular pressure (IOP), a key modifiable risk factor. While animal models have demonstrated that acute IOP elevation induces oxidative stress, microglial activation, and senescence-associated secretory phenotype (SASP) signaling, the molecular dynamics of these responses in the human retina have yet to be directly evaluated. The regional specificity of these responses also remains unclear, particularly given emerging evidence that the superior and inferior macula may be more susceptible to IOP-induced injury. This study investigates the regional activation of microglia, oxidative stress, and SASP pathways in the macula following acute IOP elevation in research-consented, brain-dead human organ donors.One eye each from three separate donors underwent sustained IOP elevation via viscoelastic gel injection into the anterior chamber (mean IOP: 41 mmHg) for 8-9 hours. Post-enucleation, retinal tissues were processed for immunohistochemistry, RNA fluorescent *in situ* hybridization, and spatial transcriptomics across six parafoveal regions and the fovea.Quantitative immunohistochemistry revealed increased IBA1-positive microglial surface area (Δ=7.724±4.2 μm²) in the inner nuclear layer of the superior fovea in treated eyes. Region-specific transcriptomic analysis showed differential expression of SASP-related genes, including IL6 (Δ=-3.52±0.52), FASR (Δ=-1.01±0.52), FGF2 (Δ=0.89±0.21), and CCL5 (Δ=1.66±0.44). Transcripts encoding enzymes involved in the oxidative stress response were also differentially expressed in response to IOP elevation. Superoxide dismutase 1 and 2 displayed increased differential expression (SOD1 Δ=3.37±1.83, SOD2 Δ=2.66±1.28) in the ganglion cell layer of the inferior nasal macula. Spatial transcriptomics further identified upregulation of oxidative stress markers, IL6 signaling, MHC class I/II antigen presentation, and toll-like receptor pathways—hallmarks of neuroinflammatory and senescence-associated responses.These findings suggest that acute IOP elevation induces a regional increase in microglial activation in the superior macula, consistent with this region's heightened susceptibility to injury. Additionally, the data support senescence-associated responses throughout the human macula. The conservation of these pathways with those in animal models underscores their relevance to age-related neurodegeneration and highlights potential therapeutic targets for mitigating IOP-induced vulnerability in glaucoma.

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Grossman: A. Employment/Salary (full or part-time): Advancing Sight Network. **C.A. Girkin:** None. **A.K. Gross:** None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.04/C18

Topic: C.01. Brain Wellness and Aging

Support: SECIHTI Grant 319578

Title: Analysis of aging markers in neural precursor cells of the human olfactory neuroepithelium over six decades of age.

Authors: *S. VAZQUEZ ZULOETA[1,2], O. LORA-MARIN[2], J. PADILLA-MENDOZA[2], M. CARDENAS-AGUAYO[2];
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[2]Physiology, Lab. of Cell. Reprogramming, Sch. of Medicine, Natl. Autonomous Univ. of Mexico (UNAM), Ciudad de Mexico, Mexico

Abstract: Background: Aging is a natural process of change over time, characterized by the progressive loss of physiological integrity. Various factors, including lifestyle, environment, and genetics, can influence whether an individual ages healthily or develops age-related pathologies. The study of human aging has been implemented in animal models; however, few human models exist. Here, we propose the use of human olfactory neuroepithelial neural precursor cells (hONE-NPCs) as a neural stem cell model for the study of aging. **Objectives:** Our aim was to assess age-related phenotypic and functional alterations in human olfactory neuroepithelium-derived neural precursor cells (hONE-NPCs) across six distinct age groups. **Methods:** We characterized age-related changes in human olfactory neuroepithelium-derived neural precursor cells (hONE-NPCs) from 24 volunteers aged 10 to 68 years, distributed equally across six decade-based age groups (n=4 per group). According to the School of Medicine, UNAM Research and Ethics Committee, and following informed consent signature, we obtained blood samples of each individual and subsequent nasal olfactory epithelial exfoliation to establish hONE-NPCs primary cell cultures for each donor. Phenotypic and functional analyses were performed using immunocytochemistry (phenotypic, proliferation, and autophagy markers) and senescence-associated functional assays (beta-Galactosidase staining). **Results:** hONE-NPCs canonically exhibit stemness and neural lineage markers, as well as an active proliferation state. Cell proliferation is altered within the 30s, 40s, and 60s, indicating a turning point in proliferation during the 30s decade. Likewise, non-lineal fluctuations in the cellular processes of protein degradation (autophagy) and metabolic processes were observed in these same groups 30s, 40s, and 60s. **Conclusions:** In conclusion, while aging is associated with multiple cellular alterations, our findings demonstrate that these changes occur non-linearly and exhibit significant interindividual variability within each age group. The importance of understanding these

processes in each age group lies in detecting potential biomarkers among healthy individuals, thereby preventing and/or treating pathological processes that may occur throughout life.

Disclosures: S. Vazquez Zuloeta: None. **O. Lora-Marin:** None. **J. Padilla-Mendoza:** None. **M. Cardenas-Aguayo:** None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.05/C19

Topic: C.01. Brain Wellness and Aging

Title: Real-time metabolic profiling in brain tissue biopsies using the Seahorse XF Flexsystem

Authors: P. SWAIN[1], V. SILVA[1], S. ARMITSTEAD[1], ***N. ROMERO**[2];
[2]Cell. and Biomolecular Analysis Div., [1]Agilent Technologies, Lexington, MA

Abstract: OBJECTIVE / RATIONALE Neuronal development and function are among the most energy-demanding biological processes in the body. Disruptions in oxygen metabolism and mitochondrial function are hallmark features of aging and neurodegenerative diseases. Different brain regions have distinct functions and energy demands, yet many studies rely on cultured neurons or brain isolated mitochondria. These approaches require large tissue quantities and fail to capture the complex microenvironment and cellular interactions of intact brain tissue. To address this, we developed a novel 3D Capture Microplate that when used together with the Agilent Seahorse XF Flex Analyzer and dedicated consumables, it enables real-time energetic metabolic analysis of small biopsy punches from discrete brain regions. **METHODS / RESULTS** Rat brains were dissected on the morning of the Seahorse XF assay and immediately placed in chilled, oxygenated artificial cerebrospinal fluid. Viable tissue slices were prepared using a Compresstome vibratome (Precisionary. Inc.). Biopsy punches were then collected from selected brain regions to assess the metabolic profile using the new Seahorse XF Flex 3D Capture Microplate-L (Agilent Technologies) in combination with the XF 3D Mito Stress Test (Agilent Technologies). Sample tissue preparation, dose of mitochondrial modulators and normalization strategies were optimized in order to yield robust basal oxygen consumption rates (OCR) and key mitochondrial function parameters. Representative data, workflow steps, and assay optimization strategies are presented. The assay demonstrated sufficient sensitivity to detect regional metabolic differences and responses to mitochondrial modulators. **CONCLUSIONS** The new Seahorse XF Flex Analyzer, in combination with the XF 3D Capture Microplate-L, enables physiologically relevant metabolic analysis in three-dimensional brain tissue models. This system provides the sensitivity needed to detect robust tissue respiration signals and dynamic responses to mitochondrial perturbations. With optimized and streamlined workflows, this approach facilitates real-time metabolic interrogation of intact brain tissue, offering a valuable tool for studying regional bioenergetics in health and disease models.

Disclosures: **P. Swain:** A. Employment/Salary (full or part-time): Agilent Technologies. **V. Silva:** A. Employment/Salary (full or part-time): Agilent Technologies. **S. Armitstead:** A. Employment/Salary (full or part-time): Agilent Technologies. **N. Romero:** A. Employment/Salary (full or part-time): Agilent Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Agilent Technologies.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.06/C20

Topic: C.01. Brain Wellness and Aging

Support: DGAPA-PAPIIT 204324 TO S-RA
POSDOCTORAL FELLOWSHIP SECIHTI CVU 385286 TO A-MM

Title: Effect of chronic oxidative stress produced by exposure to repeated doses of ozone on the blood-brain barrier

Authors: *A. E. RODRIGUEZ, A. MIRANDA-MARTINEZ, Sr., P. BARRAGÁN RESÉNDIZ, S. L. RIVAS-ARANCIBIA;
Univ. Nacional Autónoma de México, CDMX, Mexico

Abstract: Environmental pollution represents one of the most significant public health problems, as it acts as a risk factor in the development of chronic degenerative diseases. Exposure to ozone is known to induce the production of reactive oxygen species, which induces oxidative stress in various organs and systems, including the brain.The objective of this study was to study the effect of oxidative stress on the localization and distribution of haptoglobin and Glial Fibrillary Acidic Protein in the hippocampus of rats exposed to low doses of ozone (O_3). For this study, 72 male Wistar rats were divided into six experimental groups (n=12). The control group was exposed to ozone-free air, while the remaining groups were exposed to 0.25 ppm ozone for 4 hours daily for 7, 15, 30, 60, and 90 days, respectively. After completing the treatments, the animals were deeply anesthetized (NOM-033-SAG-ZOO-2014) and brain tissue was removed. The tissues were processed for Western blotting and immunofluorescence techniques to study the role of haptoglobin and glial fibrillary acidic protein in the hippocampus of rats exposed to this gas.The WB results show a significant increase in haptoglobin content in the hippocampus at 15, 30, and 90 days of O_3 exposure ($p<0.05$); this increase is also observed in the endothelial cells of blood vessels, closely associated with glial cell activation in response to oxidative stress. In conclusion, repeated exposure to low doses of ozone produces changes in haptoglobin content in the rat hippocampus, which would be associated with alterations in the blood-brain barrier, the loss of permeability of the blood-brain barrier (BBB), the passage of molecules from the peripheral circulation to the CNS and the activation of glial cells in the hippocampus of rats exposed to ozone.

Disclosures: A.E. Rodriguez: None. **A. Miranda-Martinez:** None. **P. Barragán Reséndiz:** None. **S.L. Rivas-Arancibia:** None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.07/C21

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG093606
Macular Degeneration Foundation
Reeves Foundation

Title: Mitochondrial dysfunction drives neurodegeneration in the aging visual system

Authors: *T. SHWANI[1,2], W. LIU[3], J. VU[3], J. SLONE[3], M. DEANGELIS[4,5];
[2]Neurosci. Program, [3]Pediatrics, [4]Ophthalmology, [1]State Univ. of New York at Buffalo, Buffalo, NY; [5]The Univ. of Utah, Salt Lake City, UT

Abstract: Aging leads to widespread cellular decline across the central nervous system (CNS), including the retina—a neuron-rich extension of the CNS. Mitochondrial dysfunction, a hallmark of aging and neurodegeneration, is particularly consequential in the retina and retinal pigment epithelium (RPE)/choroid, which support visual processing through constant high energy demand. Mitochondria possess their own genome (mtDNA), which accumulates mutations over time and may contribute to neurodegenerative changes in the aging visual system. However, the extent and impact of mtDNA variation across human CNS tissues remains poorly understood. In this study, we investigate how mtDNA contributes to mitochondrial and neuronal decline in aging human retina and retinal pigment epithelium (RPE)/choroid. Using rapidly dissected (<6 hours postmortem interval time), rigorously phenotyped eye tissue from aged donors (>60 years), we performed high-resolution profiling of mtDNA mutations with STAMP (Sequencing by Targeted Amplification of Multiplex Probes). This method incorporates unique molecular identifiers (UMIs) to detect low-frequency variants with high fidelity. In parallel, mtDNA copy number was also assessed using quantitative real-time PCR with primers targeting mitochondrial CytB and nuclear B2M genes. The 10X Xenium spatial transcriptomics platform was utilized to map age-associated mtDNA alterations and gene expression changes in situ. Donor-derived lymphoblastoid cell lines (LCLs) were used for functional validation. Preliminary analyses reveal increased mtDNA mutational burden in aged retina. In contrast, the aged RPE/choroid exhibits elevated mtDNA copy number with age, suggesting tissue-specific mitochondrial adaptations. To contextualize these findings, Xenium provided a high-resolution map of mtDNA-associated transcriptional changes. Taken together, these data point to a complex, tissue-specific mitochondrial response to aging within the visual system. By integrating genomics, spatial transcriptomics, and functional validation, this work advances our understanding of

mitochondrial genome instability in CNS aging and positions the eye as a tractable model for studying mechanisms of age-related neurodegeneration.

Disclosures: T. Shwani: None. **W. Liu:** None. **J. Vu:** None. **J. Slone:** None. **M. DeAngelis:** None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.08/C22

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant P20GM103443

Title: The role of the redox sensor nucleoredoxin in BMAA-induced neurotoxicity

Authors: *H. K. SHOMUDRO;
Natural Sci., Black hills state university, Spearfish, SD

Abstract: β-N-methylamino-L-alanine (BMAA) is a neurotoxin that is produced by cyanobacteria in algae blooms and is often found in pounds, rivers, oceans, and moist areas. BMAA exposure is associated with sporadic neurodegenerative disease in humans, however its mechanism of action is unclear. Previous research from our lab identified several important hallmarks of BMAA neurotoxicity in human cells including activation of Wnt signaling, accumulation of cellular reactive oxygen species (ROS), proliferative defects, and changes to cell differentiation state. The intracellular protein nucleoredoxin (NRX) influences gene expression in response to oxidative stress and the accumulation of cellular reactive oxygen species (an indicator of metabolic stress). Interestingly, crosstalk between NRX and Wnt pathways has previously been reported. Here we test the hypothesis that NRX is a key component in neurotoxicity induced by BMAA via its sensitivity to ROS and influence on Wnt signaling and downstream expression of target genes involved in cell stress, proliferation, differentiation, and metabolism. Experiments in SH-Sy5Y human neuroblastoma cells utilizing reporter assays, microscopy, NRX siRNA and gene expression analysis support the hypothesis that cellular redox sensing by NRX is a critical component of BMAA toxicity and suggest that antioxidant compounds capable of modulating NRX activity may be an effective therapy for BMAA-induced neurodegenerative conditions.

Disclosures: H.K. Shomudro: None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.09/C23

Topic: C.01. Brain Wellness and Aging

Title: Overexpression of acetyl-CoA transporter SLC33A1 induces hyperactive growth and metabolism in neurons

Authors: *C. MCGILL[1], E. MCGREGOR[2], L. PUGLIELLI[3], R. ANDERSON[2];
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Abstract: Mitochondrial dysfunction is a hallmark of aging; however, the intricate regulation of mitochondrial metabolism and how perturbations in intracellular systems change mitochondrial homeostasis is poorly understood. Acetyl-CoA is a central metabolite that serves as a node at which multiple metabolic processes converge, including the TCA cycle, cholesterol biosynthesis, and post-translational modifications of proteins, among others. Thus, acetyl-CoA connects energy metabolism to broader cell functions. SLC33A1 (AT-1) is an endoplasmic reticulum (ER) membrane-bound transporter that shuttles acetyl-CoA from the cytosol into the ER lumen, where it plays a major role in protein quality control as part of the secretory pathway. In humans, alterations in the expression of AT-1 have been implicated in several neurologic disorders, including autism spectrum disorder and spastic paraplegia. In mice, the systemic AT-1 overexpression (OE) leads to cognitive deficits and a progeroid phenotype. Prior studies reported changes in the secretory pathway and proteostasis. Here we focus on the metabolic response to AT-1 OE in primary neurons and brain tissue from transgenic mice. Increased expression of PGC-1a, a master regulator of mitochondrial function and neuronal arboration, suggested a potential mechanism for mitochondrial adaptation to increased AT-1. To investigate mechanisms underpinning pleiotropic outcomes, we performed bulk transcriptome, lipidome and proteome profiling on primary AT-1 OE neurons. At the gene level, we find significant differences in pathways relating to mitochondrial processes, oxidative phosphorylation, lipid storage and synaptic pruning. Lipidomic analysis finds most lipids with significant differential abundance associated with membrane components. In neurons, functional assays reveal an impact on mitochondrial membrane potential, cellular respiration, and redox metabolism. Looking next in vivo, cortical proteomics confirms a role for AT-1 in metabolic regulation. Our mitochondrial energetic phenotypes together with previously reported endoplasmic reticulum proteostatic phenotypes have prompted current work focusing on inter-organelle communication, including endoplasmic reticulum and mitochondrial contacts. Understanding the mechanisms underlying shared intracellular networks involved in various neurologic disorders could aid in the development of therapies to treat or prevent these conditions.

Disclosures: C. McGill: None. **E. McGregor:** None. **L. Puglielli:** None. **R. Anderson:** None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.10/C24

Topic: C.01. Brain Wellness and Aging

Support: NSF Grant IOS 2207023
NIH T32 fellowship (T32 AG044402).

Title: Assessing the influence of Nrf2 on age-related NSPC quiescence and senescence

Authors: *A. ISHII[1], S. PILLUTLA[2], M. SKODA[2], M. J. CORENBLUM[1], N. MENAKURU[2], L. MADHAVAN[1];
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Abstract: Quiescence and senescence are key states that define the aging trajectory of adult neural stem/progenitor cells (NSPCs) in the subventricular zone (SVZ) and dentate gyrus (DG). These states contribute to reduced neurogenesis and stem cell dysfunction with age, but the regulatory mechanisms are not fully understood. Our previous work has identified the Nrf2 (nuclear factor (erythroid-derived 2)-like 2) transcription factor as an important regulator of NSPC function. Nrf2 is an important homeostatic factor which is known to influence cellular quiescence and senescence in other domains. However, its effects on these processes in NSPCs is unknown. To assess this question, we used male and female Fischer 344 wild-type (WT) and Nrf2 knockout (KO) of specific age-groups, centered around critical aging periods we had identified previously. Female animals were ovariectomized or remained intact to assess the role of the ovarian sex hormones. The rats were then subjected to NSPC-relevant behavioral tests and their brains examined for markers of quiescence and senescence. Preliminary results show that Nrf2 KO male rats display lower performance in fine olfactory discrimination compared to WT rats at both 9 and 14 months of age. In female rats, a decreasing trend in discrimination performance was observed in KO-SHAM animals at 6 and 10 months, with a marginal difference noted at 10 months. Ovariectomized WT females also exhibited reduced performance, suggesting a possible modulatory role of ovarian hormones in Nrf2-related effects. KO females data from the pattern separation is being collected. Quiescence and senescence of NSPCs in WT and Nrf2 KO rats are currently being examined and ChIP-Seq analysis on WT rats across age and sex is being performed to further define age and sex dependent Nrf2-mediated transcriptional control. Together, our data will further explicate Nrf2-based regulation of NSPC activity and function with age.

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Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

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Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R21AG081998-01
NIH Grant P51RR000170

Title: Biomarker Signatures of Chronic Disease in Aging Rhesus Macaques (Macaca mulatta)

Authors: *L. CENICEROS[1,2], A. CRUZ[3], A. CUNNINGHAM[3], R. SUBEDI[4], A. BROWN[3], E. L. KINNALLY[5];
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Abstract: As global life expectancy continues to rise, the growing cost and burden of age-related diseases has emerged as an escalating topic of concern. Identifying early biomarker signatures of physiological decline can offer a promising avenue for early detection and targeted interventions. In the present study, we investigated whether chronically diseased rhesus macaques (Macaca mulatta) demonstrated altered age-related trajectories across blood chemistry and morphometric measures collected during a 25-hour biobehavioral assessment. Our sample included male (n = 69) and female (n = 142) subjects ranging from 14.58 to 26.01 years (mean age = 17.57). Subjects were grouped according to health status, defined by the presence or absence of a previously diagnosed chronic condition at the time of testing (diseased: n = 51; non-diseased: n = 160). These chronic conditions included cardiovascular, metabolic, musculoskeletal, and oncological diseases. A multiple linear regression was conducted to predict individual physiological biomarkers based on chronological age, health status, their interaction, and sex as a covariate. Our results demonstrated several significant Age x Health Status interactions across biomarkers of cardiovascular (blood pressure: systolic B = 2.73, p = .03, diastolic: B = 2.45, p = .004), homeostatic regulation (sodium: B = -.60, p = .04; osmolality: B = -1.52, p = .011), and metabolic function (glucose: B = -9.30, p = .030; C-reactive protein: B = -.87, p = .002); no significant effects of sex were observed for these biometrics. Findings revealed that in some biomarkers, such as osmolality levels, younger diseased animals resembled patterns similar to those of older, non-diseased counterparts. These patterns suggest that diseased animals may experience earlier dysfunction and quicker decline indicative of altered aging processes.

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Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

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Program #/Poster #: PSTR107.12/C26

Topic: C.01. Brain Wellness and Aging

Support: NIH RO1ES031511

Title: Methylation Inhibition of m⁶A Induces Senescence in Microglial Cells

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Abstract: Abstract: Cellular senescence, a hallmark of aging, contributes to neurodegenerative and inflammatory processes in the brain. Recent studies suggest that RNA modifications, particularly N6-methyladenosine (m⁶A), may play an active role in regulating stress responses and aging phenotypes. In this study, we explored how oxidative stress and m⁶A disruption contribute to senescence in human microglial cells. Using HMC3 microglial cells, we induced stress-related aging using sodium arsenate. We inhibited m⁶A RNA methylation using STM2457, a selective METTL3 inhibitor. Our primary objective was to determine if these treatments may promote cellular senescence. Through SPiDER β-Gal staining, our data revealed a robust increase in senescent cells in both sodium arsenate- and STM2457-treated groups, compared to untreated controls. This supports the hypothesis that both oxidative stress and m⁶A inhibition promote senescence in microglia, even in the absence of long-term treatment or genetic manipulation. Our RNA-seq also revealed increased inflammatory cytokines and immune modulators in m6A disruption and stress conditions. We have employed transcriptome-wide m⁶A mapping (GLORI) to elucidate the m6A changes driving the observed senescent phenotype in both m6A disruption and oxidative stress conditions. This study contributes to the understanding of how epitranscriptomic regulation interfaces with cellular aging. Findings may promote future exploration of the role m⁶A has in neuroinflammation and age-associated brain dysfunction. This research was funded in part by the Paula and Rusty Walter and Walter Oil & Gas Corp Endowment

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Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

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Topic: C.01. Brain Wellness and Aging

Support: NIH R01AG076704
MGH Department of Anesthesia
T32HL007901

Title: Ketone-induced modulation of sleep and memory in the aged brain

Authors: *F. A. MIR[1], A. R. LARK[2], F. TIAN[2], J. CHOI[2], A. CARPENTER[4], K. SMITH[4], C. SYME[4], B. TORO[4], C. J. NEHS[3], E. CROWLEY[4], N. AMBAREEN[5];
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Abstract: Sleep impairments and metabolic dysregulation are among the most significant consequences of aging, contributing to cognitive decline and dementia in age-associated neurodegeneration. Dietary interventions, such as the ketogenic diet (KD) and exogenous ketone supplements, have shown considerable potential in enhancing sleep quality and cognitive functions, particularly in older individuals. In the aging brain, the ability to use glucose as a fuel diminishes, whereas the capacity to utilize ketones as an alternative carbon source remains relatively intact. We hypothesize that increasing ketone availability in aged animals through a KD or exogenous ketone esters may improve sleep quality and cognitive function. To test this, we investigated the effects of ketone supplementation and a KD on sleep-wake architecture and memory impairments induced by sleep deprivation in aged (22-23 months) male and female Fischer-344 rats. All animals received stereotaxic surgery to implant EEG electrodes in the frontoparietal cortex and EMG electrodes in nuchal muscles. After a 7-day recovery, baseline sleep was recorded for 48 hours using a wireless telemetry system (Pinnacle Inc.). Animals were then assigned to either ketone ester gavage (2.5 g/kg) vs. water control (n=8, 50% female) or ketogenic diet vs. control diet (n=16, 8/group). Sleep stages were scored using Accusleep in MATLAB. Sleep quality was assessed via episode percentage, number, and duration. Cognitive performance post-sleep deprivation was evaluated using novel place recognition, open-field, and novel arm Y-maze tasks. Preliminary findings suggest that both ketone ester ($p=0.0113$, one-sample t-test) and ketogenic diet ($p=0.0112$, one-sample t-test) improved REM sleep architecture in females during the light and dark phases, respectively. Additionally, females on KD showed recovery from sleep deprivation-induced memory impairments, spending more time on novel objects ($t(7)=2.82$, $p=0.025$) and exhibiting a higher discrimination index ($t(7)=2.59$, $p=0.035$), supporting ketone-driven modulation of sleep and cognition in a sex- and memory system-specific manner.

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Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

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Topic: C.01. Brain Wellness and Aging

Support: NIH grant R01NS094535

Title: Bifunctional nanozymes promote hematoma resolution and attenuate DNA damage senescence and glial activation in a murine intracerebral hemorrhage model

Authors: *V. H. MALOJI RAO[1], A. MIKHEEV[3], M. KODAVATI[6], E. PERLI[7], X. TANG[4], G. W. BRITZ[8], P. J. HORNER[2], T. KENT[7], M. L. HEGDE[5];
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Abstract: Abstract Intracerebral hemorrhage (ICH) remains a major cause of neurological disability. Mechanisms likely include hemin and iron accumulation that drive secondary neuronal injuries. We previously reported that in neuronal cultures, that hemin in low concentrations induce DNA double-strand breaks (DSBs) that trigger a transient senescence-like phenotype prior to induction of heme-oxygenase-1 (HO-1), both of which are long lasting following repeated hemin dosing. To test whether these same mechanisms are recapitulated in-vivo, we established a reproducible autologous whole-blood double-injection model in adult mice, targeting the striatum to generate consistent basal ganglia hematomas. Hematoma formation was verified three days post-surgery by gross inspection and H&E staining. Coronal sections of perihematomal tissue revealed significant accumulation of DNA damage marker γ-h2ax foci, predominantly within $Map2^+$ neurons encircled by $Gfap^+$ astrocytes and $Iba1^+$ microglia. Senescence-associated β-galactosidase staining markedly increased in senescent cells compared with sham controls. Immunofluorescence co-staining showed robust HO-1 expression in $Map2^+$ neurons, whereas astrocytes and microglia displayed negligible HO-1 overlap. We then evaluated in-vivo therapeutic potential of bifunctional nanozyme deferoxamine-covalently bound to peg(ylated) catalytic carbon nanozyme (DEF-OAC-PEG), recently characterized by us for its ability to reduce hemin-induced toxicity in cultured neurons (Malojirao, V. H. et al. Commun. Biol. 2025 and Mouli, K. et al. Adv. Healthc. Mater-2025). Mice received two I.P. doses (2 mg/kg) of DEF-OAC-PEG at 2 h and 48 h after ICH. Nanozyme treatment accelerated hematoma clearance (gross imaging and H&E), attenuated secondary injury markers, reducing Gfap and DNA repair response marker pATM immunoreactivity to near-baseline levels, and significantly decreased perihematomal senescence-associated SA-β-gal activity. Together, these findings validate a robust in vivo platform for dissecting hemin-driven senescence and HO-1 dynamics and highlight bifunctional nanozymes as promising agents for mitigating DNA damage, glial activation, and senescence following hemorrhagic stroke.

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Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

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Topic: C.01. Brain Wellness and Aging

Support: National Science Foundation Graduate Research Fellowship Program
Jointly Sponsored Ruth L. Kirschstein National Research Service Award Institutional Predoctoral Training Program in the Neurosciences (JSPTPN) T32
Mind Brain Computation and Technology (MBCT) Training Program, Wu Tsai Neurosciences Institute, Stanford University
Stanford Interdisciplinary Graduate Fellowship, Wu Tsai Neurosciences Institute, Stanford University

Title: Converging mechanisms of lysosomal dysfunction and compensation in murine models of Batten disease

Authors: *N. MANFRED;
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Abstract: Lysosomes are dynamic organelles that maintain cellular homeostasis through secretory protein regulation, metabolism, plasma membrane repair, organelle crosstalk, and signaling. Underscoring the importance of lysosomal function, lysosomal gene haploinsufficiencies are risk factors for many sporadic neurodegenerative diseases (i.e. Alzheimer's, Parkinson's, and frontotemporal dementia). Rare instances of biallelic lysosomal gene mutations further exacerbate dysfunction, causing childhood neurodegeneration. In Batten disease, such mutations of ceroid lipofuscinosis neuronal protein (CLN) genes may trigger seizures, vision loss, motor impairment, cognitive deficits, and premature death. Currently, only one of the thirteen CLN gene mutations, CLN2/Tpp1, is treatable, as many CLN proteins have unknown functions. However, lysosome immunoprecipitation tools have expedited discovery of lysosomal protein functions in recent years. CLN5, for example, was identified, in vitro and in cellulo, as the elusive synthase of bismonoacylglycerophosphate (BMP), a late endosomal and lysosomal phospholipid crucial for lysosome stability, proteolysis, and vesicle trafficking. The primary lipid component of intralysosomal vesicles, BMP electrostatically stabilizes acid hydrolases, enabling catabolism. BMP is also a biomarker for Batten disease, Parkinson's disease, drug-induced phospholipidosis, and various cancers, making it a promising drug target with broader relevance. Here we confirm that CLN5 is the predominant or lone BMP synthase in vivo, and that multiple Batten disease mouse models exhibit significant BMP reduction, as well as significant converging proteomic alterations, irrespective of tissue. This implicates BMP reduction as an overarching mechanism of lysosomal dysfunction in Batten disease, with relevance to neurodegeneration at large, and hints at overarching compensatory mechanisms that require further characterization.

Disclosures: N. Manfred: None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.16/C30

Topic: C.01. Brain Wellness and Aging

Support: St Jude Children's Research Hospital Grant

Title: Polyamines Upregulation During Stress Enhances C9orf72-Associated Dipeptide Protein Repeats Toxicity

Authors: *U. YURTSEVER;
St Jude Children's Res. Hosp., MEMPHIS, TN

Abstract: One of the main causes of Amyotrophic Lateral Sclerosis (ALS) is the expansion of a hexanucleotide repeat GGGGCC (G4C2) in the C9ORF72 gene. This can lead to a loss of function of the C9ORF72 protein and a gain of function of the transcript that generates a toxic dipeptide repeat protein (DPR). Among these DPR, GR (Glycine-Arginine) repeats form hydrophobic oligomers and are detected in postmortem brain tissue of ALS patients. One of the main interactors of GR repeats is G3BP1, the central node protein of stress granules. Despite a report showing that knock-down of G3BP1 increased GR toxicity, the role of G3BP1 in the disease mechanism of GR in ALS remains unknown. Here, we used *in vitro* and *in vivo* models to dissect the interaction between GR and G3BP1. We found that GR repeats interact with the IDR1 domain of G3BP1 and promotes its liquid-liquid phase separation. Additionally, GR binding to G3BP1 is required to buffer and inhibit GR aggregation and for subsequent GR toxicity in flies. Furthermore, we show that polyamines, ubiquitous polycations that possess pleiotropic biochemical activities increase in flies with GR overexpression, and their knock-down could reverse GR toxicity. Interestingly, we found that both polyamines and GR peptides compete for binding to IDR1 domain of G3BP1 and thereby identify that polyamines can influence the ability of G3BP1 to limit GR aggregation. Taken together, these data suggests that polyamines inhibition can be a potential therapeutic approach to mediate DPR toxicity in ALS.

Disclosures: U. Yurtsever: None.

Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.17/C31

Topic: C.01. Brain Wellness and Aging

Support: SECIHTI posgrad scohlarship
VIEP BUAP

Title: Metabolic and inflammatory changes in serum and hypothalamus in a model of obesity

Authors: *G. PULIDO-FERNANDEZ, S. TREVIÑO, J. MORAN PERALES, A. HANDAL, A. DIAZ;
BUAP, Puebla, Mexico

Abstract: Obesity is a significant global health issue, linked to various chronic diseases. Obesity is a multifaceted condition influenced by genetic, environmental, and behavioral factors. Key contributors to its development include energy imbalance, genetics, environmental conditions, and psychological factors, which may vary from person to person. The increment in the mass and dysregulation in adipose tissue can exert and detrimental effect on the hypothalamus. It's proposed that its mechanism of damage maybe by a inflammatory and oxidative stress damage. However, these mechanisms are not clear yet. The aim of the present work is to evaluate the changes in zoometry, oxidative and inflammation markers in the Zucker rat model of obesity. For this work 5 weeks-old Zucker male rats were used. Animals were divided into four groups (n=8/group): 1)lean Zucker +normocaloric diet, 2) lean Zucker +hiperlipidic diet, 3) obese Zucker + normocaloric diet, 4) obese Zucker +hiperlipidic diet.The data were reported as the mean ± standard error (SE). A Two-Way ANOVA followed by a Dunnet post-test where $p < 0.05$ was considered significant.
The results show hyperfagia in both obese groups starting at 12 weeks of age. At the same time an increase in weight and adipose tissue percentage in the obese groups independent of the diet. The postprandial glucose and insulin levels are increased in these groups. And these obese groups develop dyslipidemia. In addition, we observed an increase in leptin level accompanied by a decrease in adiponectin level in the obese groups. Nevertheless, the increase in the proinflammatory cytokines its compensated by the increase of anti-inflammatory cytokines in serum. In the hypothalamus, the pro/antinflammatory cytokine levels have no changes. But the markers of oxidative stress increase in the obese groups. These results suggest that obesity affect the glucose and lipid metabolism. But the increase of adipose tissue doesn't mean adipose tissue dysfunction. Our results show a low level of alteration compared with level of obesity both hypothalamic and systemic. This suggests the action of mechanisms that prevent or delay the development of obesity related disorders.

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Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

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Topic: C.01. Brain Wellness and Aging

Support: NINDS T32 5T32NS007220
NIGMS R35GM128823
KIBM

Title: Regulation of mitochondria dynamics and neuronal activity via ketone body metabolism

Authors: *Z. D. WHIDDON[1], A. ZHANG[4], N. CARLSON[2], H. WANG[3], A. DIVAKARUNI[5], G. PEKKURNAZ[6];

[1]UCSD, San Diego, CA; [2]Biomed. Sci., UCSD, La Jolla, CA; [3]Biol. science, UCSD, San Diego, CA; [4]Neurosci., UCSD Dept. of Neurosciences, Encinitas, CA; [5]Pharmacol., Univ. of California Los Angeles, Los Angeles, CA; [6]Neurobio., Univ. of California San Diego, La Jolla, CA

Abstract: Neurons primarily rely on glucose metabolism to generate ATP molecules required for synaptic communication. During energy constraints such as fasting or prolonged exercise, glucose availability is reduced. In response, the liver oxidizes fatty acids to produce ketone bodies. Beta-hydroxybutyrate (BHB), the most abundant ketone body produced, is transported to the brain via the bloodstream and generates ATP through oxidative phosphorylation. The ketogenic diet, a dietary practice involving carbohydrate restriction and increased ketone body production, is clinically used to reduce epileptic seizures and alleviate memory loss in Alzheimer's Disease. However, the fundamental mechanisms behind neuronal ketone body utilization and the neuroprotective effects of ketogenic diets remain elusive. Here, we report that neuronal mitochondria are capable of utilizing BHB as fuel source, but the ATP generated by BHB oxidation is insufficient to continuously sustain synaptic activities. We examined the respiratory capacity of mitochondria isolated from murine brain tissues under ad libitum and 24-hour fasting conditions, using pyruvate or BHB as the fuel source. A 24-hour fast led to a decrease in blood glucose levels and a four fold increase in BHB levels. Brain mitochondria from both conditions exhibited comparable fuel-induced increase in cellular respiration, which suggests that brain mitochondria are primed to use BHB for rapid ATP production. To determine whether neurons specifically metabolize BHB, we performed metabolite tracing and demonstrated that carbon from BHB is incorporated into TCA intermediates. However, using an intracellular ATP sensor, we demonstrate that BHB alone is insufficient to sustain axonal ATP levels after stimulation. Analysis of synaptic vesicle recycling, the most energy-intensive aspect of neuronal activity, revealed decreased vesicle recycling when BHB was supplied instead of pyruvate or glucose. Furthermore, analysis of mitochondria dynamics revealed that the presence of BHB increases mitochondrial motility and alters the mitochondrial network. We hypothesize that the neuroprotective effects of the ketogenic diet observed in epilepsy and Alzheimer's Disease treatment stem from reduced neuronal activity due to attenuated ATP production and from mitochondrial network remodeling, which potentially alleviate mitochondrial dysfunction.

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Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR107.19/C33

Topic: C.01. Brain Wellness and Aging

Support: 4023093

Title: Hippocampal inflammaing and oxidative stress in a peripheral origin neurodegenerative model

Authors: *G. GONZÁLEZ, A. DIAZ, S. TREVIÑO;
Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: Metabolic syndrome (MetS) is defined as a condition characterized by a cluster of metabolic disturbances. Inflammation, typically a protective immune response to injury, infection, or disease, plays a central role in host defense. However, in metabolic diseases, this response manifests as a chronic, low-grade inflammation lacking the classical acute features. In parallel, increasing evidence implicates oxidative stress, an imbalance between the production and detoxification of reactive oxygen species (ROS) in the pathogenesis of chronic diseases, including metabolic disorders. Together, metaflammation and oxidative stress create a redundant loop contributing to the development of metabolic comorbidities such as dyslipidemia, hypertension, and glucose intolerance, ultimately leading to systemic metabolic dysfunction. Given the rising prevalence of MetS, understanding the downstream pathophysiological consequences, particularly those emerging from chronic inflammation and oxidative stress is critical, as they increase the risk of neurodegenerative conditions. In this study, male Wistar rats (N=20, ~100 g) were randomly assigned to one of two dietary groups: a normocaloric diet (NCD) or a high-calorie diet (HCD), administered over 3 months. At the end of the treatment period, blood and hippocampal tissue were collected. In both, levels of the cytokines IL-1β, IL-6, IL-17, IL-10, IL-4, TNF-α, and TGF-β were quantified. Oxidative balance was assessed through measurements of nitrite (NO_2^-), malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and catalase activity. In parallel, acridine orange staining was performed on 5 µm paraffin-embedded tissue sections to evaluate cell viability. Our findings suggest that carbohydrate rich diets in MetS induce a compartment specific response, where peripheral tissues exhibit a pronounced pro-oxidant imbalance, reflected systemically. Chronic exposure to this altered redox state may drive the activation of pro-inflammatory signaling cascades. In contrast, the central nervous system (CNS), particularly the hippocampus, displays compensatory regulatory mechanisms capable of buffering peripheral oxidative and inflammatory signals. These adaptations appear to maintain redox and immune homeostasis in the hippocampal microenvironment, effectively preventing excessive cellular damage and death.

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Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

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Topic: C.01. Brain Wellness and Aging

Support: P01AG026572 to RDB (Project 1 and Analytic Core to FY; Animal Core to TW)

RF1AG068175 to FY
RF1AG079157 to FY

Title: Apoe4 modifies central and peripheral metabolic adaptations to female reproductive aging

Authors: *H. PAN[1], Y. MI[1], K. JENKINS[1], G. QI[2], T. WANG[1], R. D. BRINTON[3], F. YIN[1]; [1]Ctr. for Innovation in Brain Sci., Univ. of Arizona, Tucson, AZ; [2]Ctr. for Innovation in Brain Sci., Univ. of Arizona, Tuscon, AZ; [3]Ctr. for Innov in Brain Sci., Univ. of Arizona, Tucson, AZ

Abstract: Age, hormone depletion at menopause and the ApoE4 genotype are among the top risk factors for developing late-onset Alzheimer's disease (AD). Previous findings from our group and others suggest both ApoE4 and perimenopausal transition as regulators of metabolic and inflammatory phenotypes related to AD. Here, we aimed to determine how these two factors interactively modulate metabolic pathways and modify AD risk. Humanized ApoE3 (E3) and ApoE4 (E4) knock-in mice were characterized into groups based on age and endocrine cycling status (regular, irregular, acyclic) at 6, 9, and 15 months. Cross-sectional plasma metabolomic and lipidomic analyses were performed using mass spectrometry. ApoE4 disrupted menopause-associated changes in circulating lipids, with E4 mice showing lower levels of phospholipids, fatty acids (FA), acyl carnitines, and sphingolipid species compared to E3 mice, particularly during the peri- and post-menopausal stages. Building on these findings, we further investigated how ApoE4 influences metabolic adaptation of the brain to ovarian hormone loss using a surgical menopausal model. Five-month-old female E3 and E4 mice underwent sham surgery or ovariectomy (OVX) with euthanasia 2 months later. We then assessed hippocampal gene expression related to key metabolic processes. OVX elevated ApoE mRNA in the hippocampus of E3, but not E4 mice. Furthermore, OVX significantly upregulated genes involved in FA synthesis, lipogenesis, phospholipid hydrolysis, FA activation and FA unsaturation in E3 mice, whereas E4 mice exhibited dampened responses. In contrast, mRNA levels of key genes regulating FA oxidation (FAO) including the rate-limiting enzyme carnitine palmitoyl transferase 1A (Cpt1a) and the upstream regulator peroxisome proliferator-activated receptor alpha (Ppara), decreased in E4, but not E3, mice after OVX. Collectively, our findings suggest that ApoE4 disrupts metabolic adaptations across brain and periphery during female reproductive aging, which may underlie the substantially higher AD risk among ApoE4-carrying post-menopausal women. This work has been supported by the NIH/NIA grants P01AG026572 to RDB (Project 1 and Analytic Core to FY; Animal Core to TW), RF1AG068175 and RF1AG079157 to FY.

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Poster

PSTR107: Neuroinflammation, Metabolism, and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.21/C35

Topic: C.01. Brain Wellness and Aging

Support: SECIHTI Grant 319578
Postdoctoral Fellowship DGAPA/UNAM Granted to J.R.P.-M. (2023-2025)

Title: The inverse relationship between neurodegeneration and cancer: unraveling shared survival and autophagy pathways in cell cycle dysregulation

Authors: *J. PADILLA-MENDOZA[1,2], M. SILVA-LUCERO[2], M. CARDENAS-AGUAYO[2]; [1]Sch. of Medicine, Univ. Nacional Autónoma de México, Mexico City, Mexico; [2]Physiology, Lab. of Cell. Reprogramming, Sch. of Medicine, Natl. Autonomous Univ. of Mexico (UNAM), Ciudad de Mexico, Mexico

Abstract: Background: Neurodegenerative diseases and various types of cancer are consistently described as complex and unique illnesses. However, a close relationship between these two pathologies has been observed. Consequently, several shared pathophysiological characteristics have been identified, such as genomic instability, environmental alterations, nutrient dysregulation, mitochondrial dysregulation, cellular senescence, and dysregulation of intercellular communication, among others. Conversely, some pathological mechanisms can be opposite between the two diseases. These characteristics alter different molecular processes that may be significant for both carcinogenesis and neurodegeneration. **Methodology:** We used neuroblastoma, glioblastoma, and melanoma cell lines and compared them with two fibroblast lines from patients with neurodegenerative diseases (Familial Alzheimer's and Niemann-Pick) and one fibroblast line from a control individual. We then analyzed cell cycle behavior in all cell cultures. Afterward, we performed immunodetection of markers for cell cycle checkpoints and the PI3K/Akt/mTOR pathway. **Results:** Cell cycle data showed that fibroblast from patients with neurodegenerative diseases and from the healthy control remained in the G1 phase for a longer duration (90-97%) with a low percentage of apoptosis. This contrasts with cancer cell lines, which showed 50-80% in G1 but no apoptosis. Furthermore, immunodetection of checkpoint markers suggested decreased expression in cancer cell lines. Immunodetection of the PI3K/Akt/mTOR pathway revealed a decrease in phospho mTOR in cancer lines, but an increase in phosphor Akt was detected. **Conclusions:** Our results suggest a trend of commonalities between the two diseases; however, specific variations require further investigation to confirm this trend.

Disclosures: J. Padilla-Mendoza: None. **M. Silva-Lucero:** None. **M. Cardenas-Aguayo:** None.

Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.01/C36

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: TJL Directors Innovation Fund
AARF Alzheimer's Association

Title: Lipid Dysregulation in Normal Aging and Alzheimer’s disease: Spatial and Cellular Insights using Mass Spectrometry Imaging

Authors: *S. SINGH[1], T. STODOLA[1], B. N. GURDON[1], A. DUNN[2], B. HOFFMANN[1], K. O'CONNELL[1];
[1]The Jackson Lab., Bar Harbor, ME; [2]The Jackson Lab., BAR HARBOR, ME

Abstract: Lipids are a major component of brain tissue and play a crucial role in overall brain health. Numerous studies indicate disruption of lipid homeostasis in physiological aging, and various neurodegenerative diseases. Recent technological advancements have expanded our understanding of the complex biochemical landscape of the brain, among them are mass spectrometry-based methods which could provide compound-level resolution of molecules including proteins/lipids and provide insight into their functional roles in the brain. In our current study, we performed MALDI mass spectrometry imaging (MSI) using timsTOF fleX to understand the region- and cell- type specific changes in lipid composition during normal aging and Alzheimer’s disease (AD). We used male and female, 5XFAD (AD) and C57BL/6J (Ntg) mice at young (4 months), middle (18 months), and old (25 months) age (total n= 37). We identified ~476 unique named lipids in our dataset. Significant changes in lipid composition were observed in normal aging and Alzheimer’s disease groups. Further for targeted analysis of lipid changes in the brain we used Biocrates Quant 500 XL on the Thermo Altis Plus QQQ mass spectrometer coupled to a Vanquish chromatography system to study 1019 compounds, including 912 lipids. Overall, our study presents novel insights into regional and cell type specific changes in lipid composition in normal aging and AD, combining this information with other single single-cell approaches can provide a deeper understanding of molecular events leading to AD progression, as well as identify novel therapeutic targets that may be leveraged in early or late disease stages to improve clinical outcomes.

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Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.02/C37

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Director's Innovation Fund, TJL
Simons Collaboration on Plasticity in the Aging Brain

Title: Use of Patch-Proteomics for multimodal analysis of electrophysiological and proteomic properties of single neurons in aging and Alzheimer's disease

Authors: B. HOFFMANN[1], T. ZHAO[2], T. STODOLA[1], N. IACOVOU[2], H. KAUR[3], A. DUNN[1], ***K. O'CONNELL**[2];
[1]The Jackson Lab., BAR HARBOR, ME; [3]Res., [2]The Jackson Lab., Bar Harbor, ME

Abstract: Neurons and circuits are dynamic systems that need to be able to rapidly and stably tune their output in response to variable input for high-fidelity information processing, storage, and transfer. Molecular degeneracy in this process is likely essential to achieve the flexibility and plasticity required for neurons to adapt to changing stimuli and points to a potential mechanism governing resilience and susceptibility to age-related cognitive decline and overall brain health. Transcriptome-based approaches such as Patch-seq have been invaluable for understanding the molecular diversity of the brain in the context of neuronal function, but the predictive value of mRNA-based information is based on the assumption that transcript levels are well-correlated with protein expression and thus, neuronal function. It is increasingly clear that transcript and protein levels can be highly discordant, particularly in the brain. Defects in proteostasis and post-translational pathways are commonly observed in the aging brain and in neurodegenerative diseases such as Alzheimer's disease. The loss of concordance between transcript levels and protein expression may be a causal factor in age- and disease-associated declines in cognitive function. Here, we leverage recent advances in the speed and sensitivity of mass spectrometry technology for unbiased assessment of the expression of thousands of proteins in single neurons. We used whole-cell patch clamp of subicular neurons from the hippocampus of male and female, Ntg and 5XFAD mice at 6, 12, and 18m of age to characterize the impact of age, sex, and genotype on neuronal function, then measured unbiased protein expression using a Bruker timsTOF Ultra2 mass spectrometer. In 96 patched neurons, we detected 7120 unique proteins, with an average of 5011 proteins/cell. We also measured protein levels in 2-cell pools to estimate saturation of the cellular proteome; only 6 proteins were unique to the pooled samples. The scProteomes had coverage of 4 Nav, 15 Kv, 5 Cav, and 2 HCN channel subunits, along with 15 glutamate receptor subunits and 3 GABA-A subunits, suggesting that Patch-proteomics captures nearly the entire somatic proteome, including ion channels and receptors known to govern neuronal excitability.

Disclosures: B. Hoffmann: None. **T. Zhao:** None. **T. Stodola:** None. **N. Iacovou:** None. **H. Kaur:** None. **A. Dunn:** None. **K. O'Connell:** None.

Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.03/C38

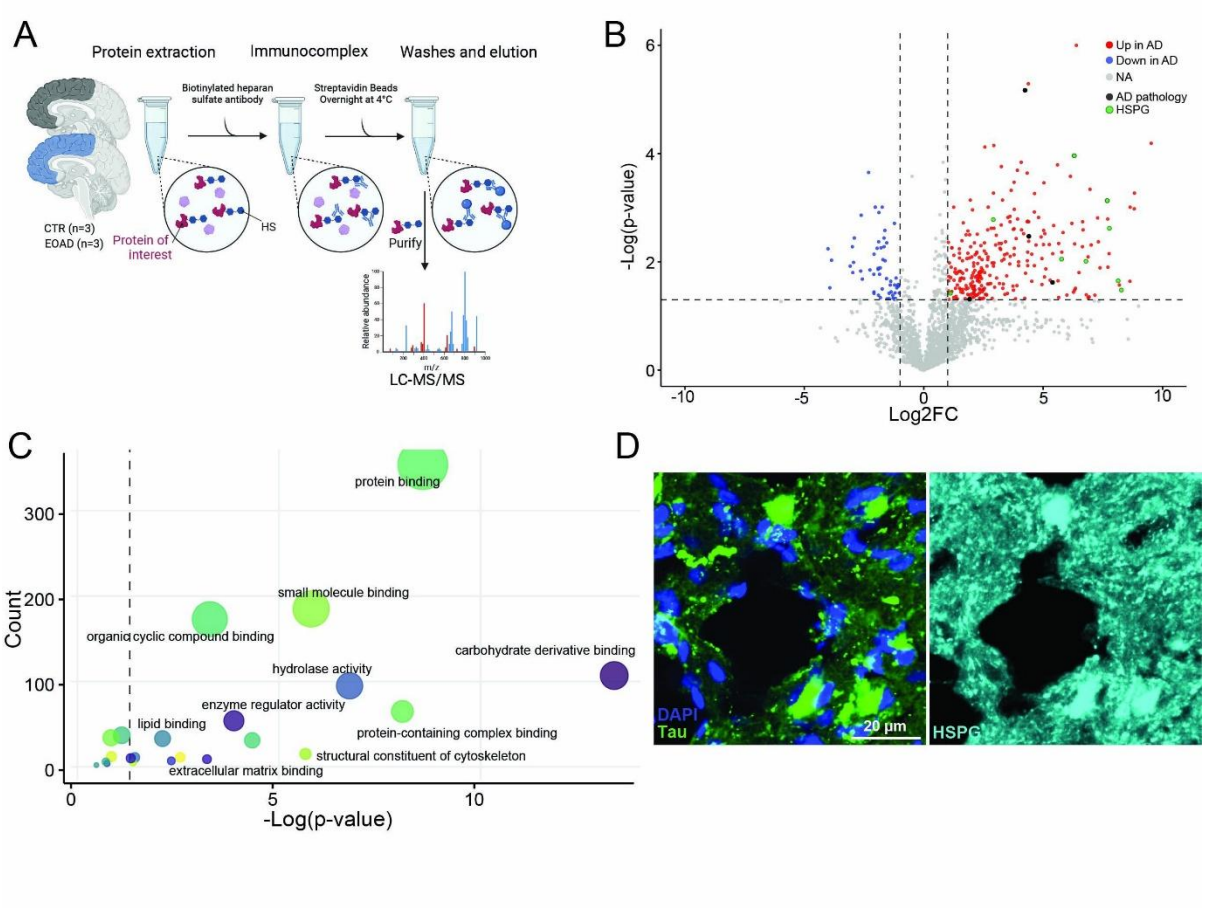
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Open Philanthropy
Aging Brain Initiative through the Picower Institute of Learning and Memory
Lisa Yang
NIH Grant R01AG087374
Tom Stocky and Avni Shah
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Kathleen Octavio

Title: Heparan sulfate proteoglycans mediate Tau pathology in Alzheimer's disease

Authors: *S. WANG[1,2], C. ORTIZ[1,2], O. KING[1], E. YU[1], L. AKAY[1], E. RIVERA[3], N. VILLALBA MORENO[4], J. VILLALBA MORENO[4], S. NAGUIB[5], P. PEREZ[6], C. MARINO[7], L. GAN[5], K. S. KOSIK[3], J. ARBOLEDA-VELASQUEZ[6], D. SEPULVEDA-FALLA[4], L.-H. TSAI[1], E. S. BOYDEN[1,8], L. L. KIESSLING[1,2];
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Abstract: Heparan sulfate proteoglycans (HSPGs) have emerged as critical modulators of Alzheimer's disease (AD) pathogenesis and resistance. Notably, individuals carrying the PSEN1 E280A mutation who also carry genetic variants that affect HSPG binding—such as the APOE3 Christchurch (which reduces ApoE-HSPG binding) or the RELN-COLBOS (which increases Reelin-HSPG binding)—have delayed cognitive decline despite having expected AD pathology. These observations suggest that HSPG interactions contribute to disease resilience and motivate further investigation into their mechanistic role in AD.
We investigated the role of HSPGs in AD pathology and tau internalization through a multifaceted approach using optimized immunoprecipitation and expansion microscopy protocols for HSPGs. In familial AD patient brain tissue, we found marked upregulation of HSPGs and their interacting partners—including Tau, ApoE, and LDL receptor-related proteins (LPRs)—compared to non-AD controls. Spatial mapping via expansion microscopy further revealed HSPG colocalizing with canonical AD markers across disease stages in patient brains, underscoring their involvement in the molecular architecture of AD.
Finally, informed by immunoprecipitation and imaging results, we conducted functional studies in neuron-astrocyte co-cultures and studied the impact of HSPG deletions on tau internalization. Collectively, our findings establish HSPGs as pivotal regulators of AD pathology and identify potential therapeutic targets for promoting cognitive resilience.



Disclosures: **S. Wang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SW is an inventor on patents related to expansion microscopy. **C. Ortiz:** None. **O. King:** None. **E. Yu:** None. **L. Akay:** None. **E. Rivera:** None. **N. Villalba Moreno:** None. **J. Villalba Moreno:** None. **S. Naguib:** None. **P. Perez:** None. **C. Marino:** None. **L. Gan:** None. **K.S. Kosik:** None. **J. Arboleda-Velasquez:** None. **D. Sepulveda-Falla:** None. **L. Tsai:** None. **E.S. Boyden:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ESB is an inventor on many patents related to expansion microscopy, and co-founded a company to explore commercial applications thereof. **L.L. Kiessling:** None.

Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.04/C39

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: K24AG053435
AG064314
AG060477
Rainwater Charitable Foundation

Title: Resilience of histaminergic neurons to tau toxicity: A therapeutic target to mitigate sleep-wake dysfunction in Alzheimer's disease

Authors: *A. SATPATI[1], F. PEREIRA[2], A. SOLOVIEV[4], M. MLADINOV[6], S. LI[5], C.-L. TU[7], A. J. EHRENBERG[8], R. E.P LEITE[9], C. SUEMOTO[10], C. M. WALSH[4], S. SPINA[4], W. W. SEELEY[5], T. NEYLAN[5], L. GRINBERG[3];
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Abstract: Sleep disturbances are common in Alzheimer's disease (AD) and often precede cognitive decline**.** Recent findings, including key contributions from our group, suggest that disruptions in the *wake* portion of the sleep-wake cycle are prominent and are driven by early tau-related degeneration of key wake-promoting neurons, such as the adrenergic and orexinergic neurons. In contrast, wake-promoting histaminergic (HA) neurons appear to be relatively spared. This selective resilience suggests that HA neurons may be a potential therapeutic target for modulating wakefulness in AD. However, more research is needed to fully understand the structural and molecular changes these neurons undergo during AD progression, and what underlies their apparent resistance. Here, we interrogated the transcriptomic signatures and changes in the TMN neuronal phenotype across progressive AD stages in post-mortem human brain samples. We employed customized neuropathology and glial-profile panels of the Nanostring nCounter platform for transcriptome profiling (n=27). We compared the groups with Wald's statistical test, with the genes identified as differentially expressed at $p<0.05$. Concurrently, we quantified double-immunolabeled hypothalamic sections using unbiased stereology to track changes in the TMN neuronal population (n=26). Comparisons of volume, total neuronal counts, number of HA, and non-HA neurons with or without p-tau (Ser202) between the groups in progressive stages were performed using the paired Wilcoxon test. Transcriptomics data revealed enrichment of the cytokine-cytokine receptor interaction KEGG pathway, with upregulation of anti-inflammatory and pro-survival genes in TMN at the Braak stages (BB) V-VI, compared to stages 0-II. HA synthesizing gene HDC was downregulated; in contrast, HA receptor genes H1 and H2 were upregulated, indicating a possible compensatory shift in the HA system. The stereological analysis demonstrated that the TMN volume and total neuronal numbers remained constant during the progression of AD. However, a significant alteration in the neuronal phenotype in the TMN was evident, where the number of $HA^{p\text{-}tau+}$ neurons increased exponentially in BB III-IV and V-VI over 0-II. In contrast, $HA^{p\text{-}tau-}$ neurons declined significantly in BB V-VI compared to 0-II and III-IV. Our results indicate that, despite extensive p-tau accumulation, HA neurons demonstrate resilience through upregulation of anti-inflammatory and pro-survival genes. Interventions aimed at reversing the phenotypic changes in HA neurons and modulating immune gene/pathways can restore the sleep-wake cycle and enhance the quality of life for AD patients.

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Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.05/C40

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA R01AG068293
Rainwater Foundation
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Cure Alzheimer's Fund

Title: 3d reconstruction of tau pathology in alzheimer's hippocampus using subcellular spatial multiomics

Authors: K. ROBERTS[1], T. ORR[3], S. KOUTARAPU[4], L. WU[5], K. YOUNG[6], C. WILLIAMS[6], M. HOANG[7], C. S. LATIMER[9], C. D. KEENE[10], E. ROSA-MOLINAR[11], D. M. OAKLEY[2], J. BEECHEM[8], ***M. E. ORR**[4];
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Abstract: In Alzheimer's disease (AD), phosphorylated tau accumulates in dystrophic neurites and forms neurofibrillary tangles (NFTs) within neurons. These hallmark lesions strongly associate with neurodegeneration and cognitive decline, yet NFT-bearing neurons resist apoptosis. To investigate the molecular architecture and spatial context of these cells, we applied the CosMx Spatial Molecular Imager (SMI), enabling high-plex, subcellular-resolution detection of RNA and proteins in formalin-fixed, paraffin-embedded (FFPE) human hippocampal tissue. Using oligonucleotide-conjugated antibodies followed by barcoded RNA probes, we profiled over 68 proteins—including total and phosphorylated tau isoforms—alongside whole-transcriptome RNA data in samples from individuals with AD and age-matched controls. To examine the ultrastructural context of pathology-associated cells, we performed post-CosMx serial section electron microscopy on lifted sections, generating 3D reconstructions of NFT-bearing neurons and their neurites. This approach provided nanometer-scale detail of cytoarchitecture and the surrounding cellular milieu, enabling correlation of spatial molecular profiles with ultrastructural features. Our analysis revealed that NFT-bearing neurons evade

death by entering a senescent-like state, characterized by stable cell cycle arrest and proinflammatory signaling. We identified morphological changes and altered neuronal architecture associated with tau pathology, along with distinct glial environments. Spatial analysis uncovered co-expressed gene and protein modules, as well as molecular pathways enriched within and around dystrophic neurites and NFTs. These findings, contextualized by 3D EM, reveal structural and molecular remodeling in neurons and glia associated with tau pathology. By integrating spatial multiomics with ultrastructural imaging, our study suggests that AD lesions may promote cellular senescence and contribute to local tissue reorganization, generating new hypotheses about disease mechanisms and potential therapeutic strategies.

Disclosures: K. Roberts: None. **T. Orr:** Other; Bruker Spatial Biology Center of Excellence. **S. Koutarapu:** None. **L. Wu:** A. Employment/Salary (full or part-time): Nanostring, a Bruker Company. **K. Young:** A. Employment/Salary (full or part-time): Nanostring, a Bruker Company. **C. Williams:** A. Employment/Salary (full or part-time): Nanostring, a Bruker Company. **M. Hoang:** A. Employment/Salary (full or part-time): Nanostring, a Bruker Company. **C.S. Latimer:** None. **C.D. Keene:** None. **E. Rosa-Molinar:** None. **D.M. Oakley:** None. **J. Beechem:** A. Employment/Salary (full or part-time): Nanostring, a Bruker Company. **M.E. Orr:** Other; Bruker Spatial Biology Center of Excellence.

Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.06/C41

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Institutes of Health Grant U01 AG024904
ADNI DOD (Department of Defense award number W81XWH-12-2-0012)
NLM R01 LM012535
NIA R03 AG063250
NIA R01 AG19771
NIA P30 AG10133
NIA P30 AG072976

Title: Epigenetic signatures as indicators of Alzheimer’s Disease (AD)

Authors: *S. LIU[1], T. PARK[1], A. KRUNIC[3], T. J. MELLOTT[4], J. K. BLUSZTAJN[5], A. J. SAYKIN[2], I. DELALLE[6], A. FISCHER[7], K. NHO[2];
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Abstract: Despite advances in blood-based biomarkers for detecting AD-associated beta-amyloid or Tau pathology, significant challenges remain due to the complex nature of AD, which is characterized by dysregulated gene expression driven by a combination of genetic and environmental risk factors. There is substantial gain in identifying the upstream molecular signals that cause abnormal gene expression. Recent studies using the *App*$^{NL-G-F}$ mouse model of AD have shown that perinatal choline supplementation leads to reduced Aβ42 deposition and improved cognitive performance through the reduction of amyloidogenic APP processing, oxidative stress and mitochondrial dysfunction. The underlying mechanism is likely mediated by changes in DNA methylation as dietary choline leads to the production of S-adenosylmethionine used to methylate DNA. Genome-environment interactions are further orchestrated by microRNAs (miRNAs, miRs), short non-coding RNAs that regulate gene expression and proteostasis implicated in cognition and, as such, have been extensively studied in the context of AD. Consistently, our small RNA sequencing of plasma samples collected at baseline from 847 participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) identified miRNAs with levels significantly associated with A/T/N positivity and AD diagnosis. Importantly, we discovered miRNAs with changes in the level of expression which helped predict the conversion from *early* mild cognitive impairment (MCI) to AD. Here we sought to explore whether miRNA candidate biomarkers of EMCI to AD, when combined with DNA methylation, could further enhance the prediction of diagnosis and conversion. To that end, we evaluated subgroup of our ADNI participants data set comprised of 335 individuals (30 AD, 212 MCI, and 93 controls, CN) with plasma small RNAome, as well as DNA methylation data (~800,000 CpGs) available. We identified an association between methylation at cg11717189 and the expression of hsa-miR-483, which is upregulated in amyloid-positive individuals. Currently, we are investigting these epigenetic mechanisms in mouse models to understand their functional roles, with the ultimate goal of developing stratified therapeutic strategies for AD.

Disclosures: S. Liu: None. **T. Park:** None. **A. Krunic:** None. **T.J. Mellott:** None. **J.K. Blusztajn:** None. **A.J. Saykin:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Avid Radiopharmaceuticals, a subsidiary of Eli Lilly (in kind contribution of PET tracer precursor). F. Consulting Fees (e.g., advisory boards); Bayer Oncology, Eisai, Novo Nordisk, and Siemens Medical Solutions USA, Inc, an Observational Study Monitoring Board (MESA, NIH NHLBI), several other NIA External Advisory Committees. Other; Editor-in-Chief of Brain Imaging and Behavior, a Springer-Nature Journal.. **I. Delalle:** None. **A. Fischer:** None. **K. Nho:** None.

Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.07/C42

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01AG064314
NIH R01AG075802-03

Title: Spatially resolved molecular signatures of selective tau vulnerability in the human master circadian clock in Alzheimer's disease

Authors: *G. SON[1,2], M. MLADINOV[2], F. PEREIRA[1,2], G. JUDGE[2], S. LI[2], W. LEE[2], C.-L. TU[3], Y. YANG[2], C. SUEMOTO[5], S. SPINA[2], W. SEELEY[2], W. CHANG[3], T. NEYLAN[2,4], L. GRINBERG[1,2,5];
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Abstract: Individuals with Alzheimer's disease (AD) frequently experience circadian rhythm disruptions. These rhythms are orchestrated by the suprachiasmatic nucleus (SCN), a small bilaterally positioned in the hypothalamus considered the master circadian clock in humans. While numerous studies have investigated circadian disturbances in AD models, our understanding of in situ molecular and pathological changes in the human SCN during AD progression remains limited. This gap is largely due to the scarcity of well-characterized, high-quality human SCN tissue and technical limitations. To address this gap, we leveraged access to a unique clinicopathological cohort, deep expertise in quantitative neuropathology, and emerging spatial omics optimized for postmortem tissue. We analyzed 40 human SCN, including controls and individuals at progressive AD based on Braak staging (Braak). We conducted quantitative neuropathological analyses to test neuronal loss and lesion burden. We quantified the number of neurons expressing arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP), essential for circadian regulation, and evaluated the accumulation of neurofibrillary tangles (NFT) and neuritic plaques. We then applied the GeoMx Digital Spatial Profiler (DSP) to quantify 57 spatially resolved proteins involved in AD pathology. To contextualize SCN specific findings, we included two adjacent hypothalamic nuclei, the supraoptic nucleus (SON) and paraventricular nucleus (PVN). These regions contain neurons with similar neurochemical profiles to the SCN but are known to exhibit different neuronal vulnerability to AD. Our findings indicate that NFT selectively accumulate within the SCN during AD progression. Conversely, NFT were absent in the SON, and only mild phosphorylated tau (pTau) dysregulation was noted in PVN and SON at Braak VI. Neuritic plaques were not observed in all three nuclei, whereas diffuse plaques were detected exclusively in the PVN. Additionally, glial proteins increased in the SCN as early as Braak I, accompanied by dysregulation in autophagy and lysosomal proteins with pTau. These changes either remained stable or exhibited distinct patterns in the SON and PVN. In conclusion, the SCN displays a distinct profile of AD-related tau accumulation, glial and autophagy dysregulation beginning in the AD progression, a pattern not observed in adjacent nuclei. This selective vulnerability suggests a potential mechanistic link to the circadian rhythm disturbances in AD. Future studies integrating functional assessments with spatial and molecular analyses will be essential to determine how these early SCN alteration.

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Neylan: A. Employment/Salary (full or part-time): UCSF. **L. Grinberg:** A. Employment/Salary (full or part-time): Mayo Clinic.

Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.08/C43

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fisher Foundation

Title: CLIP-FANS: Identifying Cell-type Specific RNA Regulation Changes in Human Postmortem Tissue

Authors: *D. OH[1], R. SINGER[2], M. SIANTOPUTRI[3], N. HEINTZ[3], R. B. DARNELL[2]; [1]Rockefeller Univ., New York, NY; [2]Lab. of Mol. Neuro-Oncology, [3]Lab. of Mol. Biol., The Rockefeller Univ., New York, NY

Abstract: Spatial and temporal regulation of RNA is key to cellular homeostasis and can become disrupted in disease. The lifecycle of RNA can include splicing, modification, transport, and translation, which all require RNA-binding proteins (RBPs), a class of proteins that bind and regulate RNAs. Specifically in the brain, there are many neuronal and non-neuronal cell types that are each comprised of distinctive sets of transcripts with unique RNA regulatory machineries. There thus exists a need to study RNA regulation in a cell-type specific manner, which is currently inaccessible in human postmortem brain tissue. Crosslinking Immunoprecipitation-Fluorescence Activated Nuclei Sorting (CLIP-FANS) allows us to achieve this goal by building on two previous methodologies: fluorescence-activated nuclei sorting (FANS) to achieve cell-type specificity, followed by high-throughput sequencing of RNA isolated by crosslinking immunoprecipitation (HITS-CLIP) to analyze gene regulation in sorted populations. Here, we have built an ordered approach, which we have termed CLIP-FANS, and show similarities and differences in the Hu-binding between excitatory and inhibitory neurons in the human entorhinal cortex and the BA9 region of the dorsolateral prefrontal cortex of control and Alzheimer’s disease (AD) donors as a first iteration of CLIP-FANS. Furthermore, we compare CLIP-FANS generated cell-type specific data to a previously generated cell-agnostic CLIP dataset in BA9 of control and AD samples. Additionally, we have developed a sorting strategy to isolate cell types of interest in the entorhinal cortex, a key region of interest in AD progression, to study gene expression and RBP-mediated RNA regulatory differences in Alzheimer’s disease samples. We will further utilize CLIP-FANS to address a wide range of biological questions about the factors regulating RNAs and their role in neurological disorders.

Disclosures: D. Oh: None. **R. Singer:** None. **M. siantoputri:** None. **N. Heintz:** None. **R.B. Darnell:** None.

Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.09/C44

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fisher Foundation

Title: Deep molecular profiling of neuronal cell types in the human hippocampus

Authors: *M. SIANTOPUTRI[1], D. OH[2], C. PRESSL[2], N. HEINTZ[3];
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Abstract: The hippocampus, a critical region for learning, memory, and spatial cognition, is selectively vulnerable in Alzheimer's Disease (AD). CA1 pyramidal neurons of the hippocampus accumulate tau neurofibrillary inclusions and degenerate in the early stages of AD, followed closely by the onset of clinical symptoms. The molecular mechanisms that dictate the differential vulnerability of CA1 neurons compared to other neuronal cell types have been elusive. Here, we utilized Fluorescent Activated Nuclei Sorting (FANS) followed by RNA sequencing to characterize major neuronal cell types from postmortem human hippocampus. This project aims to characterize intrinsic molecular pathways in hippocampal neurons that render them more susceptible to tau and discover a way to inhibit them, thereby preventing the progression of symptoms in AD.

Disclosures: M. siantoputri: None. **N. Heintz:** None.

Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.10/C45

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: 5R01HG01063
Howard Hughes Medical Institute

Title: Single-cell multiomic profiling reveals disease-associated cell states in Alzheimer's disease brains

Authors: *W. WANG[1], P. BERUBE[2], B. YANG[3], N. R. ZEMKE[4], D. H. OAKLEY[5], B. REN[6], B. HYMAN[7], J. R. ECKER[8];

[1]Salk Inst. for Biol. Studies, San Diego, China; [2]UCSD, La Jolla, CA; [4]Cell. and Mol. Med., [3]UCSD, San Diego, CA; [5]Pathology, Massachusetts Gen. Hosp. & Harvard Med. S, Charlestown, MA; [6]UC San Diego, La Jolla, CA; [7]Neurol., Massachusetts Gen. Hosp., madison, NH; [8]PBIO-E, Salk Inst., La Jolla, CA

Abstract: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, yet its cell type-specific epigenomic regulation remains incompletely understood. To address this, we collected postmortem brain tissue from 11 individuals with AD and 9 age- and sex-matched controls across three brain regions: the temporal cortex, prefrontal cortex, and primary visual cortex. We performed single-cell multiomic profiling, integrating DNA methylation, chromatin conformation, chromatin accessibility, and transcriptional data. Our analysis uncovered widespread DNA methylation alterations across multiple brain regions and cell types. In parallel, we observed significant changes in 3D genome architecture, including alterations in A/B compartments, topologically associating domains (TADs), and chromatin loops. Using linear regression modeling, we identified features associated with AD within each modality and found that brain region strongly influenced disease associations: features in the temporal cortex and primary visual cortex showed opposing AD-related patterns, with the prefrontal cortex exhibiting intermediate profiles. Importantly, we identified disease-associated cell states across multiple cell types in all three brain regions, characterized by coordinated changes across the four molecular layers. Together, this work provides a comprehensive multi-regional and multi-modal single-cell epigenomic atlas of the AD brain and reveals region- and cell-type-specific regulatory changes underlying AD pathology.

Disclosures: W. Wang: None. **P. Berube:** None. **B. Yang:** None. **N.R. Zemke:** None. **D.H. Oakley:** None. **B. Ren:** None. **B. Hyman:** None. **J.R. Ecker:** None.

Poster

PSTR108: Omics Approaches for Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.11/C46

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG064656
NIH Grant AG079797

Title: Identification of Epigenomic Aberrations in Humans with Mild Cognitive Impairment or Alzheimer's Disease

Authors: *P. J. PATEL, Z. YAN;
Physiol. and Biophysics, State Univ. of New York at Buffalo, Buffalo, NY

Abstract: Epigenetic mechanisms, particularly histone modifications at gene promoters, are crucial for neuronal gene regulation. Aberrant histone marks may contribute to the transcriptional changes underlying Alzheimer's Disease (AD) progression. This study aimed to

map alterations in two key histone modifications—H3K4me3 (associated with gene activation) and H3K27me3 (associated with gene repression)—at promoter regions in human brain tissue from individuals with Mild Cognitive Impairment (MCI) and AD, and to correlate these changes with gene expression profiles. H3K4me3 and H3K27me3 ChIP-seq (chromatin immunoprecipitation followed by sequencing) data were obtained from postmortem prefrontal cortex samples from cognitively normal controls (Ctrl, n=11), MCI (n=11), and AD (n=17) donors. Differential binding analyses identified promoters with significantly altered histone occupancy in disease versus control (Fold $\geq |1.1|$, p-value ≤ 0.05). Weighted Gene Correlation Network Analysis (WGCNA) was employed to cluster genes into module eigengenes (MEs) based on shared binding dynamics. The differential analysis results were integrated into the resulting MEs to generate correlation networks with significantly altered genes. Functional enrichment pathway analyses were conducted to ascertain biological impact. Compared to controls, brains of individuals with MCI and AD exhibited pronounced losses of H3K4me3 at promoters of genes enriched in synaptic plasticity and neurotransmission. These losses were paralleled by significant gains of H3K4me3 at promoters of genes enriched in transcriptional regulation. AD brains displayed more substantial losses of synaptic genes compared to MCI. Conversely, significant gains of repressive H3K27me3 were observed at synaptic gene promoters in both disease groups, with MCI exhibiting more pronounced gains than AD. WGCNA revealed multiple modules characterizing distinct patterns of gains and losses of histone modifications during the transition from MCI to AD. Integrative analysis of epigenomic and transcriptomic data indicated that histone mark alterations were well correlated with the down-regulation of synaptic gene expression and up-regulation of transcriptional regulators in AD. This comprehensive profiling uncovers a stage-dependent reorganization of histone modifications at critical neuronal gene loci, implicating these events in the molecular cascade of AD pathogenesis. Targeting dysregulated chromatin states may offer novel therapeutic avenues for early intervention.

Disclosures: P.J. Patel: None. **Z. Yan:** None.

Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.01/C47

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Accelerating the maturation of human iPSC-derived neurons for modeling synaptic dysfunction

Authors: T. MIYAJIMA, M. FUJIKADO, K. MURAMATSU, S. SHIOMOTO, Y. EGUCHI, ***W. LIN**;
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Abstract: The analysis of synapse formation and function using human induced pluripotent stem cell (iPSC)-derived neurons is expected to drive progress in the elucidation of neurodegenerative disease mechanisms and the evaluation of drug responses. We have previously reported the successful generation of functionally mature neurons by transcription factor-induced differentiation of human iPSCs. However, extended culture periods of several weeks are necessary to attain full maturation, which includes the acquisition of a postnatal-like profile and the extensive formation of dendritic spines. This poses a considerable challenge to practical application in assay development.
To address this issue, we investigated the effects of a compound that has been found to promote dendrite elongation in a chemical library screening assay. A three-month time-course study demonstrated that the iPSC-derived neurons exposed to the compound exhibited a significant increase in dendrite length and in the expression of genes associated with synapse formation compared to the vehicle-treated control group. Furthermore, artificial intelligence (AI)-assisted imaging analysis revealed an increased presence of Synapsin I and drebrin clusters along the dendrites, confirming the enhanced formation of synapses and dendritic spines. Concomitantly, electrophysiological analysis using high-density microelectrode arrays (HD-MEA) revealed the occurrence of network bursts at an earlier stage in the compound-treated neurons. Finally, as an example of application using mature iPSC-derived neurons, we conducted a comparative analysis of Alzheimer's disease (AD) patient-derived neurons and healthy donor-derived neurons. The results indicated substantial differences in characteristics discernible exclusively in fully mature neurons, including deficiencies in spine formation and impaired network connectivity.
The present study demonstrates that the maturation and synaptogenesis of human iPSC-derived neurons can be significantly accelerated *in vitro* through the optimization of culture conditions, facilitating the investigation of phenotypes relevant to human brain functions. This advancement holds great promise for leveraging iPSC-derived neurons in drug screening and disease modeling, paving the way for innovative future research in this field.

Disclosures: **T. Miyajima:** A. Employment/Salary (full or part-time): Ricoh Company, Ltd. **M. Fujikado:** A. Employment/Salary (full or part-time): Ricoh Company, Ltd. **K. Muramatsu:** A. Employment/Salary (full or part-time): Ricoh Company, Ltd. **S. Shiomoto:** A. Employment/Salary (full or part-time): Ricoh Company, Ltd. **Y. Eguchi:** A. Employment/Salary (full or part-time): Ricoh Company, Ltd. **W. Lin:** A. Employment/Salary (full or part-time): Ricoh Company, Ltd..

Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.02/C48

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: UK DRI Ltd Grant XCPD2019–01 funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK
Wellcome Trust Grant 218293/Z/19/Z

Title: The cortical synaptome signature in Alzheimer's Disease and the aging brain

Authors: *J. L. GRIFFITHS[1], B. NOTMAN[1], Z. QIU[1,2], K. YUAN[1], D. DOMINIC[1], W. QUAH[1], C. SMITH[1], S. G. GRANT[1];
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Abstract: Synaptic alterations are hallmark features of aging and neurodegenerative diseases such as Alzheimer's disease (AD). However, the nature, extent, and mechanisms of these changes differ between healthy aging and AD. The human synaptome—the complete set of synapses in the brain—is highly diverse, comprising numerous types and subtypes that vary in molecular composition, turnover rates, nanoarchitecture, and morphology. Selective vulnerability of certain synapse populations to age and AD-related pathology may underlie mechanisms of cognitive decline. To investigate this, we have developed a single-synapse resolution synaptome mapping technology to analyse billions of individual synapses in human post-mortem cortical tissue. We applied immunofluorescent labelling, high-resolution spinning disk confocal microscopy, and a machine learning-based analysis to detect and classify individual synapse types and subtypes in human post-mortem tissue. We employed a high-throughput screening approach to analyse key pre- (SYP, SV2A, VGLUT1, VGLUT2, VGAT) and post- (PSD95, PSD93, GluN1, GluA2, GPHN) synaptic proteins across three cortical regions along the rostro-caudal axis—the prefrontal, middle temporal, and primary visual cortex—sampling all layers of the cortex. We identified region- and layer-specific losses of specific synapse types in aging and AD, with differential effects on excitatory and inhibitory synapses, and between pre- and post-synaptic terminals. Some common features were observed between AD and aging, suggesting AD exacerbates aspects of the normal aging process. Spatial analyses revealed distinct relationships between synaptic changes and neuropathological markers such as phosphorylated tau (pTau, AT8) and amyloid-beta (Aβ, 6E10). Our comprehensive synaptome maps reveal both vulnerable and resilient synapse populations in aging and AD. These findings advance understanding of the synaptic basis of cognitive decline and highlight potential targets for therapeutic intervention. Mapping synapse vulnerability is key to developing strategies for diagnosing and treating age-related and AD-associated neurodegeneration.

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Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.03/C49

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R01AG057964-01
VA Merit 1I01 BX002211-01A2
NIA R21AG055090-01A1.
NIA T32 AG021890.

Title: Transmission of pathogenic tau to astrocytes induces astrocyte senescence and compromises neuronal integrity

Authors: *H. MAKHLOUF[1], R. KAYED[2], V. GALVAN[3];
[1]Univ. of Oklahoma Hlth. Sci. Ctr., OKC, OK; [2]Neurol., Univ. of Texas Med. Br., Galveston, TX; [3]Dept. of Biochem. and Physiol., Univ. of Oklahoma Hlth., Oklahoma City, OK

Abstract: Alzheimer's disease (AD), the most prevalent form of dementia, is characterized by the accumulation of intracellular tau aggregates. In AD, tau in neurons becomes hyperphosphorylated and misfolded, forming pathogenic soluble aggregates (tau oligomers) that detach from microtubules and destabilize the microtubule cytoskeleton. Pathogenic tau is released from neurons during neuronal activation and is transmitted to postsynaptic cells in a prion-like manner. In addition to neurons, tau is expressed in a variety of brain cell types, including astrocytes. Astrocyte dysfunction has emerged as a key contributor to disease progression in AD. Cellular senescence is a permanent state of cell cycle arrest also characterized by the secretion of proinflammatory mediators, the senescence-associated secretory phenotype (SASP). Aging, cellular stress, and damage are known inducers of cellular senescence. In this study, we tested the hypothesis that pathogenic tau can be transmitted to astrocytes and that tau transmission to astrocytes induces senescence, compromising astrocyte support of neuronal structure. Specifically, we asked whether tau-induced astrocyte senescence would alter astrocyte-neuron interactions and contribute to dendritic and synaptic deterioration, a hallmark of neuronal dysfunction that leads to cognitive impairment in AD. We found that pathogenic tau oligomers are readily transmitted to primary human astrocytes, where they trigger phosphorylation of endogenous astrocyte tau and destabilize the microtubule cytoskeleton. Tau transmission to astrocytes also induced senescence, measured as the concomitant upregulation of multiple cell cycle arrest and SASP markers. Of note, neurons exposed to tau-senescent astrocytes lost over 50% of dendritic spine density and 75 % of their dendritic area. Our data established, for the first time, that tau transmission to astrocytes induces astrocyte senescence and that astrocyte senescence can compromise neuronal integrity and thus contribute to synaptic dysfunction in AD.

Disclosures: H. Makhlouf: None. **R. Kayed:** None. **V. Galvan:** None.

Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.04/C50

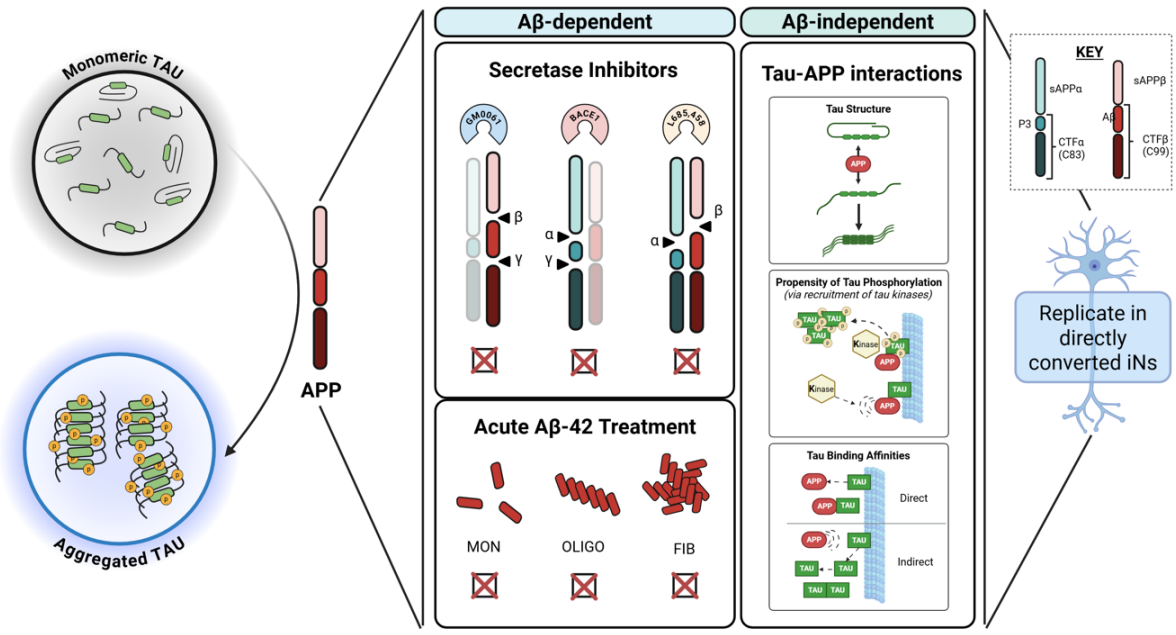
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R01 AG058851
Clear Thoughts Foundation

Title: The role of the amyloid precursor protein (APP) on tau pathogenesis in Alzheimer's Disease (AD)

Authors: *A. YUWONO, T. RAFAEL GUIMARAES, A. THATHIAH;
Neurobio., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Background. Alzheimer's Disease (AD) is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs). Intriguingly, the amyloid precursor protein (APP), which is cleaved to generate Aβ, is specifically upregulated in NFT-bearing neurons. Moreover, familial mutations in *APP*, but not *MAPT*, play a causal role in AD development. Although APP pathobiology is undoubtably involved in AD progression, lack of appropriate models has hindered our understanding of the APP-tau relationship in AD.
Method. We investigated the involvement of APP in tau pathogenesis using HEK293 cells and patient-derived directly converted induced neurons (iNs), overexpressing APP and a novel, light-inducible optogenetic system of tau aggregation (optoTAU). We utilized biochemical and immunocytochemical analysis of total tau, phosphorylated tau (pTau), and APP to investigate a causal role and putative mechanisms through which APP influences tau pathogenesis.
Result. First, we show that APP overexpression in optoTAU expressing cells increases tau aggregation and pTau accumulation at several AD relevant sites. Despite correlational evidence for an Aβ and tau pathogenesis relationship, inhibition of APP proteolysis with secretase inhibitors and treatments with disease-relevant Aβ species does not affect tau aggregation. As such, we investigated Aβ-independent mechanisms through which APP may influence tau aggregation. We determined that tau and APP directly interact, and this interaction is increased in cells undergoing tau aggregation. Lastly, we show that APP overexpression enhances cytotoxicity regardless of tau aggregation, implicating APP as the putative trigger for neurodegeneration in AD brains.
Conclusion. Our results elucidate a direct role for APP on tau aggregation and provide evidence for a direct role of APP, not Aβ, on tau pathogenesis. Future studies aimed at investigating Aβ-independent mechanisms and cell death pathways in iNs will identify APP-dependent mechanisms governing tau pathogenesis.



Disclosures: A. Yuwono: None. **T. Rafael Guimaraes:** None. **A. Thathiah:** None.

Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

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Program #/Poster #: PSTR109.05/C51

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant R01 AG075809-01
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USU-UMN DOD partnership grant
R21-NS084007-01
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NSF CMMI 1935834

Title: Morphine prompts synaptic dysfunction via phosphorylation-dependent tau mislocalization.

Authors: *M. A. AGUINAGA[1], D. LIAO[2];
[1]Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Dept Neurosci, Univ. Minnesota, Minneapolis, MN

Abstract: Opioid use disorder (OUD) is a global health crisis and encapsulates a multitude of associated health complications including cognitive impairments such as memory loss. Gross neuropathology in OUD and neurodegenerative diseases, including Alzheimer's disease (AD), exhibit intracellular inclusions of hyperphosphorylated tau protein suggesting the potential for commonalities between their underlying cellular and molecular pathophysiological mechanisms. One mechanism shared between various neurodegenerative diseases is synaptic dysfunction preceded by phosphorylation-dependent tau mislocalization to dendritic spines. In primary hippocampal cultures from both sexes of neonatal rats and mice, we found that morphine treatment also induces tau phosphorylation, mislocalization, and decreases both amplitude and frequency of miniature excitatory postsynaptic currents (mEPSCs). The glycogen synthase kinase-3 beta (GSK3β) inhibitor CHIR99021, but not the CDK5 inhibitor CYC202, blocked morphine-induced tau mislocalization and the reduction in mEPSC amplitude, indicating the necessary role of tau phosphorylation by GSK3β in AMPA receptor (AMPAR) internalization. Notably, CHIR99201 did not block the reduction in mEPSC frequency, revealing that presynaptic dysfunction associated with morphine treatment does not rely on GSK3β. Tau knockout mice did not exhibit a decrease in mEPSC amplitude or frequency after morphine treatment, indicating that tau plays a vital role in both presynaptic and postsynaptic morphine induced impairments. Our work unveils an unreported mechanism in which morphine prompts pathophysiological tau interactions driving pre- and postsynaptic dysfunction of excitatory glutamatergic synapses, revealing deeper cellular and molecular parallels behind OUD and neurodegenerative disease.

Disclosures: M.A. Aguinaga: None. **D. Liao:** None.

Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

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Program #/Poster #: PSTR109.06/C52

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R01AG067762
NINDS R01NS082730

Title: Determinants of the interaction between tau and protein phosphatase 1

Authors: *M. A. PEREZ, N. M. KANAAN;
Translational Neurosci., Michigan State Univ., Grand Rapids, MI

Abstract: Tau is a microtubule-associated protein involved in microtubule-dependent and independent cellular functions, including acting as a scaffolding protein that regulates biological pathways. For example, tau plays such a role in regulating protein phosphatase 1 (PP1), a serine/threonine phosphatase. Like tau, PP1 is found in multiple neuronal compartments and is

involved in various biological processes. Notably, evidence suggests physiological and pathogenic tau species act as a PP1-scaffolding protein to modulate PP1γ1 function in fast axonal transport. However, several knowledge gaps remain in understanding the interaction between tau and PP1γ1. More specifically, it is unclear which residues or protein-binding motifs facilitate tau-PP1γ1 interactions. Tau contains three RVxF motifs (a well-established PP1-binding motif) and two endogenous cysteines (C291 and C322), which may facilitate intermolecular PP1γ1 interactions. Prior studies demonstrated that mutagenesis of PP1 residues D71, W206, and Y272 results in products which retain catalytic activity but attenuate interactions with established PP1 substrates or regulators. Therefore, we generated site- or motif-modified tau (all C-terminal NanoLuc tagged) and PP1γ1 (all N-terminal HaloTag) fusion constructs for use in HEK293T-based pulldown assays (all N=4 independent replicates, two-way ANOVA with Tukey's *post hoc* test). Protein biochemistry revealed that both cysless and ΔRVxF tau reduced interactions with PP1γ1, and modification of PP1γ1 residues reduced interactions with tau in the pulldown assays. NanoBRET, a quantitative in-cell protein-protein interaction assay, confirmed that the tau and PP1γ1 proteins assessed interact in live HEK293T cells (all N=4 independent replicates, one-way ANOVA with Dunnet's *post hoc* test). Ongoing work is focused on adapting the NanoBRET and HaloTag pulldown assays for use with primary neuron cultures and investigating the potential functional implications of tau-PP1γ1 interactions beyond the axon. Together, this work provides insights into the regions/residues in tau and PP1γ1 that may mediate the functional interaction between these proteins.

Disclosures: M.A. Perez: None. **N.M. Kanaan:** None.

Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

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Program #/Poster #: PSTR109.07/C53

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA 1R21AG077827-01

Title: Studying the role of brain enriched E3 Ubiquitin Ligase TRIM9 in Alzheimer's Disease/Tauopathies

Authors: *A. FRASINEANU[1], T. J. COHEN[2], S. L. GUPTON[3];
[1]Cell Biol. and Physiol., UNC CHAPEL HILL, Chapel Hill, NC; [2]Univ. of North Carolina - Chapel Hill, Chapel Hill, NC, ; [3]Cell Biol. and Physioloyg, UNC, Chapel Hill, NC

Abstract: In the last decade, we have demonstrated that the brain-enriched E3 ubiquitin ligase TRIM9 regulates cytoskeletal dynamics, membrane remodeling, and netrin-dependent signaling pathways in all stages of neuron development, including the maturation of dendritic spines and synaptic firing frequency. Moreover, TRIM9 protein levels are increased in the adult brain and

maintained throughout adulthood. TRIM9 is enriched within the postsynaptic density (PSD), a proteinaceous rich region in the post synapse, containing neurotransmitter receptors, scaffolding proteins, and cytoskeletal elements. Our proximity labelling experiments to characterize the TRIM9 interactome identified several proteins implicated in synaptic function and Alzheimer's disease (AD), including Tau. Here we investigate the role of TRIM9 in tau-mediated neurodegeneration, using the P301S (PS19) mouse model and primary neuronal cultures to understand the mechanistic role that TRIM9 plays in the adult brain. Broadly our data implicate TRIM9 in several aspects of neuronal degeneration, including cytoskeletal modification and aggregation, mitochondrial dysfunction, and neuroinflammation. For example, we found that Iba1+microglia are enriched in the hippocampus, entorhinal cortex, and amygdala of six month old *Trim9*$^{-/-}$*:PS19* mice compared to *Trim9*$^{+/+}$*:PS19* mice. Pathological tau (p-Tau stained with AT8) accumulation was significantly higher in the hippocampus and cortex of *Trim9*$^{-/-}$*:PS19* mice compared to *Trim9*$^{+/+}$*:PS19* mice. Ongoing experiments are exploring how pathology differs in 8 and 10 month old brain tissues, and if pathological tau accumulation is different in neuronal cultures from *Trim9*$^{+/+}$ or *Trim9*$^{-/-}$ mice. Unbiased quantitative proteomics of the cortical PSD fractions from six month old mice from showed that a subset of mitochondrial proteins were decreased in the PSD of *Trim9*$^{-/-}$*:PS19* mice compared to *Trim9*$^{+/+}$*:PS19* mice. These decreases in mitoribosomes suggest that mitochondria function may be impaired. We are exploring mitochondrial morpho-dynamics in cultured neurons with or without TRIM9 and tau pathology, and mitochondrial respiration in brain and culture. Additionally, we confirmed the TRIM9-PEX5 interaction, whose ubiquitylation plays a role in peroxisome homeostasis, and are working to determine if TRIM9 has a role in this ubiquitination, with or without pathological tau. Future experiments will map the interaction between TRIM9 and these AD-relevant proteins, and investigate how abrogating these interactions changes AD pathology progression at the molecular and cellular level. Eventually, we hope that TRIM9 can be a potential therapeutic target.

Disclosures: A. Frasineanu: None. **S.L. Gupton:** None.

Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.08/C54

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: A role for the p75NTR - hB7.1 interaction in Alzheimer's disease.

Authors: *H. DAS[1], R. HIGHTOWER[2], B. D. CARTER[3];
[1]Dept. of Biochem., [2]Vanderbilt Univ., Nashville, TN; [3]Dept. of Biochem. Vanderbilt Brain Inst., Vanderbilt Univ. Med. Sch., Nashville, TN

Abstract: The p75 neurotrophin receptor (p75 NTR) is mostly known for its ability to bind all the neurotrophins (NGF, BDNF, NT3, NT4), both their pro- and mature forms. However, Morano et al, 2022, recently identified human B7.1/CD80 (hB7.1) as a new ligand for p75NTR. B7.1 is an immunomodulatory ligand expressed by antigen presenting cells, such as macrophages and microglia. The interaction between p75NTR and B7.1 is a recent evolutionary adaptation found only in primates (monkey, human) but absent in rodents (mice,rat). The canonical role of hB7.1 is to directly regulate the activation of T cells through binding to CD28 and CTLA-4 receptors. In hippocampal neurons, hB7.1 binds p75NTR and induces dendritic spine collapse. These findings led us to hypothesize that this interaction between p75NTR and hB7.1 may contribute to synaptic pruning in neurodegenerative conditions, such as Alzheimer's disease (AD). P75 NTR is widely expressed in the developing mammalian brain, becomes increasingly restricted to specific niches in the adult brain but upregulated in response to injuries or diseases, including AD. Human B7.1 levels are increased in response to infection or neuroinflammation, such as in Multiples Sclerosis, but its expression in AD remains to be determined. To investigate the role of hB7.1-p75NTR interaction in AD, we determined the effects of hB7.1 on synapses in cultured murine cortical neurons. We found hB7.1 caused a loss in both pre (Bassoon) and post synaptic (PSD95) puncta within 2hrs. A similar decrease was also found in murine hippocampal neurons, in agreement with Morano et al. 2022. To confirm an involvement of p75NTR, we co-treated the neurons with hB7.1 and an antibody to p75NTR that blocks ligand binding and found it prevented the loss of synapses. The mechanism by which hB7.1 mediates its actions involves the GTPase, RhoA, as we detected an increase in active RhoA following hB7.1 treatment. We propose that in AD microglia express hB7.1 in response to accumulating amyloid, thereby causing a reduction in synapses via p75NTR. Therefore, we treated the human microglial cell line, HMC3, with oligomeric Abeta and measured hB7.1 expression. We found a significant increase in hB7.1 protein within 48 hours of amyloid exposure. The single cell RNA sequencing data from SEA-AD (Seattle AD Brain cell Atlas) Comparative Viewer supports this finding, indicating increased levels of hB7.1 mRNA expression in microglia from AD patient samples relative to control reference group. Current efforts are focused on co-culturing cortical neurons with amyloid treated human microglial cells to determine whether the increase in hB7.1 results in synaptic pruning.

Disclosures: H. Das: None. **R. Hightower:** None. **B.D. Carter:** None.

Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.09/C55

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant AG082903

Title: Amyloid-beta (Aβ) increases the interaction of Protein kinase C alpha (PKCα) with the postsynaptic scaffolding protein PSD95 and IQGAP1, an effect regulated by PKCα activity

Authors: *M. DINATA[1], A. SNYDER[1], S. T. DINH[1], M. SHARMA[2], A. NEWTON[2], K. B. DORE[1];
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Abstract: Alzheimer's disease (AD) affects 6.9 million individuals 65+ in the US, and is predicted to double by 2060, however no effective treatment nor early diagnosis methods are available.Genome-wide associated screens (GWAS) have identified a highly penetrant mutation in the protein kinase C alpha (PKCα) gene - M489V - in individuals with familial AD. This mutation increases enzymatic activity of PKCα by 30%, and dysregulated PKCα has been implicated in AD pathology. PKCα, a second-messenger, is thought to interact with various scaffolding proteins such as PSD95 and IQGAP1, possibly playing a role in synaptic function. Notably, Bisindolylmaleimide IV (BisIV), an inhibitor of PKC that can act on scaffolded PKC, may offer therapeutic potential to dampen the hyperactive PKCα-M489V signaling. To further understand PKCα-PSD95 and PKCα-IQGAP1 interactions in normal neurons and neurons affected by AD pathology, we used primary hippocampal neurons from WT rodents and AD model mice (APP/PS1). Neurons were transfected with PSD95-GFP or IQGAP1-GFP and PKCα-WT-mCherry or PKCα-M489V-mCherry. Some were infected with the Aβ-producing fragment CT100, others were treated with BisIV. Using fluorescence lifetime imaging (FLIM) with fluorescence resonance energy transfer (FRET) we measured PKCα-PSD95 and PKCα-IQGAP1 binding in dendritic spines. Additionally, we also utilized confocal imaging to quantify the enrichment of PKCα in dendritic spines. Our FLIM results indicated that CT100 increases the interaction between PKCα-WT or PKCα-M489V with PSD95 or IQGAP1 in WT neurons, suggesting that Aβ induces recruitment of PKCα to the postsynaptic density. Interestingly, we also found that BisIV significantly increased PKCαWT-PSD95 interactions in APP/PS1 neurons but had no effect in WT neurons. Also, using confocal imaging we found that the M489V PKCα variant was more enriched in dendritic spines than PKCα-WT when co-expressed with IQGAP1 or PSD95. This suggests that more PKCα activity leads to increased trafficking of IQGAP1 and PSD95 to dendritic spines. Overall, we generated further insight into how PKCα interacts with the scaffolding proteins PSD95 and IQGAP1 in WT neurons or in AD model neurons; further elucidating these mechanisms should help when designing AD treatments.

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Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.10/C56

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Abl kinase signaling mediates monomeric Aβ42-driven inhibitory synaptic dysfunction

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Abstract: Neuronal communication is critically dependent on precisely regulated neurotransmitter release at synapses. In Alzheimer's disease (AD), this regulation is compromised at an early stage, leading to synaptic dysfunction. Amyloid beta 42 peptide (Aβ42), a central pathological hallmark of AD, accumulates within the synaptic cleft, where it interacts with synaptic proteins and contributes to early synaptic impairment. Aβ42 can adopt multiple structural conformations: monomers, oligomers, and fibrils based on their folding and assembly. While oligomeric and fibrillar forms of Aβ42 have been extensively studied, the physiological and pathological roles of monomeric Aβ42 (mAβ42) remain unexplored.Our previous studies identified Abl kinases as downstream effectors in the signaling cascade initiated by mAβ42, mediating its impact on excitatory synaptic function. Specifically, acute exposure to mAβ42 was shown to reduce the amplitude of miniature excitatory postsynaptic currents (mEPSCs) via activation of Abl kinases.In this study, we investigated the effects of mAβ42 on inhibitory synaptic density and spontaneous neurotransmission in cultured primary neurons. Immunocytochemistry revealed activation of Abl kinase following prolonged mAβ42 exposure that led to a significant reduction in inhibitory synaptic density. This was evidenced by diminished colocalization of synaptic markers, the vesicular GABA transporter (vGAT) and the postsynaptic scaffolding protein gephyrin.These findings indicate that mAβ42 perturbs the maintenance of inhibitory synapses. Electrophysiological analyses further revealed that acute Abl kinase activation by mAβ42 enhances spontaneous inhibitory neurotransmission; however, pharmacological inhibition of Abl kinases failed to rescue the mAβ42-induced changes in miniature inhibitory postsynaptic currents (mIPSCs). Collectively, our findings demonstrate that mAβ42 alters both the structural integrity and functional activity of inhibitory synapses through mechanisms involving Abl kinases. These alterations may contribute to the early synaptic destabilization observed in the prodromal stages of Alzheimer's disease.

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Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.11/C57

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Differential electrophysiological alterations in vulnerable neuronal subpopulations during early-stage Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder strongly associated with aging and characterized by complex pathophysiological mechanisms. Notably, specific neuronal populations within the neocortex, particularly in the entorhinal cortex (EC), prefrontal cortex (PFC), and locus coeruleus (LC), exhibit heightened vulnerability in the early stages of the disease. The underlying reasons for this regional and cell-type-specific susceptibility remain poorly understood. One early hallmark of AD is neuronal hyperexcitability, which may contribute to synaptic dysfunction, neuropsychiatric symptoms, and cognitive decline. In this study, we hypothesize that early hyperexcitability in vulnerable neuronal populations, particularly within the EC and LC, arises from AD-related disruptions in glutamatergic neurotransmission and synaptic integrity. Therefore, we examined the electrophysiological properties of lateral EC pyramidal neurons and LC noradrenergic (NE) neurons in 3xTg-AD mice at 2 and 4 months of age, representing early stages of AD pathology. Our findings reveal a significant increase in the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) in Layer III but not Layer V pyramidal neurons of the EC in 3xTg-AD mice compared to age-matched wild-type (WT) controls. Importantly, this increase occurred without changes in sEPSC amplitude or evoked action potential firing, suggesting enhanced presynaptic glutamatergic input or an increased number of functional excitatory synapses. In contrast, NE neurons in the LC displayed a decrease in both sEPSC frequency and evoked action potential firing, accompanied by an increase in spontaneous firing activity, indicating a distinct pattern of electrophysiological disruption. Together, these results highlight region- and cell-type-specific differences in synaptic alterations during the early stages of AD. Our data suggest that increased presynaptic glutamatergic activity is an early feature in selective EC neuronal populations, while LC neurons exhibit signs of impaired synaptic input alongside heightened intrinsic excitability. These differential electrophysiological profiles may underlie the selective vulnerability of these brain regions in AD and provide insights into early circuit dysfunction in the disease.**Key words**: Alzheimer's disease; entorhinal cortex; locus coeruleus; sEPSCs; electrophysiology

Disclosures: B. Zhao: None. **J. Li:** None.

Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.12/C58

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIHAG067330
T32DK00765

Title: Adiponectin receptor activation reduces tau burden and rescues hippocampal excitability

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Abstract: The specific mechanisms of cognitive decline and dementia associated with Alzheimer's disease (AD) remain unclear; however, changes in brain mitochondrial metabolism are coincident with functional decline associated with AD. Despite evidence that mitochondrial abnormalities coincide with functional decline in AD, effective therapeutic strategies targeting this relationship are lacking. Here, we investigate the therapeutic potential of mitochondrial targeting via the adiponectin receptor activator AdipoRon (AR). Adiponectin is an adipose tissue-derived hormone linked to metabolic syndrome and aging, and adiponectin receptors are expressed in all brain cell types. We utilized primary neurons and ex vivo hippocampal slices from hTau P301S mice or their WT littermates to study the impact of neurofibrillary tangle pathology on metabolism and how the tau-associated metabolic changes connect to electrophysiological properties. Our findings demonstrate that the mitochondrial targeting intervention AR lowers neurofibrillary tangle (NFT, a hallmark of AD) burden and rescues diverse tauopathy-associated defects. In primary neurons, AR reduced levels of phospho-tau and NFT burden by a mechanism requiring AMPK, an energy-sensing kinase linked to adiponectin signaling. AR also corrected mitochondrial and ATP production deficits induced by NFTs. Whole-cell patch-clamp experiments identified NFT-associated defects in electrophysiological passive parameters and lower action potential firing rates, both of which were corrected by AR. Translational studies showed that the benefits of AR treatment observed *in vitro* were recapitulated *in vivo*. CA1 pyramidal neurons in the P301S mice showed an inability to fire action potentials at the same rate as wildtype mice. Four months of daily AR administration in hTau P301S mice was sufficient to prevent Tau-associated deficits in spike firing. Voltage clamp experiments revealed Tau pathology caused a lower frequency of miniature inhibitory post-synaptic currents and that AR feeding prevented the loss of inhibitory synaptic function. Metabolic changes in the hippocampus will be investigated through 2-photon metabolic imaging and immunohistochemistry. Collectively, these data reveal a neuronal intracellular network linking mitochondrial function to cellular maintenance processes and electrical function that can be targeted via adiponectin receptor activation. This work was supported by NIHAG067330, T32DK00765.

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Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.13/C59

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fondecyt 1221080

Title: Impaired excitability and neurotransmission properties in a cultured accumbal cell model derived from the Alzheimer´s Disease APP/PS1 mice

Authors: P. SAAVEDRA SIEYES, I. MEZA VARGAS, N. RIFFO-LEPE, L. S. SAN MARTIN, J. GONZÁLEZ-SANMIGUEL, *L. G. AGUAYO;
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Abstract: Alzheimer's disease (AD) is a neurodegenerative pathology that affects brain areas such as the cortex and hippocampus. In advanced stages, this disease leads to cognitive impairment, primarily caused by the accumulation of beta-amyloid peptide (Aβ) and the formation of neurofibrillary tangles. However, a series of non-cognitive symptoms have recently been reported in the early stages of AD, which have been associated with alterations in the nucleus accumbens (nAc). Interestingly, the accumulation of intracellular Aβ (iAβ), which is defined as an early event in Alzheimer's disease, has recently been described in neurons of the nucleus accumbens in 6-month-old APP/PS1 mice. Additionally, reports have indicated hyperexcitability in these neurons and dysfunction of AMPA and glycine receptors. To further investigate how neurons in this region are affected in AD, our laboratory developed a primary culture protocol to study accumbal cells derived from the 2xTg APP/PS1 mouse model. The neurons derived from the APP/PS1 mice showed a significant accumulation of iAβ at 15 DIV. Additionally, APP/PS1 neurons exhibited increased membrane excitability, as evidenced by increased firing, depolarized resting membrane potential, and a reduced rheobase. In parallel, the neurons showed an increase in AMPAR-mediated miniature excitatory postsynaptic currents (mEPSCs), an effect that was accompanied by an enhanced number of PSD-95 puncta. The amplitude of mEPSCs in APP/PS1 neurons was significantly reduced by NASPM, a selective antagonist of calcium-permeable AMPA receptors (CP-AMPARs), whereas WT neurons were unaffected. In contrast, while GABAergic transmission remained unchanged between genotypes, the evoked glycinergic current density decreased in APP/PS1 neurons. These findings demonstrate that the APP/PS1 neuronal culture system at 15 DIV recapitulates key membrane alterations previously reported *in vivo*, such as enhanced excitatory transmission, increased membrane excitability and reduced inhibitory transmission. We believed that this *in vitro* model of AD could help us investigate the contribution of iAβ to early cellular alterations that may underlie nucleus accumbens (nAc) impairment during the initial stages of Alzheimer's disease.

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Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Cure Alzheimer's Fund award (#65539) to SDA and RY
the National Institute on Aging grant (R21-AG064554) to SDA and RY
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Grant #4242 "NIMOCHIP" Science Fund RS to P. Andjus

Title: Neurophysiological and proteomic alterations in heterozygous AppNL-G-F mouse model of Alzheimer's disease: an ex vivo study

Authors: *K. MILICEVIC[1,3], Y. M. ZHU[1], V. IVANOVA[1], R. YAN[1], S. D. ANTIC[2]; [1]Neurosci. Dept., [2]Neurosci., Univ. of Connecticut Hlth., Farmington, CT; [3]Inst. for the Brain and Cognitive Sci., University of Connecticut, CT

Abstract: In Alzheimer's disease (AD), the emergence of hallmark pathological features such as amyloid plaques marks a late, irreversible stage at which therapeutic intervention is largely ineffective. As such, there is a growing consensus that future treatments must target the prodromal phase of the disease. While current research has focused heavily on molecular biomarkers in blood and cerebrospinal fluid (CSF), early physiological changes in the brain may provide equally critical insights into AD pathogenesis. To investigate such early neurophysiological alterations, we employed the heterozygous AppNL-G-F knock-in mouse model, which exhibits age-dependent amyloidosis and mild cognitive and histopathological phenotypes, more closely resembling the human condition than its homozygous counterpart. We conducted a multimodal analysis combining whole-cell electrophysiology, multi-site voltage imaging, and label-free proteomics in both young (<100 days) and aged (>200 days) cohorts. Compared to wild-type littermates, heterozygous AppNL-G-F mice displayed increased neuronal input resistance (Rin), elevated hyperpolarization-activated current (I-h), enhanced input/output firing dynamics, and a significant reduction in cortical laminar signal propagation velocity of synaptically-evoked cortical depolarizations. Next we tested seizure succeptibility in brain slices, using K+ channel blocker, 4-aminopyridine. Surprisingly, paroxismal discharges induced by 4-aminopyridine were comparable between AD and control slices, as was the response to gap junction blockade using carbenoxolone. Proteomic profiling via UPLC-MS/MS revealed upregulation of both ionotropic and metabotropic glutamate receptors in AD slices, along with changes in ankyrin, GABA-B receptor, and SynGAP1. Notably, we observed reduced levels of neural cell adhesion molecule-2 (NCAM2), Syntaxin-7, and Synaptotagmin-11, suggesting disruptions in synaptic architecture and membrane excitability. This study provides the first integrated physiological and proteomic characterization of the heterozygous AppNL-G-F model. Our findings identify specific neurophysiological alterations that may serve as early indicators of disease progression, and potential targets for intervention prior to overt amyloid pathology.

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Poster

PSTR109: Using *In Vitro* Models to Understand Synaptic Dysfunction in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.15/C61

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01-AG080731-01

Title: Early donepezil treatments protects neuromuscular function in 5xFAD mice

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Abstract: Alzheimer's disease (AD) progresses along a continuum, with loss of muscle mass and strength as characteristic of the pre-clinical phase that precedes cognitive impairment. Using the 5xFAD mouse model of AD, we previously characterized the development of impaired motor nerve-stimulated muscle contraction by 4 months of age, prior to development of cognitive impairment. Donepezil is a reversible acetylcholinesterase inhibitor primarily utilized for treating cognitive and behavioral symptoms of AD, that has also been demonstrated to improve muscle health in pre-AD subjects. We hypothesized that donepezil treatment, begun prior to neuromuscular decline, would delay manifestation of neuromuscular impairment in 5xFAD mice. We orally treated 3-month-old 5xFAD mice and wild type (WT) littermates with 0.075mg of Donepezil or placebo daily for 4 weeks. We then assessed tibial nerve-stimulated plantar flexion torque and sciatic nerve compound (motor) neuron action potential (CNAP) in-vivo at 4 months of age. Donepezil-treated mice maintained tibial nerve stimulated torque production, comparable to WT littermates. CNAP duration in 5xFAD mice was better maintained with Donepezil over placebo but both groups had slower CNAP compared to WT. Together, these data suggest Donepezil treatment can slow development of neuromuscular dysfunction in 5xFAD mice. To determine if Donepezil could improve neuromuscular function, we treated 5-month-old mice for four weeks. However, at 6 months of age neither torque production nor CNAP duration improved. To gain insight of the protective mechanism of Donepezil on neuromuscular dysfunction, sciatic nerves were collected for TMT-labelled proteomic profiling in 4-month-old mice. Proteomic profiling of sciatic nerves revealed Donepezil restrained increases in mitochondrial immune response that coincided with altered calcium buffering and inflammation. Declines in the peripheral nerve function may be a pre-clinical identifier for AD, in which a pharmaceutical intervention targeting acetylcholinesterase may delay pathology manifestation via alterations in calcium handling and immune activity via mitochondrial pathways.

Disclosures: D.Q. Nieves-Esparcia: None. **J. Drake:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.01/C62

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Grant-in-Aid for Scientific Research (A)
Moonshot Research and Development Program
Japan Agency for Medical Research and Development

Title: Reconstitution of Alzheimer's specific tau filament folds with designed mutations

Authors: *M. KANO[1], T. KIMURA[2], S. HOMMA[5], M. TAJITSU[5], S. NAGAHAMA[5], X. LI[3], H. YANAGISAWA[4], M. KIKKAWA[4], Y. MATSUNAGA[5,6], T. TOMITA[1];
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Abstract: Tauopathies are neurodegenerative disorders characterized by tau aggregation, with Alzheimer's disease (AD) being a representative example where hyperphosphorylated tau forms filaments that deposit in the brain. Cryo-electron microscopy (cryo-EM) has revealed disease-specific polymorphisms in tau filaments, suggesting that such structural diversity underlies disease specificity. However, recombinant full-length wild-type tau proteins generated in vitro fail to replicate the paired helical filament (PHF) fold observed in AD patient brains. Similarly, tau filaments accumulated in the tau transgenic mice exhibit conformation distinct from that of PHF. Although the recombinant tau protein corresponding to the PHF fold resolved by cryo-EM (i.e., AD core region, residues 306-398 of tau) can reconstitute PHF fold-like conformation under high-salt conditions in vitro, heterologous expression of this region in cells or mice did not reproduce PHF filaments. Moreover, recently, time-resolved cryo-EM analyses revealed that the formation of a first intermediate amyloid (FIA), an early-stage filamentous structure, is a key step for the PHF assembly. Therefore, we aimed to identify artificial mutations that promote PHF fold-like conformation by stabilization of PHF fold or FIA formation to reconstitute the disease-specific tau filament structures in vivo. Using ColabDesign, a structure-guided design tool based on AlphaFold2, in combination with molecular dynamics simulations, we selected candidates of mutant tau sequences that showed both high pLDDT scores and structural stabilization with low root-mean-square deviation during the simulation. These mutant sequences retained ~40% sequence identity with that of the AD core region. Overexpressed tau mutants in cultured cells exhibited increased aggregability, as evidenced by an accumulation of detergent (sarkosyl)-insoluble tau fractions. Simulated interaction analyses further revealed key residues that mediate intermolecular association along the Z-axis of tau filaments. In addition, we identified distinct mutations that selectively promoted the formation of FIA. These residues were distinct from those involved in PHF stabilization, suggesting that FIA formation and PHF stabilization are mediated by mechanistically distinct and sequential processes. Future studies using these tau

mutants in cells and mice will assess their capacity to recapitulate PHF-like conformations and associated pathologies. This work provides a structural foundation to model conformation-specific tauopathies and explore targeted therapeutic strategies for AD.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.02/C63

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 AG072719 (T.I.)
RF1 AG082704 (S.I., T.I.)
R01 AG079859 (S.I.)

Title: Humanized MAPT and APP accelerate tau propagation and alter neuronal excitability in a novel ECII-targeted mouse model of early Alzheimer’s disease

Authors: *A. HAGITA-TATSUMOTO, A. RAVULA, B. GIBBS, J. ELLISON, N. BASU RAY, A. LONGTREE-PRECIADO, S. IKEZU, T. IKEZU;
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Abstract: Aims: We recently developed a mouse model recapitulating tau propagation from Wolframin-1 (Wfs1)-expressing pyramidal neurons in the medial entorhinal cortex layer II (ECII) to the CA1 region of the hippocampus, reflecting early-stage tau pathology in Alzheimer’s disease (AD). To investigate the impact of humanized MAPT and APP on tau spread and neuronal excitability, we generated human MAPT knock-in (Tau:Wfs1-Cre) and APP^{NL-G-F}:Tau:Wfs1-Cre mouse lines for immunohistochemical and electrophysiological studies. **Methods:** At 7 months of age, AAV-Flex-Tau^{P301L} was injected into ECII of Wfs1-Cre, Tau:Wfs1-Cre, and APP^{NL-G-F}:Tau:Wfs1-Cre mice, ensuring expression of human mutant P301L tau specifically in Wfs1+ pyramidal neurons. Three months post-injection, tau propagation in the hippocampus (Hp) and visual cortex (VC) was evaluated using immunofluorescence for HT7 (human tau) and AT8 ($pSer^{202}$/$pThr^{205}$-tau), along with neurogranin (NG, excitatory neuron) and GAD67 (interneuron). Intrinsic neuronal excitability was evaluated through field recordings in the CA1/subiculum and VC regions, both in the presence and absence of a $GABA_A$ receptor antagonist Gabazine. **Results:** HT7+ tau was detected in the subiculum and CA1 of all groups, but no $AT8^+$ tau was seen in Wfs1-Cre mice. Conversely, both $HT7^+$ and $AT8^+$ tau were found in the VC, subiculum, and CA1 of Tau:Wfs1-Cre and APP:Tau:Wfs1-Cre mice. AT8+ tau colocalized with NG in 34.7% of labeled cells, suggesting preferential spread to excitatory neurons, though the identity of the remaining 65.3% is under transcriptomic analysis. Notably,

APP^{NL-G-F}:Tau:Wfs1-Cre mice exhibited reduced GAD67 expression in the Hp and VC relative to Wfs1-Cre mice, independent of tau spread. Electrophysiological recordings revealed increased spontaneous firing frequency in CA1 and VC of APP^{NL-G-F}:Tau:Wfs1-Cre mice relative to Wfs1-Cre mice. Notably, this increase remained largely unchanged after the introduction of Gabazine, suggesting impaired GABAergic transmission in this amyloid and human tau model.
Conclusions: These findings demonstrate that amyloid pathology and human tau expression synergistically enhance tau propagation from ECII to the VC and heighten neuronal excitability, potentially contributing to network dysfunction in early AD.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Research grant from the Cell Science Research Foundation

Title: Phosphoproteomic and molecular networking analyses identified tau-related kinases connecting Alzheimer’s disease-related tau phosphorylation and diabetes mellites

Authors: *Y. ITO[1,3], T. NAKAJIMA[2], S. YAMAMOTO[2,3], S. TESHIROGI[2,3], S. TAKEDA[1,3]; [1]Clin. Gene Therapy, [2]Geriatric and Gen. Med., The Univ. of Osaka, Suita, Osaka, Japan; [3]Osaka Psychiatric Res. Ctr., Osaka Psychiatric Med. Ctr., Hirakata, Osaka, Japan

Abstract: Background: Diabetes mellitus (DM) is a risk factor for developing Alzheimer’s disease (AD). Neurofibrillary tangles (NFTs), one of the neuropathological features of AD, which are mainly composed of phosphorylated tau. The severities of neuronal loss and cognitive decline in patients with AD correlate with the number of NFTs, indicating the crucial role of tau in neurodegeneration. We previously reported that tau phosphorylation is increased in the brain of a diabetic AD mouse model, which can be an underlying mechanism linking DM and AD. However, the key molecules mediating the tau phosphorylation by DM remain unknown. Objective: In the present study, we aimed to identify candidate kinases that regulate tau phosphorylation by DM using a phosphoproteomic analysis. Design: We generated diabetic tau-transgenic (TauTg) mice by high-fat diet (HFD; 60% kcal fat) feeding from the age of one and a half to nine months. Metabolic parameters (body weight, abdominal fat weight, and plasma insulin levels) were evaluated at eight months of age. We conducted a phosphoproteomic

analysis of their brain tissues from the diabetic and non-diabetic TauTg mice. Results: TauTg mice fed with HFD showed diabetic conditions (obesity and hyperinsulinemia) compared with TauTg mice fed with NCD ($p < 0.01$). The accumulation of phosphorylated tau was increased in the brains of diabetic TauTg mice ($p < 0.05$). We identified 30 kinases whose levels of phosphorylation were significantly altered in the brains of the diabetic TauTg mice. Molecular networking analysis found that six of the 30 kinases were associated with tau phosphorylation. Among the six kinases, the decrease in the phosphorylation levels of CaMK2α, which reflected the severity of diabetic conditions, was associated with the exacerbation of accumulation of phosphorylated tau in the brains of TauTg mice ($p < 0.05$). Conclusion: Tau-related kinases that potentially link diabetic conditions and tau phosphorylation were identified using phosphoproteomic and molecular networking analyses. These kinases could be therapeutic targets for preventing AD in patients with DM.

Disclosures: Y. Ito: None. **T. Nakajima:** None. **S. Yamamoto:** None. **S. Teshirogi:** None. **S. Takeda:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.04/D1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: C-terminally intact tau in the cerebrospinal fluid reflects cognitive function in Alzheimer’s disease

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Abstract: [Background]Cerebrospinal fluid (CSF) tau concentrations are typically elevated in patients with Alzheimer’s disease (AD). Tau in CSF is known to undergo various post-translational modifications, including fragmentation. However, the clinical relevance of these truncated tau species remains poorly understood. In this study, we focused on a specific tau species with an intact C-terminal region (referred to as c-tau) and explored its potential clinical significance in AD.
[Objective]This study aimed to evaluate the clinical relevance of CSF c-tau levels in relation to core AD biomarkers and cognitive function.
[Design]We analyzed data from 96 individuals (mean age: 76.0 years) who underwent CSF biomarker testing and neuropsychological assessments at Osaka University Hospital. The concentration of c-tau in CSF was measured by ELISA. Associations among CSF c-tau levels, core AD biomarkers (Aβ42, total tau, and phosphorylated tau), and cognitive scores (MMSE) were examined. The study protocol was approved by the institutional ethics committee.
[Results]The mean CSF c-tau concentration was significantly higher in the AD biomarker-positive group (n = 80; 595 pg/mL) than in the biomarker-negative, cognitively normal group (n

= 16; 441 pg/mL). However, substantial interindividual variability in c-tau levels was observed among AD patients. CSF c-tau concentrations did not correlate with total tau or phosphorylated tau levels. Subgroup analyses of patients with both markedly elevated p-tau and decreased Aβ42 levels (n = 30) revealed that CSF c-tau levels were positively correlated with MMSE scores ($r = 0.429$, $p < 0.05$).
[Conclusion]Our findings suggest molecular heterogeneity of CSF tau fragments in AD. The presence of c-tau with an intact C-terminal region may reflect cognitive status in specific biomarker-defined subgroups of AD patients.

Disclosures: S. Teshirogi: None. **Y. Ito:** None. **S. Yamamoto:** None. **S. Takeda:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.05/D2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS KAKENHI 24K10491

Title: Tau in the Dorsal Subiculum-VTA Circuit Regulates Feeding Behavior via the Reward System

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Abstract: Tau is a microtubule-associated protein implicated in neurodegenerative disorders such as Alzheimer’s disease and frontotemporal lobar degeneration (FTLD), yet its physiological role in brain function remains incompletely understood. Here, we demonstrate that Tau knockout (Tau-KO) mice display increased food intake, abnormal feeding patterns, and excessive body weight gain. These changes are associated with attenuated dopamine (DA) release in the nucleus accumbens (NAcc) and reduced excitability of DA neurons in the ventral tegmental area (VTA), suggesting dysfunction in the mesolimbic reward system. However, selective knockdown of the Mapt gene within the VTA failed to reproduce these phenotypes, implying Tau's critical influence lies upstream. Manganese-enhanced MRI (Mn-MRI) during feeding revealed abnormal activation not only in core reward-related regions, including the VTA and NAcc, but also in the hippocampus. To identify the hippocampal subregion responsible for this effect, we performed Mapt knockdown in multiple hippocampal areas. Notably, knockdown in the dorsocaudal hippocampus, a region anatomically centered around the dorsal subiculum, was the only condition that resulted in significant weight gain and abnormalities in reward-related dopamine signaling. Using Cre-LoxP-based circuit tracing, we identified a direct projection from the dSub

to VTA-DA neurons, confirmed by hrGFP expression in tyrosine hydroxylase (TH)-positive neurons co-localized with the presynaptic marker Synaptophysin. Furthermore, we specifically inhibited the excitability of this pathway using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). This manipulation replicated the reduced DA response in the NAcc and the decreased excitability of VTA-DA neurons seen in Tau-KO mice. Finally, we reintroduced Tau specifically into this circuit in Tau-KO mice, significantly improving weight gain, reward system function, and feeding behavior patterns. These findings suggest that Tau in the dSub-VTA circuit is crucial for positively regulating VTA-DA neurons. Loss of tau function in this circuit may contribute to the reward system and feeding behavior abnormalities seen in FTLD.

Disclosures: Y. Fujioka: None. **H. Ito:** None. **K. Kawai:** None. **A. Yamanaka:** None. **S. Ishigaki:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.06/D3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Florida Department of Health Ed & Ethel Moore Alzheimer Disease Research Grant Program
UCF College of Medicine Institutional Multidisciplinary Award

Title: Identification of a novel molecular mechanism for tauopathy in neurodegeneration

Authors: *J. ZHAO[1], J. HAO[2,1], R. YANG[1], L. YU[1], X. XIA[3,1], H. ZHOU[4,1];
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Abstract: Despite the well-established role of hyperphosphorylated tau neurofibrillary tangles in the progression of neurodegenerative disorders, including Alzheimer’s disease, the underlying molecular causes remain largely unknown. This has hindered the development of effective therapies targeting pathological tau. To investigate the underlying molecular mechanisms, we specifically knocked out a transcription factor gene in mouse cerebral neurons. This gene is known to be highly expressed in adult cerebral neurons, and its deficiency in the brain has been observed in patients with Alzheimer’s disease although its role in the brain has not been studied. Behavioral tests indicate significant cognitive deficits in the knockout adult mice, but not in littermate Cre controls. Cresyl violet staining with neuronal counting, as well as Golgi staining coupled with microscopic imaging, demonstrate a loss of cortical neurons and dendritic spines in the knockout mice but not in the control mice. Immunofluorescent staining shows a marked increase in the number of microglia and astrocytes in the knockout mice only.

Immunohistochemical staining and western blotting reveal extensive hyperphosphorylation of tau in the brain of the knockout mice only. Multi-omics analyses suggest that altered gene expression in knockout cerebral neurons may play a critical role in mediating tau pathology. Taken together, these results strongly suggest a novel neuroprotective role for the transcription factor under investigation and indicate that its deficiency contributes to tau hyperphosphorylation in neurodegenerative disorders such as Alzheimer's disease.

Disclosures: J. Zhao: None. **J. Hao:** None. **R. Yang:** None. **L. Yu:** None. **X. Xia:** None. **H. Zhou:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.07/D4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Advancing Neurological Research: Mouse Models with Humanized Genes as Tools for Understanding Pathophysiology and Therapeutics

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Abstract: Mouse models with humanized genes (HUGO mouse models, humanized gene ortholog mouse models) have emerged as a crucial tool in life sciences, particularly in drug efficacy studies for human diseases. HUGO mouse models offer comprehensive insights into human-specific biological processes and disease mechanisms, bridging the gap between preclinical studies and clinical relevance. These models enable researchers to investigate the complexities of human pathophysiology in a controlled experimental environment, which is especially valuable for studying intricate neuropathological processes driven by genetic, cellular, and synaptic interactions. Cyagen has developed an extensive series of HUGO mouse models, which encompass a wide range of neurological disorders. For instance, the mouse models that feature the complete replacement of the mMapt gene with the hMAPT gene, either with or without disease-associated mutations such as P301L and P301S. These models exhibit cognitive impairment beginning at 3-6 months of age, reflecting the characteristics observed in human patients with Alzheimer's disease or frontotemporal lobar degeneration. Significantly, the P301S model demonstrates a more accelerated progression compared to the P301L model, closely paralleling human conditions and thereby enhancing the translational relevance of these models. Besides these extensively studied pathology-related genes, Cyagen has also created mouse models with humanized genes associated with rare diseases. An example includes the mouse model with the hMECP2 gene and the hMECP2 T158M mutation, related to Rett syndrome. From 1.5 months of age, the hMECP2 T158M mice begin to show motor deficits similar to their human counterparts, indicating a strong correlation between the mouse model and the corresponding human disease. In summary, Cyagen has developed a comprehensive collection of

HUGO mouse models suitable for various neurological diseases. These models are highly valuable for studies focusing on the pathophysiology and therapeutic strategies of these conditions.

Disclosures: M. Cui: A. Employment/Salary (full or part-time): Cyagen Biosciences.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.08/D5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AA028931
NIH Grant AA028931

Title: Tau pathology leads to hyperactivity of noradrenergic neurons, potentially contributing to early Alzheimer's disease

Authors: *R. MCCOY[1], R. WANG[2], C. MARCINKIEWCZ[3];
[1]Univ. of Iowa, Long Grove, IA; [2]Dept. of Pharmacol. and Toxicology, [3]Univ. of Iowa, Iowa City, IA

Abstract: The accumulation of misfolded hyperphosphorylated tau proteins (p-tau) is a cornerstone of Alzheimer's disease (AD). P-tau has been observed in the locus coeruleus (LC) well before clinical symptoms emerge and before it appears in other brain regions. Considering the broad ascending projections of LC noradrenergic (NA) neurons and their functional implications, p-tau expression in the LC NA neurons may play a significant role in the pathophysiology of early AD. In the present study, we aimed to unravel whether and how p-tau potentially alters activity of LC NA neurons and consequently affects behavior and sleep in early AD. To that end, we transduced Cre-recombinase-dependent P301Ltau (AAV2/8-Ef1α-FLEX-P301Ltau-WPRE) in the LC (coordinates: ML ±0.85; AP -5.40; DV: -3.90 mm) of DBH^{-Cre} KI mice (JAX strain: #033951), resulting in the expression of the pathological tau exclusively in NA neurons (expression efficiency: 94.38 ± 2.45%). Four and eight weeks later, whole-cell patch clamp recordings were performed in LC NA neurons. Interestingly, all LC NA neurons were spontaneously firing. P-tau expression significantly increased spontaneous firing frequency in both 4-week (controls: 3.33±0.364 Hz; tau: 4.83±0.606 Hz; $p < 0.05$) and 8-week cohorts (controls: 3.00±.438 Hz; tau: 4.57±0.488 Hz; $p < 0.05$) when compared with controls (injected with a control virus: AAV8-hSyn-DIO-mCherry). These changes reflect a ~40-60% increase in spontaneous firing, indicating a substantial shift in baseline activity due to tau pathology. Moreover, to compare excitability of LC NA neurons between groups, we held the cells at -55 mV to stop spontaneous firing and then injected currents intracellularly. No group differences were observed in rheobase, i.e., the minimum current needed to evoke action potentials (APs), at either the 4- or 8-week timepoint. Additionally, Stepwise depolarizing currents (10-200 pA, step

size: 10 pA) were applied to assess AP firing rates in a controlled, non-spontaneous state. At the 8-week timepoint, frequency of evoked APs was greater in the tau versus control group, which, however, was not observed at the 4-week timepoint. Taken together, pathological tau leads to increased activity of LC NA neurons, which appears greater with longer periods of p-tau exposure, but it is unclear whether this trend continues. Future studies will assess the progression of tauopathy and its postsynaptic consequences as well as its effects on behavior and sleep regulation.

Disclosures: R. McCoy: None. **R. Wang:** None. **C. Marcinkiewcz:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.09/D6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG074273
NIH Grant R01AG078185
AARFD-22-973252

Title: Androgen Supplementation in Female P301S Mice Regulates Tauopathy and Microgliosis

Authors: *S. LYU[1], D. E. MUNOZ-MAYORGA[2], A. S. KAUFFMAN[3], R. RISSMAN[4], X. CHEN[5];
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Abstract: Females are at a higher risk for developing Alzheimer’s disease (AD) than males. However, the underlying cause of such sex differences is not understood. The majority of females develop AD after menopause, a period when female hormones including estrogen and progesterone plummet while testosterone remains relatively stable and becomes a key sex hormone. Females with hyperandrogenism — a common condition associated with Polycystic Ovary Syndrome (PCOS) and insulin resistance — have excess testosterone, which is converted to dihydrotestosterone (DHT) in the tissues. Testosterone and DHT are reported to modulate neuronal function and AD pathology in males through androgen receptor (AR) signaling; However, how AR signaling affects female AD pathophysiology is unknown. We seek to understand the impact of excess androgen in female AD development, focusing on the pathophysiology of tau. We found that DHT supplementation in female P301S tau mice (PS19) caused significant exacerbation of tau pathology and neuroinflammation. RNA-seq analysis revealed striking proinflammatory response in microglia from female PS19 mice supplemented with DHT. Using in vitro cell cultures and ex vivo brain slice cultures, we dissected the roles of DHT-induced AR signaling in neurons. Surprisingly, we found that although DHT protects

against tau phosphorylation in neurons, it induced disease associated microglia (DAM) phenotype, manifested by increased proinflammatory cytokines and impaired tau clearance in mouse microglia cell line. Intriguingly, Trem2 knockout abrogated DHT-induced microgliosis and tau aggregation pathology. Overall, our findings suggest that hyperandrogenism in females is linked to increased vulnerability of neuroinflammation and tau pathogenesis, highlighting an intricate interplay between sex and hormones, and a need to develop high precision treatment and risk-reducing interventions for both sexes.

Disclosures: S. Lyu: None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR110.10/D7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R24AG073138
NIH Grant 3P51OD011107

Title: Early disruption in tau protein precedes neurodegeneration and neuroinflammation in a novel monkey model of Alzheimer's disease

Authors: *C. T. ERICES[1], D. BECKMAN[1], G. B. DINIZ[1], S. OTT[1], K. SCHWARTZ[1], B. HOBSON[1], A. J. CHAUDHARI[1], S. MULLER[2], P. CHAKRABARTY[3], J. H. KORDOWER[2], J. H. MORRISON[1];
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Abstract: Sporadic Alzheimer’s disease (AD) is a fatal neurodegenerative disorder that predominantly occurs in older individuals, being the most prevalent neurodegenerative disease. Despite its enormous public health costs, there are no current disease-modifying therapies that stop disease progression significantly. To better understand the degenerative phase of the disease and address limitations of existing rodent laboratory models of AD, our group developed a Rhesus monkey model of tau pathology by injecting a viral vector carrying human tau containing a double tau mutation (AAV-P301L/S320) into the entorhinal cortex (ERC). Our group has previously described that, at 12 and 24 weeks after the AAV injection, we observe extensive spread of misfolded tau, intense neuroinflammatory response driven by microglia, biomarker alterations in the CSF and plasma, and tau PET changes. In the current study, we explored the earliest events occurring before the accelerated disease by investigating the ERC and hippocampal formation (HF) of animals 6 weeks post-injection. Combining high-resolution quantitative microscopy with a longitudinal collection of fluid biomarkers, we observed several tau pathology-associated markers but less microglial and astrocytic activation than present at 12 and 24 weeks. Despite some ghost tangle formation, at this stage, neurons retained most of their

morphological attributes, including extensive phospho-tau-positive dendritic arborizations and abundant phospho-tau expression in the perforant path, supporting the idea that pathology initiated in the ERC travels through the medial temporal lobe connectome in this model. Furthermore, tau pathology was mostly associated with early signs of neuroinflammation, including the presence of activated microglia, but just in the vicinity of phospho-tau positive neurons. These results likely reflect the earliest stage of tau propagation and neuronal dysfunction, preceding the frank neurodegeneration and exacerbated neuroinflammation and glial recruitment observed at more advanced stages of the disease at 12 and 24 weeks after injection. Taken together, these results reinforce the importance of investigating the earliest alterations in the disease progression and the potential of the present animal model as a proxy for early events in the tau pathology cascade.

Disclosures: C.T. Erices: None. **D. Beckman:** None. **G.B. Diniz:** None. **S. Ott:** None. **K. Schwartz:** None. **B. Hobson:** None. **A.J. Chaudhari:** None. **S. Muller:** None. **P. Chakrabarty:** None. **J.H. Kordower:** None. **J.H. Morrison:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.11/D8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association AARF-22-972333
NIH R01AG077692

Title: Brain-wide mapping reveals that seizure induction worsens tau spread preferentially in hyperactive neurons in a tauopathy mouse model

Authors: *A. J. BARBOUR[1], K. F. HOAG[2], X. LI[3], V. M. LEE[5], D. M. TALOS[6], F. E. JENSEN[4];
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Abstract: Seizures are a common occurrence in Alzheimer’s disease and exacerbate both cognitive and pathological disease outcomes. We have recently demonstrated increased seizure susceptibility, and enhanced seizure-induced tau spread through the neuroanatomical connectome in a β-amyloid mouse model. We next sought to determine whether there are similar seizure susceptibility phenotypes and brain-wide effects of seizure induction on tau spread in a tauopathy mouse model. Given the role of tau in network excitability, we hypothesized that T40PL-GFP mice, harboring a GFP tagged pathogenic MAPT mutation (P301L), would show increased seizure susceptibility, and that seizures would worsen tau spread in these mice. To investigate seizure-tau interactions, we crossed the T40PL-GFP mouse model with targeted

recombination in active populations mice (TRAP; T40/WT-TRAP) to permanently label seizure activated neurons with tdTomato. To induce tau spread, we unilaterally injected human AD brain derived tau lysate (AD-tau) into the right hippocampus and cortex at three months of age. Seizures were induced with pentylenetetrazol (PTZ) kindling 2-3 weeks following AD-tau injection and seizure-activated neurons were labelled with tdTomato on the final PTZ administration via 4-hydroxytamoxifen administration. All mice were euthanized three months following AD-tau seeding, and intact T40-TRAP brains underwent clearing, immunolabeling for NeuN, and light sheet microscopy to image tau-GFP, tdTomato, and NeuN. Whole-brain datasets were registered to the Allen Brain Atlas and tdTomato+ and tdTomato- (NeuN+) somatic tau-GFP were mapped. We found that T40PL-GFP mice had increased seizure susceptibility compared to WT mice ($n=9-11$, $p<0.05$). We also found significantly increased tau-GFP in seizure activated tdTomato+ neurons compared to neurons in Sal treated mice in the ipsilateral and contralateral (to injection site) striatum, ipsilateral perirhinal and orbital areas, and contralateral nucleus raphe ($n=4-5$, $p<0.05$). tdTomato+ neurons also had elevated tau-GFP compared to the surrounding tdTomato- neurons in the ipsilateral striatum and perirhinal area ($n=4-5$, $p<0.05$). Together, these results demonstrate a bidirectional relationship between neuronal hyperactivity and tau pathology, and suggest seizures and seizure activated neurons as targets to slow progression of tau pathology.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.12/D9

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Characterization of Second-Hit Mouse Models for Alzheimer’s disease, Amyotrophic Lateral Sclerosis, and Parkinson’s Disease Using Plasma Neurofilament Light Chain as a Biomarker

Authors: *E. AUER, R. RABL, L. BREZNIK, I. SCHILCHER, T. LÖFFLER, K. PLATTNER, M. LJEKAJ, M. DAURER, S. FLUNKERT, M. PROKESCH;
Scantox Neuro GmbH, Grambach, Austria

Abstract: Neurodegenerative diseases such as Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson’s disease (PD) are characterized by progressive neuronal loss and overlapping pathological mechanisms. To enhance translational relevance and phenotypic robustness of transgenic animal models for these diseases, we employed second-hit paradigms in established respective transgenic mouse lines: ARTE10 for AD, heterozygous TAR6/6 for ALS, and M83 for PD. Each model was subjected to a disease-relevant secondary insult to potentiate pathology: ARTE10 mice received intracerebral injections of AD brain-derived tau seeds or tau

preformed fibrils (PFFs); TAR6/6 mice were administered AAV-TDP-43 intrathecally; and M83 mice were injected with α-synuclein PFFs. The primary objective was to evaluate the impact of these second hits on disease progression and biomarker expression, with a focus on neurofilament light chain (NF-L) levels in plasma and cerebrospinal fluid (CSF). NF-L, a sensitive marker of axonal damage, was quantified longitudinally to assess its utility in differentiating disease burden across models and interventions. Our findings demonstrate that second-hit paradigms significantly amplify neurodegenerative phenotypes, reflected by elevated NF-L levels in plasma, with preliminary data from CSF supporting these findings. This comparative approach underscores the value of combinatorial modelling in preclinical research and highlights NF-L as a cross-disease biomarker for neurodegeneration.

Disclosures: E. Auer: A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **R. Rabl:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **L. Breznik:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **I. Schilcher:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **T. Löffler:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **K. Plattner:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **M. Ljekaj:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **M. Daurer:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **S. Flunkert:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **M. Prokesch:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.13/D10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH-R01-AA028782
NIH-P60-AA011605

Title: Use of a novel mouse model of tau seeding to identify alcohol-induced changes in pathological tau

Authors: E. SHANNON[1], *S. P. FACCIDOMO[4], J. L. HOFFMAN[2], A. KIM[5], C. W. HODGE[3]; [1]Bowles Ctr. for Alcohol Studies, [2]Alcohol Studies Ctr., [3]Psychiatry, Univ. of North Carolina-Chapel Hill, Chapel Hill, NC; [5]Bowles Ctr. for Alcohol Studies, [4]Univ. of North Carolina - Chapel Hill, Chapel Hill, NC

Abstract: *Background:* Moderate alcohol drinking impairs cognition and is an environmental risk factor for Alzheimer's Disease and related dementia (ADRD) and microtubule associated protein tau (Tau) merits attention as a potential alcohol-sensitive target. Although links between alcohol use and Tau-associated pathology have been established, more research is needed to

understand the impact of alcohol drinking on the underlying neurobiological mechanisms and genomic adaptations associated with ADRD. *Objective:* To evaluate the impact of chronic alcohol drinking and the development and progression of ADRD neural pathology throughout the brain using an innovative AAV strategy for human Tau-P301L (huTau-P301L) “seeding” in the entorhinal cortex (EC) of C57BL/6J mice. *Methods:* C57BL/6J mice were bilaterally infused with the huTau-P301L AAV into the EC. After recovery from surgery, mice were given free access to 20% alcohol and water or water only (control mice) in their home cage for 4 weeks. Next, free-floating immunohistochemistry was performed to evaluate pathological huTau-P301 expression (Tau 13 antibody) and Tau misfolding (MC1 antibody) at the site of AAV infusion and propagation throughout the brain. To minimize background signals, primary antibodies were directly tagged with AlexaFluor647 for visualization. *Results*: Mice showed a preference for alcohol vs water and self-administered an average of 22.9 g/kg/day. As expected, the viral expression was highest in the EC in both alcohol self-administering and control mice and tapered off in more distal regions as the virus cleaved and propagated throughout the brain. Moreover, MC1 immunofluorescence was quantified in regions adjected to the EC such as the lateral EC and ventral CA1 and CA2 regions of the hippocampus and was significantly potentiated in mice with a history of alcohol drinking. *Conclusions:* This AAV huTau-P301L Tau seeding approach is a great preclinical model to study the spread and propagation of huTau throughout the mouse brain. We show that Tau is an alcohol-sensitive target of neurodegeneration and predict that other aspects of Tau pathology are similarly exacerbated by a history of alcohol drinking. Future research will explore this mechanism and correlate neuropathology with behavioral deficits.

Disclosures: E. Shannon: None. **S.P. Faccidomo:** None. **J.L. Hoffman:** None. **A. Kim:** None. **C.W. Hodge:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

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Program #/Poster #: PSTR110.14/D11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PNRR grant (T.H.E.) ECS_00000017
CNR grant NutrAge (nr. DSB.AD005.225)

Title: The role of Extracellular vesicles in the spreading of tauopathies

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Abstract: Synaptic dysfunction is an early mechanism in Alzheimer's disease (AD) that progressively affects larger areas of the brain over time. However, the initiation and propagation of this alteration remain unknown. Both β-Amyloid and tau are key pathological hallmarks of

AD and play a significant role in synaptic dysfunction. We have previously investigated the biological properties of microglia-derived inflammatory extracellular vesicles (EVs) carrying Aβ. We demonstrated that amyloid-β released by microglia, in association with large extracellular vesicles (Aβ-EVs), alters dendritic spine morphology at the site of neuron interaction *in vitro*. Then, injecting EVs into the mouse brain, to evaluate their impact on synaptic plasticity and memory, we confirmed that Aβ synaptotoxicity is exacerbated when associated with microglia-derived EVs. Notably, the propagation of Aβ effects in the brain is mediated by EVs movement along neuronal processes, following a diffusion pattern similar to that observed in human Alzheimer's disease brains. Our aim is to extend these observations and study the effects of different forms of the tau protein. In particular, we used either the wild-type form of oligomeric tau (typical of AD) or the mutated tau (P301S, typical of frontotemporal dementia, FTD). Using in vitro electrophysiology, we demonstrate that 1 h after Tau-EV injection into the mouse entorhinal cortex, long-term potentiation (LTP) is impaired in the entorhinal cortex but not in the dentate gyrus, its main target region, while 24 h later it was impaired also in the dentate gyrus, revealing a spreading of LTP deficit between the two regions. Similar results were obtained when mutated P301S tau was used observing a spreading of the effect from the prefrontal cortex. The development of synaptic dysfunction is associated with a progressive memory impairment either in the AD or the FTD model as assessed by behavioral tasks exploring the working and episodic-like memories. These experiments aim to demonstrate that abnormalities in network activity and memory performance caused by pathogenic proteins associated with microglia-derived EVs are reminiscent of the corresponding human pathologies. These models introduce a novel biological mechanism mediated by extracellular vesicles as a contributing factor to the progression of tauopathies.

Disclosures: N. Orsini: None. **T. Catani:** None. **C. Verderio:** None. **N. Origlia:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.15/D12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R01 AG078734

Title: Towards understanding the role of PHF1 site phosphorylation on tau in an APP Model

Authors: *A. A. ITURBE[1], G. XU[4], R. SEVILLENO[1], D. R. BORCHELT[2], P. CHAKRABARTY[3];
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Abstract: Phosphorylation on select Ser/Thr/Tyr residues in tau precedes the emergence of cognitive decline in neurodegenerative dementias such as Alzheimer's disease and

Frontotemporal dementia. Specifically, phosphorylation on the PHF1 epitope (Ser396/404) has been associated with intracellular inclusions of misfolded and aggregated tau protein. In this project, our aim was to biochemically interrogate the pathological features associated with phosphorylation in the PHF1 epitope in the context of Alzheimer's disease amyloidosis. Human data and preclinical data from our lab indicated strong synergy between amyloid beta (Aβ) and P301L (PL) tau, leading to hyperphosphorylation and accelerated tau misfolding when Aβ plaques are present. We examined whether combinatorial phospho-mimetic substitutions on Ser396, Ser400, Thr403 and Ser404 ('PHF1' epitope) would exacerbate the formation of tau inclusions in the presence of Aβ plaques. To test this, we incorporated these phospho-mutations in the backbone of human 0N/4R P301L mutant tau (AAV-PL-PHF1+) and expressed these in neonatal APP transgenic mice using adeno-associated virus (AAV) delivery. We selected the TgCRND8 strain that expresses the human mutant APPswe,ind transgene, forming intracerebral amyloid β (Aβ) plaques by 3-months of age. Transgenic (Tg) mice and their wild type (WT) littermates were injected with AAV-PL-PHF1+ on neonatal day P0 and examined at 6-months of age. We confirmed tau transgene expression using CP27 antibody (total tau: Dr. P. Davies). The AAV-PL-PHF1+ tau expression was mostly limited to frontal cortex and hippocampus, and was equivalent between the Tg and WT injected cohorts. Immunostaining with pSer202 AT8 antibody, a gold standard in detecting pathological tau, surprisingly revealed complete absence of this epitope in the AAV-PL-PHF1+ tau expressing Tg and WT mice. Consistent with this, mice also did not display any evidence of misfolded MC1-immunopositive pre-tangle tau. At the same time, pThr231 (AT180 antibody) was detected in both Tg and WT mice expressing AAV-PL-PHF1+ tau. Overall, our data indicates that hyperphosphorylation 'signals' on the PHF1 epitope does not necessarily exacerbate formation of misfolded and aggregated tau, even in the presence of Abeta plaques.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

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Program #/Poster #: PSTR110.16/D13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant 1R21AG085555-01A1

Title: The effect of pathogenic tau on hippocampal place cell firing

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Abstract: Over six million people in the United States have Alzheimer's disease (AD), the most common form of dementia, which causes memory loss, personality changes, and eventual death.

A primary hallmark of AD is the formation of insoluble neurofibrillary tangles, which predominantly result from the hyperphosphorylation, misfolding, and oligomerization of tau protein in neurons of the brain. During the progression of AD, the location and extent of neurofibrillary tangle formation is correlated with cognitive and memory deficits. Two of the first cortical regions to display neurofibrillary tangle formation and hyperphosphorylated tau are the entorhinal cortex and CA1 region of the hippocampus. One role of hippocampal CA1 is to encode the position of an animal within its environment, where the animal's position is represented by place cells, a subset of CA1 principal neurons that fire preferentially when the animal is at a certain location within its environment. Indeed, one of the first symptoms of AD is a deficit in spatial navigation. Previous research in rodent models has shown a correlation between tau pathology and navigational deficits. However, no study to date has examined the effect of hyperphosphorylated tau directly on CA1 pyramidal neurons during navigation. To examine the effect of pathogenic tau on mouse dorsal hippocampal CA1 pyramidal cell function, we will directly express pathogenic tau in hippocampal CA1 pyramidal neurons and measure their activity through the simultaneous expression of the genetically encoded calcium indicator (GECI) GCaMP6F. To do this, we will inject a Cre-dependent adeno-associated virus (AAV) that encodes the sequences for both a double mutant tau protein, 1N4R hTau-P301L/S320F (Koller et al 2019, Strang et al 2018), which hyperphosphorylates within weeks, and the GECI GCaMP6F, into dorsal hippocampal CA1 of Camk2a-cre mice. The activity of hippocampal CA1 pyramidal neurons will be inferred from calcium transients measured using an Inscopix nVue data acquisition system. The activity of CA1 pyramidal cells will be recorded while the mouse completes a reward location learning task. The formation of place cell activity during learning will be compared between CA1 pyramidal neurons that express hyperphosphorylated/misfolded tau and those neurons that do not. Our data may identify a potential direct effect of pathogenic tau on the ability of hippocampal CA1 place cells to encode position during learning.

Disclosures: E. Leggett: None. **P. Goswamee:** None. **R. McQuiston:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.17/D14

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Select transmembrane proteins altered in early Alzheimer's disease profoundly affect neuronal Tau dynamics and phospho-Tau levels

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Abstract: Alzheimer's disease (AD) is pathologically defined by the accumulation of amyloid-beta (Aβ) plaques, followed by the formation of neurofibrillary tangles. Previous studies reported that Aβ aggregation can initiate tau pathology, yet the molecular mechanisms linking these two AD hallmarks remain unclear. To address this gap, the Golde lab recently performed comparative proteomic analyses of AD brains and APP transgenic mouse models, identifying a shared protein network that emerges in response to Aβ accumulation (the 'amyloid responsome'). Notably, from this work, we found that several Type-1 transmembrane proteins (STPs) were among the most highly upregulated proteins. Building on this observation, we investigated whether these STPs might interact with tau, providing mechanistic insight into how Aβ may facilitate tau-driven neurodegeneration.To investigate their roles in tau biology, we co-expressed several STPs along with mutant human tau (P301L and S320F) in HEK293T cells. We observed a marked reduction in intracellular tau levels, accompanied by an increase in extracellular tau in the culture medium, suggesting that STP expression promotes tau secretion. We further validated these findings *in vivo* by delivering STP-expressing AAVs into mouse brains via stereotaxic or intracerebroventricular injection. Consistent with our *in vitro* findings, brain tissue analysis revealed significantly decreased neuronal Tau aggregation and total tau levels when STPs were co-expressed. Together, these data support a model in which STPs influence tau dynamics or clearance, possibly by modifying membrane dynamics or promoting extracellular release of tau. These findings offer new insight into how early responses to amyloid pathology may influence tauopathy and disease progression, and suggest that STPs could serve as novel therapeutic targets in AD.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR110.18/D15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH AG054345
RF1AG079125

Title: Synergistic Amyloid and Tau Pathogenesis in a Novel Knock-In Mouse Model: Multi-Omics and Spatial Profiling Across Disease Progression

Authors: *A. L. OBLAK[1], C. KALEM[2], A. PERKINS[3], M. SASNER[4], M. D. KOOB[5], B. T. LAMB[1];
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Abstract: Interactions between amyloid-β (Aβ) and tau pathologies are key drivers of neurodegeneration, yet the mechanisms of their synergy remain poorly defined. We developed a novel cross between the $hA\beta^{SAA/SAA}$ (SAA) amyloid mouse model and the MAPT(H1)-GR model harboring 10IVS+16T and N279K mutations in the MAPT H1 haplotype. This model provides a tractable system to study combined amyloid and tau pathology over disease progression. We performed comprehensive analyses across 4, 6, and 12 months of age, integrating molecular, biochemical, immunohistochemical, transcriptomic, and spatial proteomic data. Biochemical assays revealed age-dependent exacerbation of both Aβ deposition and hyperphosphorylated tau accumulation in the cross compared to parental models. Immunohistochemistry identified co-localized amyloid plaques and tau inclusions in hippocampus and cortex, with progressive gliosis. RNA-sequencing and spatial transcriptomics revealed synergistic activation of neuroinflammatory pathways, disruption of synaptic networks, and dysregulation of protein homeostasis. Spatial proteomic profiling using NanoString GeoMx uncovered region-specific alterations in cytoskeletal, synaptic, and mitochondrial protein networks, providing new insights into amyloid-tau interactions. This novel complex model exhibits progressive and spatially heterogeneous proteinopathy and neurodegeneration, offering a powerful preclinical model for mechanistic studies and evaluation of combinatorial therapeutic strategies targeting amyloid, tau and neuroinflammation.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.19/Web Only

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 AG058820
NIH Grant R01 AG075955

Title: Effects of mutations in tau’s 6th proline rich region on sleep and neural activity

Authors: *V. MUNGAMURU, K. ADDO-OSAFO, K. VOSSEL;
Univ. of California Los Angeles, Los Angeles, CA

Abstract: Alzheimer's disease patients experience epileptic activity in addition to cognitive decline, with seizures up to 60% of cases. Current therapies targeting tau protein broadly reduce total levels, which can disrupt essential functions. This study investigates whether two tau variants that specifically disrupt interactions with SH3-containing proteins (AxxA6 and R221A) can ameliorate both Alzheimer's and epileptic pathologies. Using mouse models, the research examined how targeting specific tau signaling pathways affects neuronal excitability and sleep patterns. To incorporate the epilepsy model, Kv1.1 heterozygous knock out mice were crossed

with AxxA6 (6th proline-rich motif: Pro->Ala) and R221A (human Tau 221st Arg->Ala) knockins. Mice underwent EEG surgery with electrodes placed at motor and parietal cortices. Following recovery, 24-hour video-EEG recordings were collected at 2000Hz. Signal analysis included spike detection and sleep state scoring in 10-second epochs based on EMG/EEG activity as: awake, NREM, or REM. Spectral power analysis was performed using discrete Fourier transform with 0.1Hz resolution. Kv1.1-/-_AxxA6ki/ki (n=4, mean 2.16 spikes/hour) had significantly reduced the spike rate when compared to Kv1.1-/-_AxxA6-/- (n=7, mean 28.69 spikes/hour, $p = 0.02$, unpaired t-test). During NREM, gamma power was increased in both Kv1.1-/-_AxxA6-/- (n=6) and Kv1.1-/-_AxxA6ki/ki (n=4) mice compared to Kv1.1+/+_AxxA6-/- (n=6) in both parietal cortices ($p < 0.05$, Holm-Šídák test). During REM, beta power was increased in Kv1.1-/-_AxxA6-/- mice than Kv1.1+/+_AxxA6-/- ($p < 0.05$; Holm-Šídák test) in both regions. Gamma power was increased in Kv1.1-/-_R221Aki/ki (n=12) mice than Kv1.1-/-_R221A-/- (n=12) ($p = 0.04$, Holm-Šídák test), indicating R221A amplifying Kv1.1 KO effects. Kv1.1-/-_R221Aki/ki mice had reduced NREM and REM duration than Kv1.1+/+_R221A-/- mice ($p < 0.01$, Dunnett's T3 tests). Kv1.1-/-_AxxA6-/- mice had increased transitions between Awake and NREM ($p < 0.02$, Tukey's test) compared to Kv1.1+/+_AxxA6-/- mice, which Kv1.1-/-_AxxA6ki/ki rescued ($p < 0.002$, Tukey's test). To conclude, AxxA6 reduced Kv1.1-/- induced spikes, and rescued Kv1.1-/-induced abnormal network activity during REM, whereas R221A amplified the abnormal gamma activity. R221A also amplified Kv1.1-/- induced abnormal sleep duration. AxxA6 also rescued Kv1.1-/- induced sleep fragmentation. Overall, disrupting Tau's 6th proline-rich motif interaction with SH3-containing proteins could ameliorate both Alzheimer's and epileptic pathologies.

Disclosures: V. Mungamuru: None. **K. Addo-Osafo:** None. **K. Vossel:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

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Support: NIH Grant NS135693
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Title: Intrahippocampal delivery of hyperphosphorylated human tau oligomers induces neurodegeneration in non-transgenic wild-type mice

Authors: *H.-R. CHEN[1], M.-H. KUO[2], C.-Y. KUAN[3];
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Abstract: Hyperphosphorylated tau (p-tau) forms neurofibrillary tangles, a key biomarker for Alzheimer's disease and additional neurodegenerative tauopathies. However, neurofibrillary tangles are not sufficient to cause neuronal dysfunction or death. Intrahippocampal injection of tau isolated from AD patients has limited effects on the cognitive functions of non-transgenic mice, despite the recapitulation of pathological tau deposits in the mouse brain. It therefore remains uncertain as to whether all hyperphosphorylated tau is directly responsible for AD neurodegeneration. We examined this issue by injecting recombinant p-tau oligomers to the hippocampus of non-transgenic, wildtype mice and found progressive cognitive deficits that correlate with neuron death spreading from the ipsilateral hippocampus to the cortex. Apomorphine, which retards p-tau aggregation and cytotoxicity *in vitro*, antagonized p-tau-induced cognitive deficits and neuron death. These results suggest the pathogenic role of p-tau oligomers and a novel AD model facilitating drug development.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

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Program #/Poster #: PSTR110.21/D17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R24AG073138
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Title: Tau-based model of Alzheimer's Disease in rhesus macaques: a behavioral and pathologic characterization

Authors: *D. J. GRIGGS[1], L. M. NOVIK[1], G. B. DINIZ[2], S. P. OTT[1], K. L. SCHWARTZ[1], C. T. ERICES[1], J. H. KORDOWER[3], M. G. BAXTER[4], J. H. MORRISON[1];
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[4]Pathology/Comparative Med., Wake Forest Univ. Sch. of Med., Winston-Salem, NC

Abstract: Alzheimer's Disease (AD) is among the most deadly and debilitating age-related neurodegenerative diseases and is hallmarked by amyloid-beta plaques and tau-containing neurofibrillary tangles (NFTs). Decades of work predominantly in rodents has led to limited success with USFDA-approved AD therapies targeting amyloid-beta, which has prompted us to develop a highly translational animal model of tau pathology prevalent in AD and related dementias (ADRDs). Tau NFTs are thought to be the end-stage of a pathological biochemical cascade originating with early-stage pathological tau species in the entorhinal cortex (ERC).

With this in mind, we have developed an ADRD model in rhesus macaques with bilateral ERC injections of AAV-2xTau, an AAV carrying two human tau mutations (P301L/S320F), known to make tau highly prone to aggregation. Six monkeys (3 male) received AAV-2xTau, and another 6 (3 male) received a Control vector. We used Delayed Non-Match to Sample (DNMS) to evaluate the monkeys prior to and following surgery and found that DNMS performance was mildly impaired in the 2xTau group at 3 months postop and more robustly impaired at 6 months postop. Monkeys in the 2xTau group were still impaired relative to Controls at 9 and 12 months postop but these effects were diminished compared to the 6 month time point, perhaps reflecting improvements related to practice with testing that were also apparent in Control monkeys. Immunohistochemistry of the 2xTau brains has revealed substantial spread of pathological tau throughout the ERC and hippocampus and mild pathological tau spread in the neocortex, which is a faithful replication of early tau spread in human AD brains. Together, the behavioral and immunohistochemical results make our highly translational model a promising opportunity for development of tau-based therapeutics for ADRDs.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR110.22/D18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NINDS R01NS136448
K23NS109284
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NIH/NINDS R01NS115800

Title: Ubiquitin-proteasome system impairment in developing neurons triggers a compensatory downregulation of MAPT expression

Authors: *M. R. SHIN[1,2], G. LIDDIARD[1,2], N. FIROUZSHAHI[1,2], M. WEIS[1,2], J. SIMMERING[1,3], J. GLYKYS[1,4], M. SCHULTZ[1,4], M. M. HEFTI[1,5];
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Abstract: Introduction: Impairment of the ubiquitin-proteasome system (UPS) and autophagy is a hallmark of neurodegenerative diseases such as Alzheimer's disease (AD) and related tauopathies. However, the relative contributions of these pathways to tau proteostasis remain poorly understood. We previously demonstrated that developing neurons exhibit high levels of total tau without the pathological consequences observed in aging neurons. In this study, we sought to uncover the mechanisms underlying tau proteostasis in developing human forebrain neurons.
Methods: We generated mixed dorsal forebrain cultures (equivalent to human second-trimester fetal neurons) from female human induced pluripotent stem cells (iPSCs), with or without eGFP-tau overexpression, and pharmacologically inhibited the UPS and/or autophagy. Tau proteostasis was assessed using western blotting, quantitative PCR, live-cell imaging, and RNA sequencing (aligned to hg38 with STAR aligner; quantified using subreads & DESeq2). Experimental conditions were assessed with triplicate biological replicates, and cell imaging was performed blinded to experimental conditions to prevent observer bias.
Results: Inhibition of the UPS and autophagy in normal developing neurons led to decreased total tau levels compared to control cells (unpaired t-test: $p=0.024$ & $p=0.032$, respectively). Following proteasome inhibition, we found that the decrease in total tau levels in UPS-inhibited cells compared to control cells was driven by reduced MAPT transcription (unpaired t-test: 0.005). To test the functional impact of this response, we inhibited UPS and autophagy activity in eGFP-tau overexpression neurons and saw an increase in total tau levels compared to vehicle-treated control cells (glm - $p<2x10^{-16}$ for both comparisons). To identify upstream contributors of *MAPT* regulation, we inhibited UPS function and performed RNA sequencing; the following analysis revealed five genes known to modulate tau expression.
Discussion: Our findings suggest that developing neurons rely on both the UPS and autophagy to regulate tau proteostasis, and when the ubiquitin-proteasome systems fail, healthy neurons activate transcriptional regulatory mechanisms to maintain tau homeostasis. These results highlight unique aspects of tau regulation in early neuronal development, offering insight into disease-relevant processes in Alzheimer's disease and related tauopathies.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR110.23/D19

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: SECIHTI Grant 319578
SECIHTI Postgraduated Fellowship D.E.G.-R.

Title: In vitro models from human olfactory neuroepithelial neural precursors cells to study progressive supranuclear palsy (psp) pathophysiology

Authors: *D. GOMEZ[1,2], O. LORA-MARIN[2], J. PADILLA-MENDOZA[2], M. CARDENAS-AGUAYO[2];
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Abstract: Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative tauopathy characterized by a predominance of the 4R isoform of tau protein, primarily occurring in a sporadic manner. Currently, there is no adequate diagnostic method, as it shares clinical characteristics with Parkinson's disease, and the underlying pathophysiological mechanism of PSP remains unknown. The development of an experimental model using cell lines derived from human olfactory neuroepithelium precursors cells (hONE-NPCs), as a source of peripheral neural cells, obtained from PSP patients diagnosed with probable PSP and healthy donors with 4R tau overexpression induced by the environmental neurotoxin Annonacin, holds potential for identifying molecules and pathways contributing to early neurodegenerative events in PSP. Our main objective was to establish two approaches of *in vitro* models for the study of PSP disease: one pharmacological and the other directly from PSP patients. **Methods:** The hONE-NPC culture was obtained through nasal exfoliation, from 63 63-year-old healthy donor without cognitive impairment and three patients diagnosed with probable PSP from Mexican population. The hONE-NPC cell culture was maintained, and a cell bank was made. The hONE-NPCs were characterized with immunofluorescence and Western Blot (WB) to demonstrate the presence of stem cells in the olfactory epithelium. A cell viability assay was performed using hONE-NPC from a healthy donor with varying concentrations and exposure times to Annonacin. Additionally, the overexpression, hyperphosphorylation, and oligomeric formation of the 4R tau isoform were analyzed by WB. **Results:** The hONE-NPC culture from healthy donors and patients diagnosed with probable PSP expressed markers of stem cells such as SOX2, Oct 3/4, NANOG; as well as neural compromise markers including bIIITubulin, Nestin, Olig1, and had ki67-positive. Annonacin caused a concentration-dependent decrease in cell viability in hONE-NPC from 63 a 63-year-old healthy donor. The results showed a significantly overexpression of the 4R tau isoform at a concentration of 2 uM annonacin at 96h with respect control. Also, we detected an increase in tau hyperphosphorylation and oligomeric formation under that condition. **Conclusion:** The non-invasive method for extracting and maintaining hONE-NPCs, standardized in our laboratory, was successful. The hONE-NPCs obtained from PSP patients and the overexpression of 4R tau isoform in the *in vitro* model at 2 uM of Annonacin at 96h suggest that our *in vitro* models are suitable for studying the mechanism related to PSP.

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Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG075092
R56AG066782

Title: Ectodermal-neural cortex 1 interacts with tau's microtubule-binding domain and promotes its autophagic clearance

Authors: *S. VO[1], T. KIM[1], N. SWEENEY[1], D. M. ACOSTA[1], Y.-K. JUNG[2], L. MUCKE[3], R. A. NIXON[4], H. FU[1];
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Abstract: Proteostasis disruption is increasingly recognized as a driver of selective neuronal and regional vulnerability to tau pathology in Alzheimer's disease (AD) and tauopathies. We have previously identified ectodermal-neural cortex 1 (ENC1) as a hub gene in vulnerable excitatory neurons (ENs), yet its relationship to tau remains unclear. We hypothesized that ENC1 interacts with tau via its microtubule-binding domain and thereby accelerates tau clearance through the autophagy-lysosome pathway (ALP). We mapped ENC1-tau in post-mortem cortex with Duolink proximity-ligation assays (PLA) and utilized the autophagy reporter mice (TRGL6; mRFP-eGFP-LC3) to measure autophagy dynamics *in vivo*. The PLA revealed significantly increased interaction between ENC1 and total tau (TauC) and phospho-tau (TauY9) in early- and late-stage AD than in control cases ($p < 0.001$). Furthermore, we conducted PLA assays on HEK293T cells co-transfected with FLAG-ENC1 and either full-length GFP-tagged human 1N4R tau construct or domain-deleted variants and vice versa. We found that deletion of tau's microtubule-binding repeat domain abolished ENC1-total tau binding ($p < 0.001$), whereas ΔC-terminus, ΔN-terminus or Δproline-rich domain had less of an effect. To probe the effect of ENC1 deletion on autophagy dynamics, we injected AAV8-CaMKIIα-Cre into the entorhinal cortex of ENC1$^{flox/flox}$ mice crossed with TRGL6 mice. We found that conditional deletion of ENC1 in entorhinal excitatory neurons of TRGL6; ENC1$^{flox/flox}$ significantly decreased the number of single red puncta (autolysosomes, $p < 0.01$) and increased single yellow puncta (autophagosomes, $p < 0.01$), suggesting the inhibition of the autophagic flux. Collectively, our data reveal that ENC1 interacts with tau via its microtubule-binding repeat domain and funnels it to the autophagy-lysosome pathway, pinpointing an early mechanism that can be leveraged precisely to slow the onset of AD and AD related dementias.

Disclosures: S. Vo: None. **T. Kim:** None. **N. Sweeney:** None. **D.M. Acosta:** None. **Y. Jung:** None. **L. Mucke:** None. **R.A. Nixon:** None. **H. Fu:** None.

Poster

PSTR110: Tau in Alzheimer's Disease: *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.25/D21

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Evaluation of human induced pluripotent stem cell (hiPSC)-derived tri-culture as in vitro model for Alzheimer's Disease

Authors: *C. FORMICA[1], C. VAN BERKEL[2], L. SMIT[2], J. COTOVIO[3], P. VAN LOENEN[6], M. ARGENZIANO[4], **S. JAIN**[5];
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Abstract: The development of physiologically relevant in vitro models for Alzheimer's disease (AD) remains a major challenge in translational research. Existing preclinical systems often fail to recapitulate the cellular complexity and human-specific disease mechanisms involved in neurodegeneration and neuroinflammation. To address this gap, Ncardia has developed a human induced pluripotent stem cell (iPSC)-derived tri-culture model comprising neurons, astrocytes, and microglia. This platform enables the study of AD-relevant processes, including TAU pathology, microglia-neuron interactions, and cytokine-driven neurotoxicity.
A key innovation supporting this platform is the development of robust, large-scale manufacturing of iPSC-derived microglia. These microglia are phenotypically and functionally mature, express key markers (e.g., TMEM119, P2RY12), and exhibit transcriptomic profiles similar to adult human microglia. Upon exposure to AD-associated triggers, microglia show increased pro-inflammatory cytokine secretion (IL-6, TNF-α, IL-1β, IL-18), morphological transition to an amoeboid state, and accelerated phagocytic activity, as measured by pHrodo bioparticle uptake.
Using recombinant TAU PFFs, we established a tauopathy model within the tri-culture system. This led to the induction of TAU hyperphosphorylation (pTAU), aggregation, and release of pTAU and neurofilament light chain (NfL) into the supernatant. Neuronal degeneration and glial activation were quantifiable through imaging and biochemical assays. Notably, microglia internalized pTAU either directly or through phagocytosis of damaged neurons, which exacerbated the inflammatory response.
This system provides a scalable, human-relevant platform for drug screening and mechanistic studies. It enables multi-parametric evaluation of therapeutic candidates on both primary disease drivers and downstream inflammatory and degenerative pathways. By capturing neuron-glia cross talk, synaptic dysfunction, and microglial activation in a high-throughput format, this tri-culture model supports the identification of neuroprotective and anti-inflammatory therapeutics for AD.

Disclosures: C. Formica: A. Employment/Salary (full or part-time): Ncardia Services BV. **C. van Berkel:** A. Employment/Salary (full or part-time): Ncardia Services BV. **L. Smit:** A. Employment/Salary (full or part-time): Ncardia Services BV. **J. Cotovio:** A. Employment/Salary (full or part-time): Ncardia Services BV. **P. van Loenen:** A. Employment/Salary (full or part-time): Ncardia Services BV. **M. Argenziano:** A. Employment/Salary (full or part-time): Ncardia Services BV. **S. Jain:** A. Employment/Salary (full or part-time): Ncardia Services BV.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.01/D22

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Dose-dependent effects of pomegranate juice on toxin-induced neurodegeneration in C.elegans

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by cognitive decline and the accumulation of amyloid-beta (Aβ) plaques in the brain. This study examined the potential neuroprotective effects of pomegranate juice (PJ), a polyphenol-rich dietary supplement, in reducing toxin-induced neurodegeneration using *Caenorhabditis elegans* transgenic models that express human Aβ. Two strains of transgenic worms were utilized: CL2006, which constitutively expresses Aβ, and CL4176, which expresses Aβ in a temperature-inducible manner. Worms were exposed to three common environmental toxins—lead nitrate, cadmium chloride, and paraquat—at both low and high concentrations. Each exposure condition was tested with or without dietary supplementation of PJ at either 1% or 25% volume/volume concentrations. To assess neurodegenerative outcomes, we evaluated paralysis progression, amyloid-beta aggregation using Thioflavin S staining, and oxidative stress through DCFDA fluorescence. All experiments were conducted on synchronized populations of worms at the L1 larval stage, and each condition was repeated across a minimum of three independent biological replicates. To minimize observer bias, blinding procedures were applied during image analysis. Exposure to environmental toxins led to the earlier onset of paralysis and increased Aβ aggregation, with the most pronounced effects observed at higher toxin concentrations. Supplementation with 1% PJ resulted in a slight delay in paralysis and a mild reduction in Aβ plaque formation compared to toxin-only controls, indicating a potential neuroprotective effect at low doses. In contrast, worms receiving 25% PJ displayed elevated levels of oxidative stress and greater Aβ accumulation, particularly when exposed to paraquat. Notably, neither PJ supplementation alone nor toxin exposure alone significantly altered oxidative stress levels, suggesting that the observed effects are dependent on specific toxin-diet interactions. These overall findings support the possibility of a hormetic dose-response, in which low-dose PJ confers limited neuroprotection, while high-dose supplementation may intensify neurotoxic effects. Further research is needed to clarify the mechanisms underlying these interactions and to determine the optimal conditions for leveraging dietary polyphenols in neurodegenerative disease models.

Disclosures: E.M. Giang: None. **M. Mendoza:** None. **R. Hartman:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.02/D23

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NOASTEC Foundation

Title: Bone marrow-derived mesenchymal stem cells cultured in 3D hydrogels improve cognitive impairment in an Alzheimer's disease model through the secretion of specific miRNAs in exosomes

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Abstract: Previously, we injected 2D cultured bone marrow-derived mesenchymal stem cells (MSCs) intrathecally into the Alzheimer’s disease mouse model (APP/PS1). However, no cognitive improvement was observed after the injection. Therefore, we investigated whether 3D-cultured MSCs could improve the cognitive function of APP/PS mice. In this study, we cultured MSCs in 2D culture dish (2D-MSCs) and 3D hydrogel (3D-MSCs). Then we compared the cellular stemness and exosomal microRNAs (miRNAs) secreted from both cells. The expressions of Oct4 and Nanog were significantly higher in 3D-MSCs compared to 2D-MSCs. In addition, the expressions of exosomal miR-186, miR-375, and miR-410 were significantly higher in 3D-MSCs, compared to 2D-MSCs. Because 3D-MSCs seemed to have more self-renewal character and secrete neuroprotective miRNAs, we injected 3D-MSCs intrathecally into 20-month-old APP/PS1 mice. After the injection, we did Y maze test and Morris water maze (MWM) tests for assessing cognitive function. As a result, the cognitive function was significantly higher in the APP/PS1+3D-MSC group compared to the APP/PS1+vehicle group, in both Y maze and MWM test. Then, we performed immunohistochemical analysis and evaluated the expression of miRNAs in hippocampus. Immunohistochemical analysis revealed that the APP/PS1+3D-MSC group had higher synaptic density and lower astrocytic inflammation in hippocampus compared to the APP/PS1+vehicle group. Additionally, the expressions of miR-186, miR-375, and miR-410 in hippocampus were significantly higher in APP/PS1+3D-MSC group compared to the APP/PS1+vehicle group. From these results, 3D-MSCs seem to have exerted the protective function on neurons and astrocytes by transferring exosomal miR-186, miR-375, and miR-410 into hippocampus.

Disclosures: M. Nakano: None. **K. Nagaishi:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.03/D24

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS KAKENHI Grant 23H02578

Title: Crtac1b/ lotus improves synaptic dysfunction and cognitive impairment in alzheimer's disease model mice.

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease characterized by the accumulation of amyloid-β (Aβ) peptide and the formation of neurofibrillary tangles. AD patients account for the most significant number of dementia patients; nevertheless, effective treatment for AD has not yet been developed. Aβ accumulation is a histological feature of an AD patient's brain and is regarded as the primary risk factor of AD pathogenesis. The oligomeric Aβ peptide forms amyloid plaques and interacts with several cell surface receptors, leading to synaptic dysfunction, neuronal loss, and neuroinflammation, which ultimately result in cognitive impairment in AD. We reported that lateral olfactory tract usher substance (LOTUS), also known as Crtac1B, suppressed an Aβ-induced decrease in spine density in cultured hippocampal neurons through the blockade of Aβ binding to PirB, an Aβ receptor expressed on the cell surface of neurons. These data suggest LOTUS may potentially improve synaptic dysfunction induced by Aβ. However, further research was needed to determine whether LOTUS may ameliorate AD pathology *in vivo*. In this study, we examined whether increasing LOTUS expression levels contribute to ameliorating AD pathologies, such as synaptic dysfunction and cognitive impairment in the AD model mouse (*AppNL-G-F* knock in mouse) and LOTUS overexpressing AD model mouse (*AppNL-G-F* /LOTUS-Tg). We analyzed synaptic function by measuring the expression levels of synaptic proteins in a synaptosome fraction derived from the hippocampus. The expression level of synaptic protein decreased compared with wild-type mice in *AppNL-G-F* mice. In contrast, *AppNL-G-F* /LOTUS-Tg restores the decrease of synaptic proteins. Finally, we performed behavioral tests to evaluate the cognitive function of *AppNL-G-F* /LOTUS-Tg mice. We found that the *AppNL-G-F* /LOTUS-Tg mice showed the recovery of cognitive impairment observed in *AppNL-G-F* mice. Furthermore, we attempted to rescue mice with observed cognitive impairment due to LOTUS overexpression using gene delivery methods. Here, we will present data showing that overexpressing LOTUS in mice with AD pathology is therapeutically effective.

Disclosures: Y. Kawaguchi: None. **J. Matsubayashi:** None. **M. Hijioka:** None. **T. Saito:** None. **K. Takei:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.04/D25

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: A new mouse model of Alzheimer’s disease shows core Aβ plaque pathology and neuroinflammation

Authors: P. YOU, S. WANG, R. LV, W. ZHONG, ***Y. TIAN**, X. ZHOU;
Biocytogen, Waltham, MA

Abstract: The major pathological hallmark of Alzheimer’s disease (AD), the most common type of dementia, is the deposition of amyloid β peptide (Aβ) in the brain. Numerous mutations in the amyloid precursor protein (APP) gene and the presenilin 1 (PSEN1) gene have been identified as disease-associated. Since single *App* knock-in mouse models require 12 months or more to produce Aβ plaques, or the Aβ is difficult to clear and metabolize, they are not suitable for preclinical treatment studies. Biocytogen combined *App* and *Psen1* mutations to generate a new model that shows Aβ plaque pathology and neuroinflammation.
Biocytogen humanized the mouse Aβ sequence and introduced Swedish and Beyreuther/Iberian mutations into the mouse *App* gene, and E120K and M146L mutations into the mouse *Psen1* gene using a knock-in strategy to generate a new model named B-App NL-F / Psen1*M146L*E120K mice. Mutated *App* and *Psen1* mRNA were detected in the cortex of B-App NL-F / Psen1*M146L*E120K mice and confirmed via Sanger Sequencing. Humanized Aβ was detected in the cortex and hippocampus of homozygous B-App NL-F/Psen1*M146L*E120K mice but not in wild-type mice. We next examined Aβ pathology and neuroinflammation by IHC using antibodies against Aβ, microglia (Iba1), and astrocytes (GFAP) in the brains of B-App NL-F/Psen1*M146L*E120K mice. Remarkably, a significantly large number of Aβ plaques were detected in the cortical, hippocampal, and subcortical regions of B-App NL-F / Psen1*M146L*E120K mice at 6 months of age. These mice also exhibited significant microgliosis and astrocytosis in the cortex and hippocampus, indicating that neuroinflammation had occurred.
This new mouse model recapitulates amyloid plaque pathology and neuroinflammation *in vivo* without disturbing intrinsic gene expression and will help accelerate the development of disease-modifying therapies for preclinical AD.

Disclosures: P. You: None. **S. Wang:** None. **R. Lv:** None. **W. Zhong:** None. **Y. Tian:** None. **X. Zhou:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.05/D26

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Research Foundation of Korea(NRF) funded by the Korean government(MSIT), Bio & Medical Technology Development Program (RS-2024-00441331)
Division of Life Science and Applied Life Science BK21 FOUR(BrainKorea21Four)

Title: Coagulansin-a induced hsp70 stabilization mitigates alzheimer's pathology, revealed by in silico analysis

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Abstract: The heat shock protein 70 (HSP70) family comprises of major cytoprotective molecular chaperones in cells including neurons. These proteins have many defensive roles in multiple neurodegenerative disorders, including Alzheimer's disease (AD), in which they suppress toxic amyloid beta (Aβ) protein aggregation. In this study, we used eight-week-old male single transgenic (APP) C57BL/6J-Tg (NSE-APPsw) KLAR, double transgenic APP/PS1, and C57BL/6J wild type (WT) mice. Vehicle (0.9% saline) and Coagulansin-A (Coa-A; 50 mg/kg) were administered via intraperitoneal (i.p.) injection once daily for two weeks. For the in vitro study we used SH-SY5Y cells, in which we did MTT assay and immunoprecipitation. Furthermore, in both in vivo and in vitro studies, we did western blotting, Immunofluorescence analyses, Thioflavin S staining, and ELISA assays. We performed the Morris water maze (MWM) test and Y-maze for behavioral analysis of experimental animals. To find the bioactive conformations, Coagulansin-A, into the ATP-binding pocket of Heat Shocked Protein (HSP70) we did the molecular docking. Electrophysiology in vitro and in vivo performed for long-term potentiation (LTP). Here, we have shown that Coagulansin-A (Coa-A, a steroidal lactone) extracted from Withania coagulans induced endogenous HSP70 protein upregulation to reduce AD neuropathological deficits. Coa-A treatment via HSP70 induction significantly reduced the amyloidogenic pathway of Aβ production and aggregation to improve synapse, memory, behavior, and LTP (long-term potentiation) in AD mice. Most importantly, Coa-A positively interacted with HSP70 proteins as determined via molecular docking studies. Indeed, HSP70 activation inhibited BACE1 (beta-site APP-cleaving enzyme 1) and enhanced IDE (insulin-degrading enzyme) and synaptophysin expression in vivo and in vitro AD models. Taken together, our findings demonstrate that Coa-A ameliorates cognitive deficits via endogenous HSP70 protein induction and acts as a therapeutic agent to slow AD progression by reducing multiple pathological features.

Disclosures: S. jang: None. **J. Park:** None. **M. Kang:** None. **E. Choi:** None. **K. Choe:** None. **M. Kim:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.06/D27

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Research Foundation of Korea grant 2017K1A1A2013124
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BrightFocus foundation - Alzheimer's disease research (A2023018F)
European Molecular Biology Organization (EMBO, ALTF 111-2021)

Title: Restoring mitochondrial homeostasis as a therapy for Alzheimer's disease

Authors: *Q. WANG[1], J. AUWERX[2];
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Abstract: Mitochondrial dysfunction is a conserved feature of age-related diseases including neurodegenerative disorders. Accumulating evidence suggests that age-related mitochondrial impairment plays a fundamental role in the pathogenesis of Alzheimer's disease (AD), such as insufficient energy supply and excessive ROS production. Therefore, improving mitochondrial function may simultaneously target multiple AD pathologies. Here we report that a non-antibacterial tetracycline derivative, 9-tert-butyl tetracycline (9-TB), showed therapeutic effects in animal models of AD through activating the one of the mitochondrial quality control pathways - the mitochondrial stress response (MSR). In mouse models of AD, 9-TB mitigated cognitive decline, electrocorticography abnormalities, and amyloid accumulation. Further investigations into the underlying mechanisms of action will reveal how the improved mitochondrial population benefits brain function, thus paving the way for the development of mitochondria-targeting therapies for AD.

Disclosures: Q. Wang: None. **J. Auwerx:** F. Consulting Fees (e.g., advisory boards); Amazentis, MetroBiotech, OrsoBio, Vandria.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.07/D28

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: In vivo longitudinal assessment of neural circuit dynamics and amyloid plaque progression in the motor cortex of an Alzheimer's mouse model

Authors: *J. ZAPATA[1], D. CHENG[1], S. HUANG[1], N. REN[1], P. JANZ[2], R. REDONDO[2], J. NASSI[1];
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Abstract: Traditional preclinical efficacy assessments for Alzheimer's disease (AD) often rely on terminal endpoint histopathology, which has shown limited predictive value for clinical outcomes. To advance the development of effective therapeutics, there is a critical need for more sensitive and translationally relevant assays that not only quantify histopathological changes but also evaluate neural circuit function. In this study, we employed head-mounted miniature microscopes (miniscopes) to perform longitudinal in vivo imaging of neural circuit activity and amyloid-beta (Aβ) plaque development in the primary motor cortex (M1) of the APPsl70 mouse model of AD, spanning the age range of 10 to 15 months. This approach enabled simultaneous calcium imaging of hundreds of neurons and visualization of Aβ plaques during natural open field exploratory behavior, allowing longitudinal assessment of neurobehavioral circuit dynamics and plaque progression over months. APPsl70 mice displayed reduced locomotor activity compared to wild-type (WT) littermates. In WT mice, distinct subpopulations of M1 neurons increased or decreased their activity during movement, with a higher proportion of down-modulated neurons and a net suppression of activity at the population level during movement. In contrast, APPsl70 mice exhibited a balanced proportion of up- and down-modulated neurons, resulting in no net change in activity during movement. Furthermore, neurons in APPsl70 mice showed increased pairwise correlation, indicating altered functional connectivity. Analysis of the local relationship between Aβ plaque load and neuronal activity revealed that nearby plaque density significantly influenced several neurobehavioral metrics, including individual neuron activity levels, movement-related neuronal tuning, pairwise correlations (both positive and negative), and mutual information These findings reveal altered movement encoding in M1 of APPsl70 mice and support the development of a circuit-based preclinical assay to evaluate candidate Alzheimer's therapies. Such an assay may be particularly valuable for testing monoclonal antibodies, providing a functional readout to determine whether plaque clearance also restores neural circuit integrity.

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Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.08/D29

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSERC Canada Discovert Grant (RGPIN/03909-2021)
Canada Research Chair (CRC-2020-00047)
Canada Foundation for Innovation (CFI-41428)
NSERC CGS-M

Title: Effects of chronic trazodone administration on sleep, touchscreen cognitive testing, and neuropathology in the APP^{NL-F}mouse model of Alzheimer's disease

Authors: *R. GIBSON[1], T. YILDIRIM[1], K. SHAKIBA[2], S. SOBOLEVA[2], H. HAN[1], C. STEVENS[2], A. KOHANFEKR[2], D. PURVICA[2], G. RAVICHANDRAN[2], S. MCGUIRE[2], E. SHAMS[2], J. YUE[3], M. ARAI[4], B. A. KENT[1];
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Abstract: Sleep disturbances are prevalent among individuals diagnosed with Alzheimer's disease (AD), leading to low levels of slow-wave sleep (SWS; N3 stage). Restoring SWS has been proposed as a novel target for AD therapeutics. Trazodone, an antidepressant with sleep-promoting properties, specifically enhances SWS and is well-tolerated by older adults. The current study aims to assess the effects of trazodone on sleep, cognition, and neuropathology in a mouse model of AD. We used our validated, voluntary oral administration paradigm to administer trazodone hydrochloride (60mg/kg) to 14-month-old APP^{NL-F} mice for 60 or 120 days. We assessed sleep and EEG power spectra using EEG/EMG intracranial implants. Cognitive performance was assessed using touchscreen cognitive testing (Bussey-Saksida, Lafayette Instruments; Paired Associates Learning (dPAL) and Location Discrimination (LD) tasks) and novel object recognition. Following chronic trazodone administration, amyloid plaque burden within the dorsal hippocampus and parietal cortex was quantified. Trazodone treatment in 14-month-old APP^{NL-F} mice was associated with longer NREM duration ($p = 0.018$), higher slow oscillation power ($p = 0.005$), and higher delta power ($p = 0.003$) within the first 6 hours following treatment and across 60 days of administration compared to baseline. Furthermore, male mice treated for 60 days exhibited 46% less amyloid plaques in the dorsal hippocampus ($p = 0.017$) and 18% less fibrillary plaques in the parietal cortex ($p = 0.049$). Touchscreen cognitive testing, novel object recognition, and neuropathology assessment from an extended treatment (120 days) is ongoing. Our results suggest that trazodone should be explored as a potential disease-modifying therapeutic for AD, with potential beneficial effects on sleep, cognition, and neuropathology.

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Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.09/D30

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R00AG073507
BBRF Grant 30397

Title: Abeta12-28p as an anxiolytic for alzheimer's disease

Authors: Z. GONG[1], X. GUO[2], A. KANAN[2], ***X. YANG**[1], J. JANKNECHT[2], F. TIAN[2], A. HSIEH[2], J. CHUNG[2], A. V. MASURKAR[1], T. M. WISNIEWSKI[1], S. CHEN[1];
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Abstract: Background: Anxiety is a common symptom of Alzheimer's disease (AD). It has been recently established that anxiety is associated with AD pathology characterized by amyloid-β (Aβ) plaques and neurofibrillary tangles. Our laboratory has demonstrated that acute administration of Aβ12-28P, a synthetic peptide with the potential to competitively inhibit toxic Aβ oligomers, resulted in improved cognitive function in old transgenic AD mice. However, whether inhibiting Aβ toxicity by Aβ12-28P also alleviates anxiety in AD mice remains unknown. Method: Middle-aged (12-15 months old) and old (18-24 months old) APP/PS1 dE9 mice were intraperitoneally injected with Aβ12-28P, while control mice received an equivalent volume of saline. Behavioral tests, including open field test and elevated zero maze, were conducted 2 hours post-injection to assess the acute effect of Aβ12-28P or saline on the anxiety of animals. We further performed in vivo fiber photometry to investigate anxiety-associated neural dynamics across multiple brain regions like ventral CA1 (vCA1) and lateral hypothalamic area (LHA). Adeno-associated virus expressing GCaMP8f was injected into target brain regions, above which an optic fiber was implanted. Four weeks later real-time calcium transients were recorded during open field test and elevated zero maze test. Result: In middle-aged AD mice, Aβ12-28P administration exerted acute anxiolytic effects in the open field test (n = 8 drugged versus 8 non-drugged, $p < 0.05$). Furthermore, anxiety was also significantly alleviated by Aβ12-28P in old AD mice in both the open field (n = 16 drugged versus 14 non-drugged, $p < 0.0001$) and elevated zero maze (n = 20 drugged versus 20 non-drugged, $p < 0.01$) tests. We further compared the neural activity patterns in brain regions vCA1 and LHA with or without Aβ12-28P treatment by fiber photometry. Our data suggested significant modification of anxiety-associated neural dynamics in LHA during open field test (n = 12 drugged versus 12 non-drugged, $p < 0.05$) and elevated zero maze (n = 6 drugged versus 6 non-drugged, $p < 0.05$) by Aβ12-28P administration. Conclusion: These results suggest that Aβ12-28P has an acute anxiolytic effect in both middle-aged and old AD mice. Our finding suggests a novel mechanism about how Aβ12-28P targets to Aβ-related neuropsychiatric symptoms like anxiety in AD, and provides insights into a brain region-specific mechanism behind this therapeutic strategy.

Disclosures: Z. Gong: None. **X. Guo:** None. **A. Kanan:** None. **X. Yang:** None. **J. Janknecht:** None. **F. Tian:** None. **A. Hsieh:** None. **J. Chung:** None. **A.V. Masurkar:** None. **T.M. Wisniewski:** None. **S. Chen:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.10/D31

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 23CDA1051814
24IVPHA1288043
451-03-136/2025-03/200007

Title: Food restriction counteracts the decrease in the number of parvalbumin-expressing neurons in the 5xFAD mouse model of Alzheimer's disease

Authors: M. PEROVIC[1], J. CIRIC[2], N. MILOVANOVIC[2], *V. TESIC[1];
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Abstract: Alzheimer's disease (AD), characterized by amyloid-β (Aβ) accumulation, synaptic dysfunction, and progressive neuronal loss, disrupts inhibitory networks critical for cognitive function. Cortical parvalbumin-expressing (PV) interneurons, essential for maintaining inhibitory-excitatory balance, are highly vulnerable to Aβ toxicity, contributing to network hyperexcitability and cognitive decline. Dietary interventions like every-other-day (EOD) feeding show promise in mitigating age-related neurodegeneration, but their impact on PV interneuron survival in AD remains unclear. This study investigates EOD feeding effects on PV interneurons and neurotrophic signaling in female 5xFAD mice, a model of amyloid pathology. Mice were assigned to ad libitum (AL) or EOD feeding regimen from 2 months of age. Immunohistochemical analysis in 6-month-old mice revealed significant PV interneuron loss in retrosplenial, parietal, and somatosensory cortices of AL-fed 5xFAD mice, paralleling reduced brain-derived neurotrophic factor (BDNF). Strikingly, EOD feeding restored PV neuron density to non-transgenic levels, despite further BDNF reduction in Tg-EOD mice. Western blot analysis also showed increased TrkB receptor levels in Tg-EOD mice, suggesting compensatory neurotrophic signaling, while phosphorylated TrkB (pTrkB) decreased only in Tg-AL mice. These findings demonstrate that EOD feeding preserves PV interneurons in Aβ-rich environments, potentially stabilizing inhibitory networks. However, persistent deficits in downstream plasticity markers (e.g., pCaMKII, CBP) highlight unresolved synaptic dysfunction. The study underscores EOD feeding as a non-pharmacological strategy to counteract early AD-related PV interneuron loss, though synergistic approaches may be needed to address broader molecular deficits. These insights advance understanding of dietary interventions in AD and their potential to modulate GABAergic vulnerability.

Disclosures: M. Perovic: None. **J. Ciric:** None. **N. Milovanovic:** None. **V. Tesic:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.11/D32

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Selecting APP/PS1 and 5xFAD mouse models for Alzheimer's Disease research and drug development

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Abstract: Transgenic mouse models are critical tools for elucidating Alzheimer's disease pathogenesis and advancing therapeutic development. Selecting the right Alzheimer's mouse model is crucial for ensuring accurate representation of disease progression. To offer guidance for Alzheimer's disease model selection, we compared the pathological progression of two classical Aβ-driven models, APP/PS1 and 5xFAD, via behavioral testing, histopathology, and molecular analyses. Morris water maze assays revealed that APP/PS1 mice exhibited a gradual decline in spatial memory between 8 and 16 months, whereas 5xFAD mice displayed significant cognitive impairment starting as early as 6 to 12 months. Immunohistochemical analysis showed Aβ plaque deposition in the hippocampus and cortex of APP/PS1 mice beginning at 8 months, with a progressive increase in plaque burden over time. In contrast, 5xFAD mice developed widespread extracellular Aβ deposition starting as early as 6 months, reflecting accelerated amyloid pathology. Biochemical data further demonstrated that in APP/PS1 mice, soluble $A\beta_{42}$ levels peaked at 12 months and then plateaued, while insoluble $A\beta_{42}$ levels continued to rise. In 5xFAD mice, both soluble and insoluble $A\beta_{42}$ levels increased rapidly from early stages. Transcriptomic profiling revealed distinct pathway alterations in the two models across developmental stages, including the activation of pathways regulating long-term potentiation, neuroinflammation, and early synaptic damage, among others. Our findings underline the applicability of these Alzheimer's mouse models in varied contexts. APP/PS1 mice are more suitable for studying progressive cognitive decline, while 5xFAD mice are preferable for investigations focusing on rapid and significant learning and memory impairments associated with extensive Aβ plaque accumulation. Furthermore, APP/PS1 mice are ideal for examining the gradual processes of plaque formation and maturation, whereas 5xFAD mice are better suited for early-stage, high-throughput drug screening targeting Aβ deposition. By understanding these distinctions, researchers can strategically select Alzheimer mouse models tailored to their investigative and therapeutic goals, thereby enhancing the efficiency and relevance of preclinical drug discovery for Alzheimer's disease.

Disclosures: Y. Li: None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.12/D33

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Arizona Alzheimer's Consortium

Title: Manual lymphatic drainage attenuates cognitive impairment in the 5xFAD murine model of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) affects 6.9 million people over the age of 65 years in the United States and is expected to double by 2060. While FDA approved immunotherapies slow cognitive decline in some individuals with AD, they do not improve cognition, are costly, and have significant side-effects. Therefore, new targets, approaches, and treatments for AD is an immediate necessity. Despite their recent "re-rediscovery," there are no FDA approved therapies for AD that target the brain's lymphatic system. It is well established that the toxic protein, amyloid-beta (Aβ), accumulates in the AD brain. More recent literature has further demonstrated that Aβ is cleared with interstitial and cerebrospinal fluid through a glymphatic—meningeal lymphatic vessel—deep/superficial cervical lymphatic vessel—deep/superficial cervical lymph node pathway. Therefore, any impairment along this route can lead to inefficient drainage and pathological accumulation of Aβ, progressing to AD. We propose a new approach to treating AD, manual lymphatic drainage (MLD), a light skin massage technique traditionally used to reduce fluid accumulation in lymphedema. We hypothesize that MLD targeting the cervical lymphatic vessels will improve cognitive function in AD by increasing Aβ removal from the brain. To test this hypothesis, 5-month-old 5xFAD mice were treated with MLD for 15-minutes, twice per day, for two months. In this preclinical model of AD, 5xFAD mice have significantly reduced nest building scores (One-way ANOVA, Kruskall-Wallis Dunns post-hoc analysis; **$p<0.01$; n=6-9 mice/group) and percent spontaneous alternation in the Y-maze (One-way ANOVA, Fisher's LSD post-hoc; *$p<0.05$; n=6-12 mice/group) compared to WT mice. This cognitive impairment was attenuated in both behavioral tests in 5xFAD mice treated with MLD (*$p<0.05$). After completing behavioral testing, at 7 months of age, brain tissue was harvested to investigate the effects of MLD on biomarkers of neuronal injury and AD such as neurofilament light chain and Aβ, respectively. These studies are ongoing. In conclusion, this pilot study provides proof-of-principle data for MLD's potential as a therapy for the treatment of AD.

Disclosures: M.J. Bartlett: None. **R.P. Erickson:** None. **M.H. Witte:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.13/D34

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA U54 AG054345
NIA R44 AG084491

Title: Utility of the APP^{SAA} knock-in mouse model for preclinical testing

Authors: *M. SASNER[1], L. SLOAN[2], D. GARCEAU[1], N. RYAN[1], A. PODDER[1], J. POMEROY-TUCK[1], R. CHIDAMBARAM[3], T. RAGAN[4], E. BLOSS[1], G. W. CARTER[1], A.

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Abstract: The knock-in APP^{SAA} mouse model was developed to be an alternative to transgenic APP models of familial Alzheimer's disease, which have numerous confounding artifacts and historically have had significant restrictions on use. This model has previously been demonstrated to have significant amyloid pathology and neuroinflammation (Xia et al, 2022). Here we extend neuropathological characterization, add transcriptomic, proteomic, and metabolic profiles, and show age-dependent synaptic loss and cognitive deficits. We quantified amyloid deposition by brain region at various ages using the TissueVision Marinus MP Serial Two-Photon Plus imaging platform. We then used the IBEX technique (Radtke, 2022) of multiplex immunohistochemistry on the same sections to analyze neuroinflammation. We have also used the Ambergen Neurological panel system for proteomic spatial analysis. Transcriptomics on brain homogenates demonstrates an age-dependent increase in alignment to AD consensus modules as defined by the AMP-AD program. At 12 months of age the transcriptomic signature resembles that of the 5xFAD model at 4 months of age, while there is minimal correlation with AD modules at 4 months. Viral labelling of pathways from CA1 to prefrontal cortex demonstrated robust synaptic loss at dendrites proximal to plaques, and milder synapse loss distal to plaques at 12 months of age. At the same age, the APP^{SAA} model exhibited mild learning impairments in the 5-choice serial reaction time task and deficits in cue-dependent associative memory. Advanced cognitive assays using touch screen assays are ongoing.When crossed to Tau (*MAPT*) knock-in gene replacement models carrying N279K or 10IVS+16 risk variants, amyloid deposition was exacerbated relative to the APP^{SAA} model alone. This complex model also exhibits hyperphosphorylated tau and tau inclusions in an age-dependent manner, with co-localized amyloid and tau pathology with gliosis in hippocampus and cortex.These results demonstrate that knock-in models can serve as useful preclinical models both for studying disease mechanisms and for testing of therapeutic strategies targeting amyloid, tau, or neuroinflammatory mechanisms. These models are available for academic and commercial use from the JAX mouse repository.

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Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.14/D35

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 AG069232
NIH K00 AG073558

Title: Open-source gamma sensory stimulation system in an Alzheimer's disease mouse model

Authors: J. PARK[1], ***N. TAN**[2], A. NIU[3], K. GUSAROVA[6], D. EGZIABHER[3], E. Y. WANG[4], C.-Y. YANG[5], L.-H. TSAI[3];
[1]Neurosci., [2]Brain and Cognitive Sci., [3]MIT, Cambridge, MA; [4]MIT, Cambridge, MA, ; [5]Basic Med. Sci., MIT, Cambridge, MA; [6]The Picower Inst. for Learning and Memory, Massachusetts Inst. of Technol., Cambridge, MA

Abstract: Multiple groups around the world have replicated the neuroprotective effects of non-invasive gamma (40 Hz) sensory stimulation—termed Gamma ENtrainment Using Sensory stimulation (GENUS)—to improve Alzheimer's disease pathology. However, due to the lack of a standardized protocol, groups differ greatly in how sensory stimulations are delivered to animals, potentially leading to variability in treatment efficacy. We therefore set out to standardize the methodology and create a cost-effective, reproducible, open-source sensory treatment design for mice. We find animals to receive more reliable audiovisual treatment in the new stimulus chambers compared to our previously used design. Local field potential recordings show gamma entrainment in visual cortex, auditory cortex, prefrontal cortex, and hippocampus in 6- and 12-month-old 5xFAD mice of both sexes. Chronic audiovisual GENUS in the new stimulus chambers reliably reduced amyloid plaques in the 5xFAD brains. We are expanding the GENUS treatment to investigate peripheral neuroprotective effects on gut health in 5xFAD mice. The reproducible, beneficial effects of gamma sensory stimulations—regardless of age, sex, and treatment systems—demonstrate the flexible application of GENUS treatment. The variability in neuroprotective levels also illustrates the critical need to standardize experimental and treatment designs.

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Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.15/D36

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: RO1NS14130
RO1AG075820

Title: Blockade of Kv1.3 alleviates neuropathology via neuroinflammatory and resilience pathways in a mouse model of Abeta pathology

Authors: *R. KUMARI[1], U. SRIVASTAVA[1], A. DABDAB BRANDELLI[1], C. BOWEN[2], P. KUMAR[1], D. KOUR[1], W. E. JANG[1], H. WULFF[3], S. RANGARAJU[1];
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Abstract: Kv1.3, a voltage-gated potassium channel, is a therapeutic target in various neuropathological conditions. In rodent models, several Kv1.3 inhibitors have been shown to inhibit disease-induced neuroinflammation. However, the implicated signaling pathways and underlying mechanisms of neuroprotection remain elusive. In this study, we aim to delineate the major protective mechanisms of Kv1.3 blockade in Alzheimer's disease (AD) by investigating the bulk and single nuclear transcriptomes (snRNAseq) and bulk proteomes, along with neurobehavioral and pathological changes in 5xFAD mouse brain. Following 3 months of Kv1.3 blockade via either small molecule PAP-1 or ShK-223 peptide, we observed reduced Aβ plaque burden with both drugs and improved behavior with PAP-1. snRNAseq of brain nuclei identified neuronal and glial populations with expected AD-related changes in microglia. Pseudo-bulk analyses showed that PAP-1 disproportionately impacted microglia while ShK-223 had more pronounced effects on astrocytes. PAP-1 also increased expression of myelination genes in oligodendrocytes and synaptic genes in neurons, with distinct effects on excitatory and inhibitory neurons. Cell-cell communication analyses showed that PAP-1 increased communication of neurons and astrocytes with endothelial cells. Bulk brain transcriptomics and proteomics with PAP1 showed increased levels of synaptic and pro-resilience proteins while decreased glial activation and several interferon (IFN) responsive genes/proteins. PAP-1 also decreased STAT-1 phosphorylation in the 5xFAD brain, along with preferential reduction of type 2 rather than type 1 IFN-dependent proteins. To gain further mechanistic insight into Kv1.3's role in interferon signaling in microglia, we confirmed physical interactions between Kv1.3 and STAT1 and 3 in BV2 microglia overexpressing Kv1.3. We also found that Kv1.3 blockade (PAP-1, 1μM,1h) specifically reduced only type 2 IFN (IFN-γ,10ng/ml,30 min) and not type 1 IFN -induced (IFN-α/β, 100U/ml, 30 min) phosphorylation of STAT1 and 3. We confirmed this functional coupling between Kv1.3 and type 2 IFN signaling in another microglial cell line, as well as in primary microglia derived from wild-type or Kv1.3-knockout mice. Together, this study provides a cell type-specific understanding of how Kv1.3 channel blockade reduces neuropathology, modulates neuroinflammation and glial activation, along with augmentation of resilience pathways and neuro-vascular coupling in AD pathology. We also provide novel mechanistic insights into functional coupling between Kv1.3 channels and type-2 IFN signaling pathways in microglia.

Disclosures: R. Kumari: None. **U. Srivastava:** None. **A. Dabdab Brandelli:** None. **C. Bowen:** None. **P. Kumar:** None. **D. Kour:** None. **W.E. Jang:** None. **H. Wulff:** None. **S. Rangaraju:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.16/D37

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ministerio de Ciencia, Innovación y Universidades of Spain. Grant PID2021-123865OB-I00

Title: Chronic inhibition of receptor protein tyrosine phosphatase β/ζ reduces amyloid plaque load and modulates pleiotrophin-expressing glial cells, glial-plaque interactions and genes related to amyloid-beta clearance

Authors: T. FONTÁN-BASELGA[1], H. CAÑEQUE-RUFO[1], E. RIVERA-ILLADES[1], E. GRAMAGE[2], M. VICENTE-RODRÍGUEZ[3], ***G. HERRADON**[4];
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Abstract: Alzheimer´s disease (AD) is the most common cause of dementia. Pleiotrophin (PTN) is a neurotrophic factor relevant for central nervous system repair and is upregulated in different neuroinflammatory conditions. PTN is an endogenous inhibitor of Receptor Protein Tyrosine Phosphatase (RPTP) β/ζ. In a previous study, we showed that a short treatment with the RPTPβ/ζ inhibitor MY10 reduced amyloid-beta (Aβ) plaque formation and glial activation in old APP/PS1 mice. Nevertheless, those preliminary data required new studies to test the disease-modifying potential of RPTPβ/ζ inhibition in younger animals with a chronic treatment with MY10. Thus, we have now treated for 3 months five- to seven-month-old male and female wild type (WT) and APP/PS1 mice with MY10. This treatment did not improve recognition memory in APP/PS1 mice. However, it decreased Aβ plaque formation and increased the number of microglial cells in the dorsal subiculum of APP/PS1 mice. In addition, MY10 reduced the number of GFAP+, not Iba1+, cells surrounding Aβ plaques. As expected, PTN expression was upregulated in the brain of APP/PS1 compared to WT mice and it was mainly found in Iba1+ and GFAP+ cells. Interestingly, treatment with MY10 significantly decreased the expression of PTN and the number of PTN-expressing Iba1+ and GFAP+ cells. In addition, MY10 induced a significant decrease of *Mmp9* expression in the hippocampus of APP/PS1 mice, a key enzyme in AD progression. In summary, chronic inhibition of RPTPβ/ζ in APP/PS1 mice reduces Aβ plaque deposition, modulating glial-plaque interactions and the expression of genes related to amyloid-beta clearance.

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Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR111.17/D38

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG072896
R01AG062840

Title: Effect of prolonged liver-specific silencing of LRP-1 gene on Alzheimer's disease pathology in APP/PS1 mice

Authors: *D. V. CHANDRASHEKAR[1], U. R. PANCHAL[1], G. C. ROULES[1], N. JAGADEESAN[1], J. CHU[2], D. HAN[2], R. SUMBRIA[1,3];
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Abstract: The low-density lipoprotein receptor-related protein 1 (LRP1) in the liver plays a key role in the peripheral clearance of amyloid beta (Aβ), and its dysfunction may significantly impact Aβ brain pathology of Alzheimer's disease (AD). Our previous study demonstrated that 12 weeks of liver-specific LRP-1 silencing in AD mice showed a significant increase in brain Aβ load. Here, we studied the impact of extended hepatic LRP1 downregulation on AD pathology in APP/PS1 AD mice. Four-month-old male APP/PS1 AD mice (n=7) underwent liver-specific LRP-1 silencing via intravenous injections of LRP1 microRNA (miRNA) delivered by the adeno-associated virus 8 (AAV8) in conjunction with hepato-specific promoter, thyroxine-binding globulin (TBG). The control APP/PS1 mice received control AAV8 (n=6). After seven months of hepatic-LRP-1 silencing, we assessed spatial reference memory (Y-maze test) and exploratory behavior (open-field test). Brains and plasma were assessed for Aβ load, neuroinflammatory markers (microglia, TREM2, and GFAP), and lipoproteins (APOE and APOB), using immunoassays. Western blot analysis confirmed liver-specific silencing of LRP1. Hepatic LRP-1 silencing significantly increased insoluble $A\beta_{1-42}$ ($p<0.05$) as measured by ELISA, as well as 6E10-positive Aβ load ($p<0.001$) and Thioflavin-S-positive mature Aβ load ($p<0.01$) as assessed by immunostaining in APP/PS1 mice brains. Plasma $A\beta_{1-42}$ levels were also significantly increased ($p<0.05$) with hepatic LRP-1 silencing. Notably, there was a positive correlation between the insoluble brain and plasma $A\beta_{1-42}$ levels ($p<0.05$). Further, prolonged hepatic LRP-1 silencing altered neuroinflammatory responses, evidenced by increased astrogliosis ($p<0.01$) and TREM2-positive area ($p<0.05$), while microglial activation was reduced. Behavioral tests revealed impaired spatial reference memory in the Y-maze ($p<0.05$). Hepatic LRP-1 silencing increased plasma APOB48 ($p<0.05$) and reduced plasma cholesterol ($p<0.05$), and increased brain APOE ($p<0.05$). Overall, these findings demonstrate that long-term hepatic LRP-1 silencing alone is capable of exacerbating Aβ pathology, altering neuroinflammatory responses, and impairing cognition in AD mice. The impact of hepatic LRP-1 silencing on AD pathology is robust yet complex and likely involves a significant interplay between plasma lipid homeostasis and brain pathology, which needs to be further investigated.

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Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.18/D39

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Brain-wide quantification of a BBB-crossing antibody therapeutic targeting amyloid plaques

Authors: C. REDD[1], N. GUANZON[1], Y. GALLEGOS[1], E. BLAES[1], S. P. GANDHI[2,1], U. LANGEN[3], ***D. G. WHEELER**[1,4];
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Abstract: Traditional histological methods require tissue sectioning, which limits the ability to visualize intact anatomical structures. Tissue clearing addresses this limitation by making biological specimens transparent, allowing for volumetric imaging and comprehensive analysis across entire organs. In CNS drug development, these techniques enable evaluation of regional distribution, target engagement, and phenotypic efficacy of antibody therapeutics throughout the brain. We developed an integrated pipeline using Translucence Biosystems' optimized iDISCO-based tissue clearing kits, the Mesoscale Imaging System for ZEISS Lightsheet microscopes, and our machine learning-powered Voxels™ quantification software to assess brain-wide biodistribution of antibody therapeutics in preclinical rodent models. This platform allows for cellular-resolution mapping of immunoreactivity across hundreds of anatomically annotated brain regions. Previously, we used this pipeline to measure blood-brain barrier (BBB) penetration and target engagement of a bispecific antibody engineered to bind both the transferrin receptor (TfR1)—facilitating transcytosis across the BBB—and BACE1, a therapeutic target in Alzheimer's disease (AD). Here, we apply the pipeline to evaluate a Brainshuttle™-enabled antibody designed to target amyloid plaques in an AD mouse model. Wild-type and transgenic mice were intravenously dosed with either vehicle or a human IgG-based Brainshuttle antibody therapeutic. Brains were cleared and stained with the 6E10 anti-amyloid antibody and an anti-human IgG antibody. In vehicle-treated transgenic mice, robust amyloid plaque labeling was observed, but no human IgG signal was detected. In wild-type mice dosed with Brainshuttle, anti-huIgG labeled blood vessels throughout the brain, though parenchymal staining was minimal. In contrast, transgenic brains dosed with the Brainshuttle antibody showed intense human IgG staining that colocalized with amyloid plaques. Using our Voxels™ software, we segmented and quantified the human IgG signal and β-amyloid plaques across hundreds of brain regions. Regions with high amyloid plaque burden showed correspondingly elevated levels of the human antibody therapeutic. These findings demonstrate the utility of our integrated tissue clearing and analysis platform for monitoring BBB penetration, biodistribution, and target engagement across the entire brain.

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Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.19/D40

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Brain-wide quantification of amyloid plaques, microglia, and disease modifying antibodies in AD model mice

Authors: *C. REDD[1], N. GUANZON[1], E. BLAES[1], Y. GALLEGOS[1], J. ZEITOUN[1], A. REKSOATMODJO[1], P. CHEUNG[1], S. P. GANDHI[2,1], L.-A. BARLANG[3], D. G. WHEELER[1,4]; [1]Translucence Biosystems, Irvine, CA; [2]Neurobio. and Behavior, Univ. of California, Irvine, CA; [3]Abbvie, Ludwigshafen, Germany; [4]Activity Signaling LLC, San Diego, CA

Abstract: Recent approvals of human IgG-based antibody therapeutics like Kisunla™ (Donanemab) for Alzheimer's Disease have invigorated R&D for CNS-targeting antibodies, highlighting a need for new approaches to assess the brain biodistribution and target engagement of large-molecule therapeutics in intact tissue samples. Traditional 2D histological approaches in neuroscience rely on tissue slicing, restricting observations to limited regions of interest. Recent advancements in tissue clearing and light sheet microscopy have enabled brain-wide, high-resolution imaging of intact tissue, marking a shift from 2D to 3D histology. To help the development of novel CNS antibody therapeutics, we developed a tissue clearing, imaging, and machine learning-enabled analysis platform for brain-wide measurement of β-Amyloid plaques, plaque-associated microglia (PAMs) and human IgG-based therapeutics. Whole mouse brains were cleared using an optimized iDISCO-based protocol, immunostained for β-Amyloid plaques, Iba1 and human IgG, and imaged using our Mesoscale Imaging System on a ZEISS Lightsheet Z.1 microscope. Image stacks were processed with our ML-powered software, Voxels™, which segmented immunoreactivity and registered the data to the Allen reference atlas for regional analysis. We first applied this pipeline to quantify β-Amyloid and PAMs in 5xFAD mice. Using Iba1 immunolabeling, our segmentation tools differentiated activated PAMs from homeostatic microglia, revealing strong regional correlations between PAM density and local plaque burden. These results supported the utility of PAMs as a phenotypic marker of amyloid pathology and informed our selection of the ARTE10 model for subsequent therapeutic engagement studies. In ARTE10 AD model mice dosed with a Donanemab biosimilar, human IgG was broadly distributed throughout the brain parenchyma and co-localized with β-Amyloid plaques. Regional quantification showed a strong correlation between plaque density and antibody accumulation, with higher IgG levels observed in areas of dense amyloid pathology. This study demonstrates the power of whole-brain tissue clearing, light sheet imaging, and automated quantification for assessing therapeutic distribution and disease-related phenotypes. Our pipeline provides a fast, unbiased, and anatomically comprehensive method for evaluating antibody therapeutic penetration and efficacy, supporting its use in preclinical development of Alzheimer's disease and other CNS-disease targeted therapeutics.

Disclosures: C. Redd: None. **N. Guanzon:** None. **E. Blaes:** None. **Y. Gallegos:** None. **J. Zeitoun:** None. **A. Reksoatmodjo:** None. **P. Cheung:** None. **S.P. Gandhi:** None. **L. Barlang:** None. **D.G. Wheeler:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.20/D41

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Nano Based Combinational Therapy for Alzheimer's Disease

Authors: *D. A. BUSOT[1], H. YANG[3], C. CAO[2];
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Abstract: Alzheimer’s disease (AD) is a complex neurodegenerative disorder requiring multi-target therapeutic approaches due to its multifaceted onset. Mounting evidence highlights the potential of melatonin and insulin in mitigating AD-related cognitive impairment, Amyloid beta (Aβ)-induced neuroinflammation, mitochondrial dysfunction, and neuronal loss. In addition, cannabidiol (CBD) has shown promise in slowing AD progression by inhibiting Aβ and tau hyperphosphorylation, positioning it as a viable therapeutic candidate. This study investigated the therapeutic efficacy of CBD based multi-target nanoformulations, MIC (melatonin, insulin and CBD (MIC) and MC (melatonin, and CBD), in protecting aged AOO/PS1 mice from cognitive decline and AD-related neuropathology. Daily intranasal administration of MIC or MC for three months significantly enhanced cognitive performance in APP/PS1 mice. Biochemical analyses to brain tissues demonstrated substantial reductions in AD-associated neuropathological changes following CBD-based treatment. Furthermore, mitochondrial marker expression indicated that prolonged MIC and MC treatment restored mitochondrial dynamics, enhanced mitochondrial function, and promoted mitophagy. In summary, our results underscore the significant neurocognitive benefits of CBD-based combinatorial therapies and their positive impact on AD-related mitochondrial dysfunction, indicating their potential as safe and effective long-term treatment for AD.

Disclosures: D.A. Busot: None. **H. Yang:** None. **C. Cao:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.21/D42

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Comprehensive behavioral and pathological profiling of 5xFAD mice: Gender differences and sleep dysregulation in Alzheimer's disease

Authors: *L. PARK, J. LEE, S. LEE, Y. KIM, A. LEE, M. LEE, K. PARK, S.-Y. NA, P. J. SWEENEY;
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Abstract: Alzheimer’s disease (AD) is a multifactorial neurodegenerative disorder characterized by progressive cognitive decline and behavioral disturbances. To better understand the interplay between neuropathological progression, cognitive impairment, and behavioral dysregulation, we conducted a comprehensive study using the 5xFAD transgenic mouse model. This integrated investigation examined both gender-specific differences in disease progression and sleep-wake cycle alterations using automated behavioral monitoring. We first assessed sex-based differences in amyloid-beta (Aβ) deposition, neuroinflammation, and cognitive function. Female 5xFAD mice exhibited significantly higher Aβ accumulation and inflammatory markers in the cortex and hippocampus compared to males. These pathological changes were accompanied by earlier and more severe cognitive deficits, as measured by Morris Water Maze, Y-maze, and novel object recognition tests. Neurofilament light (NF-L) levels in cerebrospinal fluid (CSF) further indicated accelerated neuronal damage in females, with differences emerging as early as 3 months of age. In parallel, we employed group-housed, 24/7 home cage analysis using the Home Cage Analyzer (HCA) (Actual Analytics Inc., Edinburgh, UK), a non-invasive, high-throughput behavioral monitoring system, to evaluate circadian rhythm and sleep-related phenotypes in the same cohort. 5xFAD mice demonstrated increased wakefulness, particularly during the daytime rest phase, with disruptions becoming more pronounced at 10 and 16 months of age. These alterations persisted despite age-related declines in locomotor activity, suggesting a decoupling of sleep regulation from general activity levels. Pharmacological validation in wild-type mice confirmed the sensitivity of the HCA to detect drug-induced behavioral changes. Taken together our findings highlight the importance of incorporating both sex as a biological variable, and as naturalistic behavioral monitoring in preclinical AD research. The integration of neuropathological, cognitive, and behavioral data provides a more holistic understanding of AD progression and enhances the translational value of the 5xFAD model for therapeutic development.

Disclosures: L. Park: None. **J. Lee:** None. **S. Lee:** None. **Y. Kim:** None. **A. Lee:** None. **M. Lee:** None. **K. Park:** None. **S. Na:** None. **P.J. Sweeney:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.22/D43

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Comprehensive microhemorrhage evaluation Method in a mouse model of anti-amyloid immunotherapy

Authors: *H. OLUOCH, G. FITZGERALD, J. HANSON, R. B. DEMATTOS, T. KWON; ELI LILLY AND CO, INDIANAPOLIS, IN

Abstract: To demonstrate a new more comprehensive method for evaluating Microhemorrhage events in Mouse Model of Anti-Amyloid Immunotherapy. Previous efforts have developed an amyloid immunotherapy-induced hemorrhage model in APP transgenic mice with labor intensive manual quantification. Traditionally, Paraffin embedded tissue blocks are prepared and then slides are prepared from the blocks by cutting 10um sections from the central domain of the mounted mouse brain. The sample collection begins once a good surface has been established. 4 sections per slide are then collected for 50 slides (total 200 sections across roughly 2mm of tissue). Extensive histological analyses surveying of these ~40 thin sections for Perls stain over 2mm of tissue takes about 6-months to histological analysis. Developing a fast and comprehensive microhemorrhage evaluation method is thus necessary to cover multiple brain locations with high throughput to support ARIA studies. Methods: Paraffin embedded hemi-brains blocks are prepared by dissecting the mouse brains coronally into two equal halves across the mid-brain. The two pieces are then mounted in parallel with cut surfaces facing up on the paraffin blocks. 50um coronal sections collection begins once a good surface is achieved and at 200um microns interval twice. This results in a total of three dorsal and three ventral 50 um sections per animal. covering a total of 2mm of the mid-domain of the mouse brain; and then mounted on charged glass slides. The slides are then stained with Prussian blue (Perl's stain) to visualize the hemorrhage events. An automated hemorrhage evaluation method was developed to detect and quantify microhemorrhage in these thick sections stained with Prussian blue. Since the vast majority of cerebral amyloid angiopathy and microhemorrhages were observed at leptomeningeal vessels, we outline ROI at pial surface to improve specificity and analysis throughput. The current algorithm allows both MH coverage (percentage of MH area) and counts of MH events for a deeper understanding of the frequency and severity of hemorrhages. The Traditional method evaluation methods involve staining and manual analysis of 6um sections took 4-6 months. The new method with the 50um thick sections was not only much more comprehensive and easier to quantify with the software-based analysis method but was much quicker and only required about 4 weeks to complete. A comprehensive and automated hemorrhage evaluation method was established to sample across >2mm of brain with 300um of stained tissue. This method robustly improves sectioning, staining, and quantification speed, thus providing higher assay throughput and objectivity.

Disclosures: H. Oluoch: A. Employment/Salary (full or part-time): ELI LILLY& CO. **G. Fitzgerald:** A. Employment/Salary (full or part-time): ELI LILLY& CO. **J. Hanson:** A. Employment/Salary (full or part-time): ELI LILLY& CO. **R.B. DeMattos:** A. Employment/Salary (full or part-time): ELI LILLY& CO. **T. Kwon:** A. Employment/Salary (full or part-time): ELI LILLY& CO.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.23/D44

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grand number: RS-2023-KH138733).

Title: Mha101 attenuates alzheimer's disease pathology via reduction of neuroinflammation and synaptic loss

Authors: *M. LEE, S. LEE, M. OH;
Kyung Hee Univ., Seoul, Korea, Republic of

Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline, with amyloid-β (Aβ) oligomers playing a key role in its early pathogenesis. MHA101, a natural product from the Polygonaceae family, has shown anti-inflammatory and neuroprotective properties, but its effects on AD remain largely unexplored. In this study, we investigated the therapeutic potential of MHA101 in Aβ oligomer-induced AD models. As results, MHA101 administration significantly improved cognitive function in behavioral tests, including the Y-maze, passive avoidance test and novel object recognition test, and restored the expression of synaptic markers such as PSD-95 and synaptophysin. Histological analysis revealed that MHA101 reduced Aβ oligomer-induced activation of microglia and astrocyte in the hippocampus. These results suggest that MHA101 alleviates Aβ oligomer-induced cognitive impairment by reducing neuroinflammation and preserving synaptic integrity, supporting its potential as a natural therapeutic agent for AD.

Disclosures: M. Lee: None. **S. Lee:** None. **M. Oh:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.24/D45

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grand number: RS-2023-KH138733)

Title: Protective effects of MHA-009 against AβO-induced neurotoxicity and synaptic loss in Alzheimer’s disease models.

Authors: *S. LEE, I. JU, M. LEE, J. KIM, Y. CHOI, M. OH;
Kyung Hee Univ., Seoul, Korea, Republic of

Abstract: Alzheimer's disease (AD) is one of the major neurodegenerative disorders characterized by the accumulation of amyloid-beta (Aβ) in the brain, leading to neuronal cell death, synaptic dysfunction, and ultimately progressive memory impairment. MHA-009, an herbal medicine belonging to the Alismataceae family, is traditionally used in East Asia and has been reported to exhibit anti-cancer, antioxidant, and anti-inflammatory effects. This study aimed to investigate the protective effects of MHA-009 against Aβ oligomer (AβO)-induced neuronal cell death, synaptic loss, and memory impairment in AD models. First, MHA-009 treatment attenuated AβO-induced neurotoxicity in the HT22 hippocampal cell. Subsequently, MHA-009 was administered to mice in which neuronal cell death, synaptic loss, and memory impairment had been induced by intrahippocampal injection of AβO via stereotaxic surgery. Behavioral assessments revealed that MHA-009 remarkably alleviated AβO-induced memory deficits. Moreover, MHA-009 administration significantly ameliorated neuronal cell death and synaptic dysfunction in the hippocampus of mice. Collectively, these results suggest that MHA-009 could ameliorate memory impairment by protecting hippocampal neurons and alleviating synaptic damage.

Disclosures: S. Lee: None. **I. Ju:** None. **M. Lee:** None. **J. Kim:** None. **Y. Choi:** None. **M. Oh:** None.

Poster

PSTR111: Alzheimer's Disease Therapeutic Strategies: Amyloidosis *In Vivo* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.25/D46

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF Grant 2021R1I1A3060435
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Chonnam National University Hospital Biomedical Research Institute Grant BCRI23041
Chonnam National University Grant 2024-1135-01
Korea Institute for Advancement of Technology Grant P0020818
Ministry of Health & Welfare, Republic of Korea Grant RS-2020-KH088567

Title: A novel miR-4536-3p inhibition ameliorates Alzheimer's disease by reducing Aβ accumulation and tau phosphorylation

Authors: *J. CHOI[1], D. KIM[2], H. JEONG[2], J. HWANG[2], M. RAMALINGAM[2], H.-H. CHO[3], B. KIM[4], H.-S. JEONG[2], S. JANG[2];
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Sch., Hwasun-gun, Korea, Republic of; [3]Dept. of Otolaryngology-Head and Neck Surgery, Chonnam Natl. Univ. Med. Sch., Gwangju, Korea, Republic of; [4]Dept. of Neurol., Chonnam Natl. Univ. Hospital, Chonnam Natl. Univ. Med. Sch., Gwangju, Korea, Republic of

Abstract: Background: Alzheimer's disease (AD) is characterized by cognitive decline, amyloid-beta (Aβ) accumulation, and tau hyperphosphorylation. Effective therapies remain limited; therefore, recent studies have explored microRNAs as potential therapeutic targets. Methods: miR-4536-3p inhibition was investigated using *in vitro* (SH-SY5Y cells) and *in vivo* (5xFAD mouse) AD models. Apoptosis, neuronal markers, and signaling pathways were assessed through functional assays. Cognitive effects were evaluated via the Morris water maze. Results: miR-4536-3p inhibition increased an expression of Drebrin1 (DBN1), a key regulator of synaptic plasticity, but it reduced Aβ deposition, tau phosphorylation, and apoptosis. The treatment improved neuronal marker levels and significantly enhanced the spatial learning and memory of 5xFAD mice. Mechanistically, miR-4536-3p inhibition activated the PI3K/Akt/GSK3β signaling pathway, suppressing apoptosis and mitigating AD pathology. Conclusions: miR-4536-3p inhibition offers a promising therapeutic strategy for AD by restoring the DBN1 expression, reducing neurodegeneration, and improving cognitive outcomes through PI3K/Akt pathway modulation.

Disclosures: J. Choi: None. **D. Kim:** None. **H. Jeong:** None. **J. Hwang:** None. **M. Ramalingam:** None. **H. Cho:** None. **B. Kim:** None. **H. Jeong:** None. **S. Jang:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.01/D47

Topic: C.03. Parkinson's Disease

Title: Assessing SPPL2B as a Promising New Risk Factor in Parkinson's Disease

Authors: *E. FRANKEL[1], A. JISHI[2], X. QI[2];
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Abstract: Parkinson's Disease (PD) is neurodegenerative disorder which causes tremors, difficulty of movement, and rigidity alongside many other non-motor symptoms. It is primarily hallmarked by the accumulation of toxic alpha synuclein (aSyn) aggregates and the death of dopaminergic neurons in the substantia nigra. Current treatments are unable to prevent long-term neurodegeneration, so more research is needed to improve long term outcomes. The multifactorial genetic nature of PD requires the identification of new risk factors and therapeutic targets. This project identified signal peptide peptidase like 2B (SPPL2B), a lysosomal aspartyl protease involved in regulated intramembrane proteolysis, as a promising potential risk factor in PD. We aim to determine the role of this factor in PD pathology specifically in relation to lysosomal and mitochondrial function. This project has primarily focused on cell culture of SH-

SY5Y neuroblastoma cells. We find SPPL2B levels consistently upregulated in aSyn overexpressing dopaminergic cell models and in the dopaminergic neurons of A53T-aSyn expressing mice. In SPPL2B knockout (KO) SH-SY5Y cells generated via CRISPR-Cas9 gene editing, we find a consistent decrease in lysosomal protein levels, lysosomal activity, and total functional lysosomes. We find this lysosomal dysfunction to connect to dysfunction of mitochondria through reduced mitochondrial lysosomal contact spots in SPPL2B KO cells, pointing a decrease in mitophagy. We also find an increase in mitochondrial oxidative stress and changes in proteins involved with mitochondrial dynamics, indicating mitochondria are not working at full capacity. In addition, we find an exacerbation of aSyn pathology upon SPPL2B KO. These results together show a potential role for SPPL2B in the pathology of PD through lysosomal and mitochondrial dysfunction and provide new possible avenues for therapeutic treatment. In the future, we plan to identify the mechanism by which SPPL2B is impacting lysosomal and mitochondrial dysfunction in addition to testing a cell line overexpressing SPPL2B.

Disclosures: E. Frankel: None. **A. Jishi:** None. **X. Qi:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.02/D48

Topic: C.03. Parkinson’s Disease

Support: PRIN_2022BXKPZ9_001

Title: Compensatory Bioenergetic Remodeling Early-Onset Parkinson’s Disease mouse model

Authors: *M. MONTANARI, Jr[1,2], S. SCARICAMAZZA, Jr[1], V. NESCI, Jr[1], M. MERINGOLO, Jr[3,4], V. CORASOLLA CARREGARI, Jr[5], L. PIERONI, Jr[3,4], N. B. MERCURI[1,2], G. MARTELLA[6], S. D'ADDARIO, Jr[1];
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Abstract: While Parkinson’s disease (PD) has long been regarded as a neurodegenerative disorder, mounting evidence supports its reinterpretation as a multisystem metabolic disease. This study explored the impact of mitochondrial dysfunction in PINK1 knockout mice (PINK1-/-), an established model of early-onset PD, focusing on both central and peripheral adaptations. Despite the absence of overt dopaminergic neurodegeneration, PINK1-/- mice displayed impaired grip strength, potentially reflecting basal ganglia circuit dysfunction. The striatal

proteomic analysis uncovered a robust upregulation of AMPK signaling and proteasome-related proteins, hallmarks of an adaptive metabolic response to mitochondrial stress. This was supported by enhanced mitochondrial spare respiratory capacity, indicating increased metabolic flexibility. Electrophysiological recordings revealed reduced excitability of striatal projection neurons, which was rescued by glibenclamide, implicating K-ATP channel dysregulation as a functional link between energy metabolism and neuronal activity. Intriguingly, peripheral muscle tissue mirrored this central adaptation: in the tibialis anterior, a shift toward oxidative fibers and elevated ATPβ expression suggested a parallel metabolic reprogramming aimed at preserving energy efficiency. This cross-compartmental coherence supports the concept of PD as a multisystem metabolic disorder, where central and peripheral tissues engage in shared bioenergetic strategies to counteract mitochondrial dysfunction.

Disclosures: M. Montanari: None. **S. Scaricamazza:** None. **V. Nesci:** None. **M. Meringolo:** None. **V. Corasolla Carregari:** None. **L. Pieroni:** None. **N.B. Mercuri:** None. **G. Martella:** None. **S. D'Addario:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR112.03/D49

Topic: C.03. Parkinson’s Disease

Support: NIH Grant DA060644
NIH Grant DA053083

Title: Leukocyte dopamine D2 receptors as biomarkers for brain dopamine levels in Parkinson's disease

Authors: C. SMALL[1], K. SMITH[3], P. E. WILLIAMS[4], J. D. OBRAY[6], K. BILLS[2], J. T. YORGASON[5], ***S. C. STEFFENSEN**[4];
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Abstract: The ability to objectively index dopamine (DA) levels in the brain has the potential to revolutionize the field of neuropsychopharmacology, as having a peripheral biomarker of brain DA would enable the objective monitoring of the progression of Parkinson’s disease (PD) and other DA-dependent psychiatric states. Of particular relevance to commercialization, it would provide an objective measure of treatment efficacy. We used a DA-depletion approach to determine if peripheral D2Rs are a biomarker for brain DA; mainly, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin model and PD subjects, which are well-known models of DA depletion in the midbrain of rodents and humans, respectively. Dopamine

depletion in the substantia nigra resulted in a significant decrease in DA and norepinephrine (NE) levels in the plasma ($p < 0.05$). Interestingly, these changes could be tracked as a time course from baseline to 15 days after injection with MPTP. Also, the proportion of D2R-expressing leukocytes steadily decreased (specifically B cells and T cells) during DA depletion ($p <0.001$). These results suggest that changes to the DA neuron population in the substantia nigra can be tracked with DA and NE level changes and D2R expression on B and T cells, providing a possible biomarker for nigral DA neuron loss to further investigate. In two cohorts of studies comparing subjects with PD vs controls, we found that Parkinson's subjects displayed significantly decreased D2R expression in classical monocyte, B cells, T cells, and NK cells ($p<0.05$). We also found that subjects with PD show increased levels in epinephrine (EPI) and DA, NE, and L-DOPA as compared to control subjects. We found a significant negative correlation (r=-0.62, p=0.008) between plasma L-DOPA and D2R expression on classical monocytes and helper T cells (r=-47, p=0.054) without significance. Classical monocytes were also associated with DA levels without significance (r=-0.28, p=0.053). The modulation of peripheral D2Rs in PD and MPTP seen in this study do show that substantia nigra DA depletion in humans and rodents do manifest in the periphery. Although our study didn't result in a clear narrative of how nigral and peripheral DA system mirror each other, our results provide more evidence that peripheral D2Rs may be both biomarkers and important substrates for treatment of DA-dependent disorders. Our results give a foundation from which future studies can investigate this connection further.

Disclosures: C. Small: None. **K. Smith:** None. **P.E. Williams:** None. **J.D. Obray:** None. **K. Bills:** None. **J.T. Yorgason:** None. **S.C. Steffensen:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.04/D50

Topic: C.03. Parkinson's Disease

Support: This study is approved by MDRU (Multidisciplinary Research Unit) via Project No.MRU.SNMC.MAY.2023.0238 dated 15.05.2023

Title: Glycated Hemoglobin (HbA1c) levels as a Marker of Motor Symptom Severity in Indian Patients with Parkinson's Disease - A Cross Sectional Study

Authors: *N. CHOUDHARY;
Physiotherapy, Government Physiotherapy Col. (Dr. SN Med. College), Jodhpur, India

Abstract: Objective
India's diversity and genetic heterogeneity highlight a gap in understanding how glycated hemoglobin (HbA1c) levels influence motor symptoms in Indian Parkinson's disease (PD) patients. **Background** Recent studies reveal a complex link between HbA1c and PD motor

severity. Both elevated and low HbA1c levels associate with faster motor decline. High HbA1c (>42 mmol/mol or 6.1%) relates to increased Unified Parkinson's Disease Rating Scale (UPDRS) scores, while levels <30 mmol/mol (5.3%) show a 2.7-fold risk of reaching Hoehn and Yahr stage 3, indicating moderate disability. These findings support exploring HbA1c's impact on motor impairment in PD. **Methods**
This cross-sectional observational study at the Department of Neurology, MDM Hospital, Jodhpur (March 2023-Feb 2024) included 100 PD patients diagnosed per UK Parkinson's Disease Society Brain Bank criteria. HbA1c, UPDRS III, Hoehn and Yahr, and MoCA scores were recorded. Subjects were grouped by HbA1c levels: ≤4.9% (Low), 5-5.9% (Euglycemic), and ≥6% (High) [Table 1]. **Results** Normal data were summarized as means ± SD; non-normal and qualitative data as medians with IQR and counts/percentages [Table 1]. Significance was set at 95% CI and $p < 0.05$. Spearman rank correlation showed a significant positive link between HbA1c and UPDRS on ($r = 0.701$, $p < 0.0001$; Fig. 1) and off ($r = 0.791$, $p < 0.0001$; Fig. 2). Higher HbA1c was linked with worse motor symptoms. MoCA scores negatively correlated with HbA1c ($r = -0.624$, $p < 0.0001$; Fig. 3), suggesting a cognitive impact. **Conclusion** Higher HbA1c (>6%) is associated with poorer motor function and cognition in Indian PD patients.

Table 1. Patient demographics by HbA1c levels.

Variables		Low HbA1c ≤ 4.9% (n=13)	Euglycemic 5 - 5.9% (n= 25)	High HbA1c ≥ 6% (n =62)	p
Age (Years) Mean (SD)		65.15 ± 3.82	67.04 ± 4.78	68.33 ± 4.20	0.044[1]
Gender	Male	10 (76%)	21 (84%)	36 (58%)	0.0477[2]
	Female	3 (24%)	4 (16%)	26 (42%)	
BMI Median (range)		24.5 (22.5-26.15)	24.6 (23.35 - 26.05)	28.4 (25.6 - 30.9)	<0.0001[3]
PD duration Median (range)		3 (2 - 4.5)	3.5 (2.5 - 5.5)	4.25 (2.5 - 6.75)	0.1434[3]
HbA1c % Median (range)		4.04 (3.66 - 4.72)	5.48 (5.25 - 5.8)	6.94 (6.8 - 7.1)	<0.0001[3]
UPDRS ON Median (range)		27 (14.5 - 41.5)	30 (18 - 38)	52 (32 - 61)	<0.0001[3]
UPDRS OFF Median (range)		32 (20-47)	38 (28 - 45.5)	63 (60 - 74.5)	<0.0001[3]
MoCA Median (range)		19 (16.5 - 24.5)	24 (18.5 - 25.5)	12 (11 - 14)	0.0002[3]
HbA1c and UPDRS On				r = 0.701	<0.0001[4]
HbA1c and UPDRS Off				r = 0.791	<0.0001[4]
HbA1c and MoCA				r = -0.624	<0.0001[4]

[1]*One Way ANOVA;* [2]*Chi - Square Test;* [3]*Kruskal-Wallis test;* [4]*Spearman Rank Correlation*

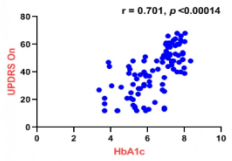


Figure. 1 Significant and positive correlation between HbA1c levels and UPDRS On.

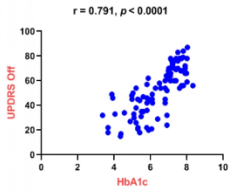


Figure 2. Significant and positive correlation between HbA1c levels and UPDRS Off.

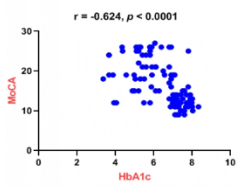


Figure. 3. Significant and negative correlation between HbA1c levels and MoCA scores.

Disclosures: N. Choudhary: None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.05/D51

Topic: C.03. Parkinson's Disease

Support: Chan Zuckerberg Initiative
Parkinson's Foundation

Title: Mitochondrial Heterogeneity Driving Dopamine Neuron Degeneration

Authors: *A. A. ABUSHAWISH, M. HUTTERER, A. MARTIN, C. LIM, M. MICOU, D. ENTERRIA-MORALES, C. KIM, G. PEKKURNAZ;
Biol. Sci., UCSD, La Jolla, CA

Abstract: Dopamine neuron degeneration in Parkinson's Disease is often induced by genetic mutations and environmental toxins that compromise mitochondrial function, highlighting the mitochondria's vital role in this process. Yet, a fundamental question persists: Why do mitochondrial defects result in the specific degeneration of dopamine neurons? It has been hypothesized that dopamine neuron vulnerability is linked to their high metabolic demands, complex morphology, and continuous pace-making activity, all of which require significant mitochondrial support and may increase susceptibility to mitochondrial dysfunction. In this study, we traced the mitochondrial network in dopamine neurons as they transition from healthy to dysfunctional. We aimed to identify the precise prodromal stage at which mitochondrial dysfunction begins to drive neuronal degeneration. TheMitoPark mouse, a transgenic mitochondrial impairment model developed by conditionally knocking out TFAM in dopaminergic neurons, is used in our studies to promote chronic mitochondrial dysfunction. This model spontaneously exhibits key characteristics of the Parkinson's disease, including adult-onset degeneration of the nigrostriatal dopamine circuitry, motor deficits, and progressive neurodegeneration. Using this model, we virally labeled and imaged mitochondria throughout dopamine axons of the intact nigrostriatal pathway in situ at the prodromal stage. Our findings have identified differences in basal axonal mitochondrial morphology across various dopamine neuron populations. We also quantitatively characterize mitochondrial network defects that precede dopamine neuron degeneration, throughout dopamine axons. We have identified a novel mechanism of dopamine neuron cell death, initiated by accumulating damaged mitochondria in the axons of the medial forebrain bundle. These mitochondrial aggresomes cause dystrophic axon swellings and breakage, instead of the typical "dying back." These swellings have been shown to interact specifically with microglia, which may facilitate axonal breakage. Changes in glial morphology also accompany these interactions. Our study provides insights that could be applicable to other neurodegenerative diseases where mitochondrial dysfunction plays a key role.

Disclosures: A.A. Abushawish: None. **C. Lim:** None. **C. Kim:** None. **G. Pekkurnaz:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.06/D52

Topic: C.03. Parkinson's Disease

Title: Lrrk2 degrader discovery: a high throughput direct-to-biology screening platform

Authors: ***F. CAVALLO**[1], A. MARTIN[1], C. ELLIS[2], B. GOURDET[1], E. M. ROSETHORNE[1], R. HJERPE[1], C. PEARCE[1], T. R. ROSENSTOCK[1], T. PHILLIPS[1], S. THOMSON[1], N. MIRZA[1];
[1]Sygnature Discovery, Nottingham, United Kingdom; [2]Univ. of Southampton, Sch. of Biol. Sci., Southampton, United Kingdom

Abstract: Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder worldwide, primarily characterized by bradykinesia, rigidity, and tremor. Among the genetic forms of PD, mutations in the *leucine-rich repeat kinase 2* (LRRK2) gene are the most frequent, making LRRK2 a key therapeutic target. Proteolysis-targeting chimeras (PROTACs) have emerged as a promising strategy to degrade LRRK2, offering an alternative to kinase inhibition and potentially avoiding off-target effects. Notably, ARV-102, a selective LRRK2 degrader developed by Arvinas, crosses the blood-brain barrier (BBB) and induces degradation of LRRK2 in the cerebral cortex following a single oral dose in mice carrying the G2019S LRRK2 mutation. ARV-102 is now in clinical development for PD. Similarly, the Alessi and Ciulli laboratories (Dundee University, UK) developed XL01126, a BBB-permeable potent LRRK2 degrader effective following oral or parenteral dosing, demonstrating that CNS-targeting PROTACs are feasible despite inherent physicochemical challenges. In this study we developed a direct-to-biology (D2B) platform to enable high-throughput screening of LRRK2 degraders. This system utilizes 384-well plate-based chemistry for rapid compound synthesis, seamlessly integrated with fully automated AlphaLISA-based detection for cell-based degradation assessment. A549 cells, which naturally express high levels of LRRK2, served as the screening model. A total of 313 candidate degraders were screened, featuring combinations of three different LRRK2-binding ligands, two E3 ligases, and a variety of linkers. The workflow, supported by liquid-handling automation (Biomek i5, Echo 550), was completed over four days: one day for compound synthesis and three for biological evaluation. Assay robustness was confirmed with strong statistical performance ($Z' = 0.62 \pm 0.1$; S:B = 6.0 ± 2.4). Degrader activity was benchmarked against the XL01126 reference compound (DC50: 15-72 nM), with Dmax values expressed as a percentage of this control. Several novel degraders were identified with nanomolar potency and Dmax values ranging from 70% to 100%. These lead compounds are now undergoing further validation in neurologically relevant systems, including primary neuronal cultures. In conclusion, D2B platform enables rapid synthesis and evaluation of PROTACs, demonstrating its utility in LRRK2 degrader discovery. The approach is scalable, efficient, and adaptable to other neurodegenerative disease targets, such as mutant huntingtin (mHTT) and GSK-3β, broadening its potential impact in CNS drug discovery.

Disclosures: F. Cavallo: None. **A. Martin:** None. **C. Ellis:** None. **B. Gourdet:** None. **E.M. Rosethorne:** None. **R. Hjerpe:** None. **C. Pearce:** None. **T.R. Rosenstock:** None. **T. Phillips:** None. **S. thomson:** None. **N. Mirza:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.07/D53

Topic: C.03. Parkinson's Disease

Support: 35/4/2020-Nano/BMS

Title: Brain-targeted nano therapy restores mitochondrial homeostasis to attenuate Parkinson's disease

Authors: *L. BISWAL;
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder marked by Lewy body formation and loss of dopaminergic neurons due to phosphorylation of α-synuclein. Imbalance of 17β-Estradiol (E2) in the human brain has been implicated in PD pathology. However, the therapeutic potential of E2 for PD is limited by peripheral side effects and a lack of understanding of its underlying molecular mechanisms. In this study, we addressed these challenges by employing dopamine receptor D3 (DRD3) conjugated E2-loaded chitosan nanoparticles (Ab-ECSnps) for targeted delivery to the brain and tried to understand the underlying molecular mechanism in both rotenone-induced in vitro and in vivo PD models. D3 conjugation to the nanoparticle surface was characterized using XPS and a spectrophotometer. Western blotting, immunostaining, and Co-Immunoprecipitation were performed to understand the underlying molecular mechanism after E2 administration in SHSY5Y (in vitro) and rats (in vivo). E2 acts as a specific calpain inhibitor that disrupts mitochondrial function. At the same time, B-cell-specific Moloney murine leukemia virus integration region 1 (BMI1), a member of Polycomb repressive complex 1 (PRC1) and an epigenetic regulator, plays a critical role in maintaining mitochondrial homeostasis. We found that the administration of Ab-ECSnps inhibits the translocation of calpain into mitochondria and promotes the mitochondrial translocation of BMI1. This dual action imparts neuroprotection by enhancing cell viability and mitochondrial DNA copy number, as well as preserving mitochondrial membrane potential, conferring neurotherapeutic effects. Furthermore, we elucidate a novel molecular mechanism where calpain regulates the BMI1 level by involving the ubiquitin proteasome system (UPS), contributing to maintaining mitochondrial homeostasis and attenuating PD. Notably, Ab-ECSnps has protected TH^{+ve} neurons from rotenone-mediated toxicity and exhibited significant neurotherapeutic potential in an in vivo PD model. This study presents, for the first time, a brain-specific targeted delivery approach that modulates calpain-mediated BMI1 expression, thereby preserving mitochondrial homeostasis to alleviate the effects of Parkinson's disease.

Disclosures: L. Biswal: None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.08/D54

Topic: C.03. Parkinson's Disease

Title: Validation of a reproducible in vitro mouse model of Parkinson's disease to evaluate pharmacological or gene therapy approaches

Authors: R. STEINSCHNEIDER[1], K. HARHOURI[1], M. XILOURI[2], C. MAZZOCCO[3], ***E. BEZARD**[4], B. DEHAY[5];
[1]Neuron Experts, Marseille, France; [2]Biomed. Res. Fndn. of the Acad. of Athens, Athens, Greece; [3]Neurosciences, Inst. of Neurodegenerative Dis. UMR CNRS 5293 Univ. of Bordeaux, Bordeaux, France; [4]Inst. of Neurodegenerative Dis., Bordeaux, France; [5]Inst. of Neurodegenerative Dis., Bordeaux Cedex, France

Abstract: A Parkinson's disease (PD) hallmark is the accumulation of phosphorylated alpha-synuclein (α-syn). The α-syn intrinsically disordered structure leads to the formation of oligomers that aggregate into insoluble protofibrils and polymerize into fibrils, resulting in the formation of inclusions called Lewy bodies. This aggregation is largely due to the impairment of the autophagy-lysosomal pathway.Restoring the activity of the faulty autophagy-lysosomal pathway is therefore a major therapeutic target that could be achieved through various means. We here developed a robust and reproducible *in vitro* synucleinopathy model using primary mouse or rat cultures of dopaminergic neurons, exposed to recombinant synuclein Pre-Formed Fibrils (Syn-PFFs). Rescuing the pathology was attempted by overexpressing LAMP2A, to activate the chaperone-mediated autophagy (CMA) for increasing α-syn clearance.Embryonic mesencephalon from pregnant C57BL/6 mice or Wistar rats was dissociated to culture primary dopaminergic neurons in 96-well plates and later exposed to Syn-PFFs. At 7- and 14-day post-exposure, we report (i) a significant decrease in neurite length and (ii) an accumulation of S129 phosphorylated α-syn in the dopaminergic neurons of mice. At 21 days post-exposure, the number of dopaminergic neurons significantly decreased, in addition to neurite loss and phosphorylated α-syn aggregation, reflecting the progressive evolution of the pathology. Unlike mouse dopaminergic cells, rat dopaminergic neurons failed to recapitulate comparable pathology. Experiments were replicated multiple times with independent cultures and Syn-PFF batches, leading to the same result. We then investigated the impact of LAMP2A overexpression to potentiate autophagic flux in the validated *in vitro* mouse dopaminergic neuron PD model. We showed that overexpression of LAMP2A promotes survival and neurite length of dopaminergic neurons, as well as leads to decreased phosphorylated α-syn levels.Altogether, we validated (i) a reproducible *in vitro* mouse dopaminergic neuron model of PD and (ii) a gene therapy approach through high-content imaging and an automated 96-well plate system enabling high-throughput screening.

Disclosures: R. Steinschneider: A. Employment/Salary (full or part-time): Neuron Experts. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuron Experts. **K. Harhouri:** A.

Employment/Salary (full or part-time): Neuron Experts. **M. Xilouri:** None. **C. mazzocco:** None. **E. Bezard:** A. Employment/Salary (full or part-time): Motac France. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac France. **B. Dehay:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.09/D55

Topic: C.03. Parkinson's Disease

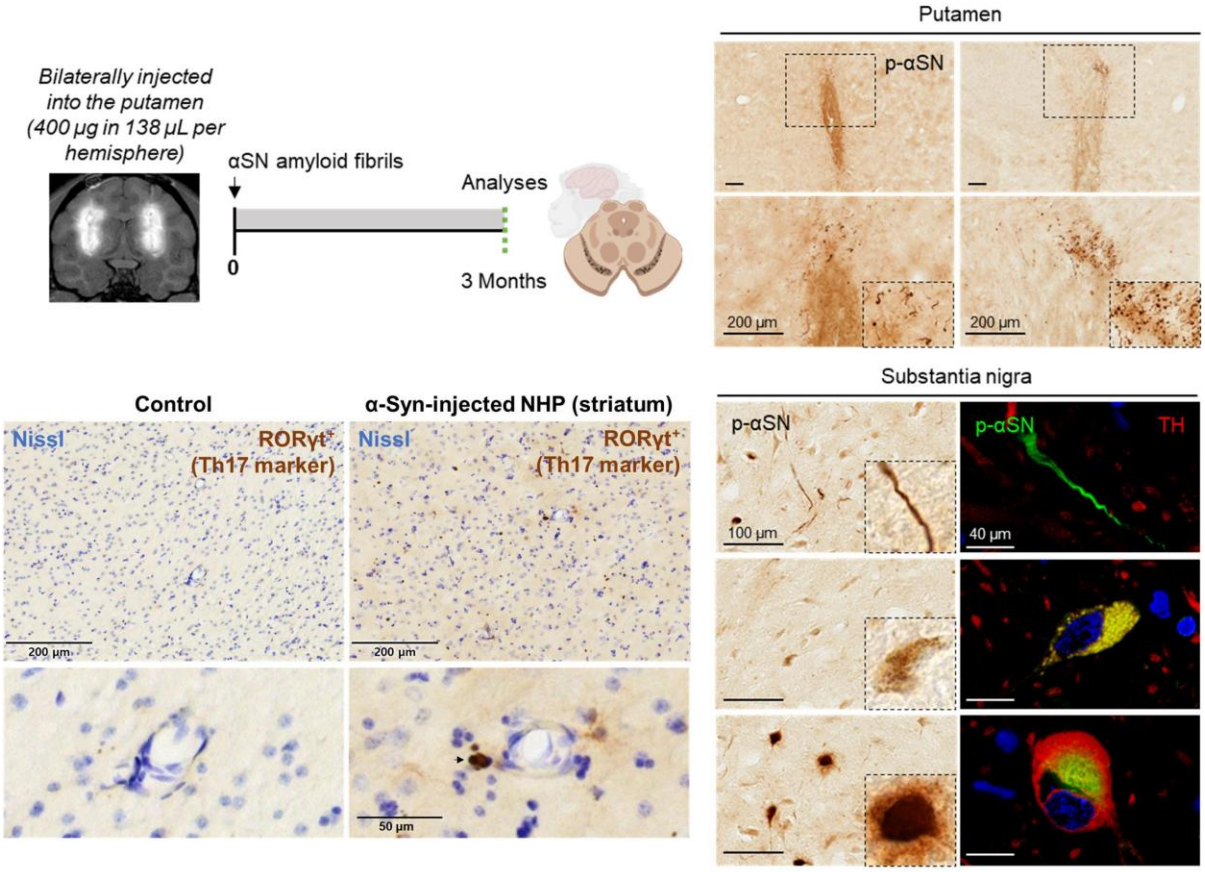
Support: Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education [RS-2024-00449397]
The Korea Research Institute of Bioscience and Biotechnology Research Initiative Program [KGM4562532]
Electronics and Telecommunications Research Institute (ETRI) grant funded by the Korean government [Collective Brain-Behavioral Modelling in Socially Interacting Group, 24YB1200]

Title: Prodromal-phase Th17 cell infiltration in a non-human primate model of Parkinson's disease with Lewy body-like pathology: A pilot study

Authors: *J. SEO[1], T. NGUYEN[1,3], J. WON[1], C.-Y. JEON[1], J. PARK[1], Y. KIM[1,4], K. LIM[2], Y.-H. LEE[5,6], Y. LEE[1];
[1]Natl. Primate Res. Ctr., Korea Res. Inst. of Biosci. and Biotech., Cheongju, Korea, Republic of; [2]Futuristic Animal Resource & Res. Ctr., Korea Res. Inst. of Biosci. and Biotech., Chungju, Korea, Republic of; [3]Dept. of Functional Genomics, KRIBB Sch. Of Bioscience,, [4]Dept. of Functional Genomics, KRIBB Sch. Of Biosci., Korea Univ. Of Sci. and Technol., Daejeon, Korea, Republic of; [5]Res. Ctr. for Bioconvergence Analysis, Korea Basic Sci. Inst. (KBSI), Cheongju, Korea, Republic of; [6]Res. Ctr. for Bioconvergence Analysis, Korea Basic Sci. Inst. (KBSI), Cheongju-si, Korea, Republic of

Abstract: Parkinson's disease (PD) is characterized by the pathological accumulation of alpha-synuclein (α-syn), resulting in Lewy bodies (LBs) and dopaminergic neurodegeneration. Although $CD4^+$ T cells, especially Th17 cells, have been implicated in PD, lymphocyte infiltration during the prodromal stage remains unclear. This study histologically examined T cell infiltration in a non-human primate (NHP) model of prodromal PD. A female rhesus monkey received bilateral injections of α-syn amyloid fibrils (400μg in 138μL per hemisphere; 800μg total) into the putamen at two sites per hemisphere, and brain tissue was analyzed three months post-injection. α-syn pathology (including LB-like inclusions) and dopaminergic alterations were observed in the striatum and substantia nigra (SN), with widespread propagation in the gray matter. Dopaminergic neuron areas were reduced in the striatum but relatively preserved in the

SN. Notably, $CD4^+$ and Th17 cell infiltration was more prominent in the nucleus accumbens ($CD4^+$, 106.2 ± 29.5; Th17, 99.4 ± 18.3), caudate nucleus ($CD4^+$, 99.7 ± 6.6; Th17, 64.6 ± 6.7 cells/mm²), and SN ($CD4^+$, 82.7 ± 15.0; Th17, 73.3 ± 13.3), compared to the putamen injection site ($CD4^+$, 58.5 ± 29.6; Th17, 30.6 ± 30.3). $CD4^+$ and Th17 cells were also detected in the temporal cortex but not in the frontal cortex or white matter. Values are presented as mean ± SD; statistical analysis was not performed due to the limited sample size. These findings demonstrate that α-syn amyloid fibril injection induces LB-like pathology and region-specific lymphocyte infiltration in NHPs at three months post-injection. The selective infiltration of $CD4^+$ and Th17 cells during the prodromal phase may be associated with early non-motor symptoms in PD. However, a longer post-injection period may be required for the development of pronounced dopaminergic neurodegeneration and motor symptoms. This study is limited by the use of a single female monkey and one control subject; therefore, the findings should be interpreted with caution and require further experimental validation.



Disclosures: J. Seo: None. **T. Nguyen:** None. **J. Won:** None. **C. Jeon:** None. **J. Park:** None. **Y. Kim:** None. **K. Lim:** None. **Y. Lee:** None. **Y. Lee:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.10/D56

Topic: C.03. Parkinson's Disease

Support: Klinischer Forschungsverbund GB.Com (KFO5024)

Title: Decoding the phospho-S129 α-Synuclein interactome: a comparative Apex2-proximity based study in enteric and dopaminergic neurons derived from α-Synuclein triplication and isogenic control iPSCs

Authors: *C. JAMES[1], B. GHIROTTO[2], K. METZNER[3], R. NIKITINA[4], B. WINNER[5]; [1]Stem cell Biol., Erlangen, Germany; [2]Stem Cell Biol., Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [3]Univ. Hosp. Erlangen, Erlangen, Germany; [4]Stem cell Biol., Uniklinikum Erlangen, Erlangen, Germany; [5]Dept. of Stem Cell Biol., FAU Erlangen-Nuernberg, Erlangen, Germany

Abstract: The accumulation and phosphorylation of α-synuclein at serine 129 (pS129) are central pathological features of Parkinson's disease (PD). Emerging evidence suggests that α-syn pathology originates in the enteric nervous system and progresses to the central nervous system, implicating a gut-to-brain axis in PD pathogenesis. However, the molecular context and interacting partners of pS129 α-synuclein in different neuronal subtypes remain poorly understood. This study aims to map and compare the interactome of pS129 α-synuclein in enteric neural lineages (ENLs) and dopaminergic neurons (DANs), both derived from the same induced pluripotent stem cell (iPSC) lines harboring SNCA gene triplication (SNCA 3x), to uncover cell-type-specific networks that may drive PD progression. We used APEX2-based proximity labeling to profile the pS129 α-syn interactome in ENLs and DANs from patients with α-syn under identical labeling conditions. Immunostaining revealed the presence of GFAP and the enteric neuron marker HuC/D in both isogenic and triplication lines, with a notable increase in α-synuclein levels specifically observed in SNCA 3x ENLs at the end of differentiation. To identify interaction partners, neuronal precursor cells were transduced with lentiviral constructs encoding C-terminal APEX2-tagged wild-type, phospho-mimetic (S129D), or phospho-null (S129A) SNCA variants. Biotinylated proteins were affinity-purified and validated via streptavidin-HRP and α-synuclein immunoblotting. Enriched proteins were then subjected to quantitative mass spectrometry. Comparative interactome analyses will be conducted using network enrichment tools and pathway annotation, focusing on differential binding partners in ENs and DANs, with phospho-mutants serving as controls to validate pS129-specific associations. This study will provide the first side-by-side comparison of the pS129 α-synuclein interactome in human-derived enteric and dopaminergic neurons from PD patients. Our findings aim to uncover cell-type-specific molecular networks involved in PD pathogenesis and identify novel targets for early therapeutic intervention.

Disclosures: C. James: None. **B. Ghirotto:** None. **K. Metzner:** None. **R. Nikitina:** None. **B. Winner:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.11/D57

Topic: C.03. Parkinson's Disease

Support: Parkinson's Foundation Grant
Nu Rho Psi Grant

Title: Assessment of Three Newer α-Synuclein Mutants Reveals Differential Toxicity Under Varying Expression Levels and PD-Relevant Altered Environments in Yeast

Authors: *S. GACEK[1], K. FEIST[1], S. CHANDAVIMOL[1], A. GRASSEL[2], C. T. BORLAND, Esq.[3], S. K. DEBBURMAN[4];
[2]Neurosci., [3]Biol., [1]Lake Forest Col., Lake Forest, IL; [4]Biol., Lake Forest Col., lake Forest, IL

Abstract: Parkinson's Disease (PD) is the second most common neurodegenerative disorder characterized by the death of midbrain dopaminergic neurons. This selective cell death is linked with the misfolding and accumulation of the protein, α-synuclein. Six α-synuclein mutants linked with early-onset familial PD (A30P, E46K, H50Q, G51D, A53T, A53E) have been extensively studied for their mechanism of toxicity. In contrast, three newer α-synuclein mutants linked with familial and sporadic forms of PD (A18T, A29S, and A53V) are less well understood for their underlying toxicity mechanisms. We have characterized these three newer mutants in a budding yeast (*S. cerevisiae*) model and report that each is differentially toxic in yeast, with A53V being the most toxic, followed by A18T, and A29S. The level of mutant toxicity is dependent on the degree of α-synuclein expression, with no noticeable toxicity under low expression but significant differences in toxicity when expressed at a higher level. The differences in toxicity are additionally correlated to the amount of aggregation, with A29S being significantly less aggregated than the other two mutants. We next compared them to the six older α-synuclein mutants and found A18T and A53V, under high expression, can be as toxic as some older α-synuclein mutants previously known to be toxic in yeast (E46K, H50Q, A53T, A53E), whereas under lower expression, all newer mutants more closely resemble the less toxic of the older mutants in yeast (A30P, G51D). The newer and older α-synuclein mutants maintained this same profile of aggregation and toxicities when assessed in a second yeast strain. Finally, we assessed the new mutants in genetically modified yeast strains that mimicked several altered cellular environments linked with PD (specifically impacting nitrative stress, SUMOylation, mitochondrial stress, and endocytosis), which revealed different sensitivity profiles specific to each mutant. A18T and A53V mutants both appeared to be sensitive to nitrative stress and low SUMOylation while A29S was drastically more sensitive to low SUMOylation and insensitive to high nitrative stress, the effects of other conditions such as mitochondrial stress revealed further differences in sensitivity. Overall, our studies add new insight into the nature of toxicity of each of these rare mutants linked with PD.

Disclosures: S. Gacek: None. **K. Feist:** None. **S. Chandavimol:** None. **A. Grassel:** None. **C.T. Borland:** None. **S.K. Debburman:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.12/D58

Topic: C.03. Parkinson’s Disease

Support: Nu Rho Psi

Title: New Molecular Insights into the Toxicity Linked with Three Newer α-Synuclein Mutants (A18T, A29S, and A53V) in a Yeast Model

Authors: *S. CHANDAVIMOL[1], K. FEIST[1], S. GACEK[1], S. ELMI[2], M. LEZONDRA[2], S. K. DEBBURMAN[3];
[2]Neurosci., [1]Lake Forest Col., Lake Forest, IL; [3]Biol., Lake Forest Col., lake Forest, IL

Abstract: Parkinson’s Disease (PD) is a common neurodegenerative disorder with its primary pathology being the selective death of midbrain substantia nigra neurons linked with the presence of Lewy bodies composed mainly composed of misfolded aggregated α-synuclein. Early-onset familial PD is well linked with six α-synuclein mutants that are well studied (A30P, E46K, H50Q, G51D, A53T, A53E), but three more recently discovered α-synuclein mutants (A18T, A29S, and A53V) linked with familial and sporadic PD are less well understood. Using our budding yeast (*S. cerevisiae*) model, we have recently found that these three newer mutants, while toxic to varying degrees, are surprisingly never more so than wildtype α-synuclein, with A29S being the least toxic and aggregated among them. Here, we have characterized these three mutants further by assessing 1) whether the loss of the original amino acid or the gain of the mutant amino acid (T, S, or V) is key to each mutant’s toxicity; 2) the effects on α-synuclein toxicity and aggregation when combining them; and, 3) the effects of altering known α-synuclein post-translational modifications (acetylation, SUMOylation, phosphorylation) on their toxicity. We report that for both A18 and A53 sites on α-synuclein, the loss of alanine is key to driving their individual toxicity. The A29 site is more complex, and it is the most toxic when substituted with arginine (R) and Threonine (T). Interestingly, for all three sites, some acidic substitutions (A18E, A29E, A53D) can reduce alpha-synuclein toxicity. When we assessed double (A18T/A29S, A29S/A53V, A18T/A53V) and triple (A18T/A29S/A53V) combinatorial mutants, we found out that A29S dominated over both A18T and A53V significant reducing their toxicities, indicating that the A29 position may be particularly important, especially when combined with A53. Together, our findings help with understanding how each of these three rare mutants may generate neurotoxicity that can explain underlying disease pathogenesis.

Disclosures: S. Chandavimol: None. **K. Feist:** None. **S. Gacek:** None. **M. Lezondra:** None. **S.K. Debburman:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.13/D59

Topic: C.03. Parkinson's Disease

Title: Assessment of Motor Function in the Alpha-Synuclein Pre-Formed Fibril Model of Parkinson's Disease

Authors: C. TORTURO, L. KRETSGE, *S. RAMBOZ;
PsychoGenics, Paramus, NJ

Abstract: A key contributor in the pathogenesis of Parkinson's Disease (PD) is α-synuclein, a presynaptic neuronal protein that is highly involved in neurotransmitter release and forms aggregates which are frequently associated with neurodegenerative disorders. Previous work inoculating synthetic α-synuclein preformed fibrils into the striatum of wildtype mice via stereotaxic surgery has demonstrated behavioral deficits, however, additional studies have not been able to reliably reproduce these behavioral symptoms. The goal of this work is to identify an α-synuclein dosing paradigm that will exhibit robust and consistent motor impairments. We have evaluated the behavioral phenotype and the corresponding brain tissue from male C57Bl6/J WT mice that received two inoculations of mouse pre-formed α-synuclein fibrils injected 60 days apart, with the goal of determining whether a second α-synuclein dose administration will lead to more severe or longer-lasting changes than a single α-synuclein dose administration. Motor function was evaluated using a selection of behavioral tests and tissues were analyzed for markers of α-synuclein and dopaminergic neurotransmission. Concluding remarks are pending additional analysis and histological readouts. The ultimate goal of this work is to identify behavioral deficits that can be used to determine the efficacy of disease modifying therapies for Parkinson's Disease.

Disclosures: C. Torturo: None. **L. Kretsge:** None. **S. Ramboz:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.14/D60

Topic: C.03. Parkinson's Disease

Support: R01AG079257
R01DK093953
R01DK132088
AHW grant (FP00028084)

Title: Sarm1, a multifaceted player in Parkinson's disease

Authors: P. JOSHI[1], F. FAN[2], S. KOTTURU[3], ***X. LOU**[2];
[1]Cell biology, Neurobio. and Anat., [2]Med. Col. of Wisconsin, Milwaukee, WI; [3]Med. Col. of Wisconsin, MILWAKEE, WI

Abstract: Background: Mitochondrial dysfunction is a hallmark of Parkinson's disease (PD), and SARM1 (Sterile Alpha and TIR Motif Containing-1) is a mitochondria-associated protein known to be crucial for axon neurodegeneration and cell death. However, the function of SARM1 in PD pathogenesis is unknown. Recent evidence implies its key role in dopaminergic (DA) neuron degeneration under stress in vitro, but SARM1 function in PD pathology in vivo remains poorly understood. We address this knowledge gap using a rotenone-induced PD mouse model and genetic deletion of SARM1. Results: We evaluated SARM1 function in PD using three groups of mice (total 66 mice, 2-month-old, both males and females). Wild-type (WT) mice treated with vehicle served as the control. WT and SARM1 knockout (KO) mice treated with rotenone served as the PD and the rescue group, respectively. Multiple behavioral assays were performed at the first and third weeks following the completion of rotenone exposure (WFR). As expected, PD males developed Parkinsonism-like phenotypes. However, in contrast to in vitro results, the rescue group showed no improvement in acute deficiency seen in the PD group across all behavioral tests performed. Open-field tests revealed the same levels of locomotion impairments between PD and rescue groups (PD group: 44.5 ± 17.2 m, $p < 0.05$; rescue: 49.2 ± 12.0 m, $p = 0.05$) in male mice. Females showed only mild locomotor impairments, without difference between PD and rescue. Rotarod tests revealed the equal level of motor impairment between PD and rescue group in males (latency to fall for control, 109 ± 2.34 s; rotenone, 71.7 ± 6.6 s; rescue, 69.3 ± 2.7 s; $p < 0.001$), whereas females exhibited no motor deficit. The elevated plus maze revealed more severe anxiety-like behaviors in males than females, without improvement in the rescue group. However, despite lacking protection at the peak time of rotenone toxicity, the rescue group showed locomotion improvement during the recovery phase, suggesting a delayed benefit of SARM1 KO. The mechanism underlying this effect is unknown, which may be relevant to SARM1 function recently reported in proximal axonal regeneration. Conclusion: SARM1 genetic inactivation does not significantly alter behavioral impairments in the rotenone-induced PD model, in contrast to prior in vitro results. However, it does accelerate the recovery of locomotion deficits. Thus, SARM1 plays a more complex role in vivo in PD than previously thought, and its delayed beneficial role in behavioral deficit recovery and associated DA-neuron resilience may be exploited as a disease-modifying target.

Disclosures: P. Joshi: None. **F. Fan:** None. **S. Kotturu:** None. **X. Lou:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.15/D61

Topic: C.03. Parkinson's Disease

Title: Gm1 ganglioside deficiency impairs autophagy and decreases AQP4 expression contributing to substantia nigra dopaminergic neuron loss

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Abstract: GM1 ganglioside plays a critical role in maintaining neuronal integrity, membrane stability, and autophagic function. Its deficiency has been implicated in the pathophysiology of Parkinson's disease (PD), yet the underlying mechanisms remain incompletely understood. We investigated the extent to which partial GM1 depletion alters autophagic signaling, AQP4 expression, and dopaminergic neuronal survival in the substantia nigra pars compacta (SNpc). GM2 synthase (GM2S) heterozygous (HZ) 12-month-old female mice that exhibit reduced GM1 levels, and age-matched wild-type (WT) females, were used for these studies. GM1 expression was semi-quantitatively assessed by fluorescence microscopy using FITC-conjugated cholera toxin B subunit, confirming reduced GM1 signal in GM2S HZ brains. Western blot was performed to assess key autophagy-related proteins (p62, Beclin1, and LC3B-II) and AQP4 expression. Tyrosine hydroxylase (TH) and NeuN immunostaining were used to quantify dopaminergic and total neurons, respectively, in the SNpc. GM2S HZ mice had significantly decreased GM1 expression in the SNpc, as well as decreased p62 and Beclin1 expression and increased LC3B-II levels, indicating disrupted autophagic processes. AQP4 expression was also significantly decreased, suggesting reduced glymphatic function. Stereological counts of TH- and NeuN-positive cells showed a significant loss of dopaminergic neurons in the SNpc in GM2S HZ mice. These findings suggest that GM1 deficiency disrupts autophagic processes and alters AQP4 expression, and that these changes contribute to dopaminergic neurodegeneration. These findings further highlight the importance of GM1 for maintaining cellular homeostasis and further support GM1 replacement as a potential disease-modifying therapy for Parkinson's disease.

Disclosures: S. Zafar: None. **J.S. Schneider:** None.

Poster

PSTR112: Parkinson's Disease: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.16/D62

Topic: C.03. Parkinson's Disease

Title: Chronic mitochondrial insult causes parkin inactivation and aggregation modulated by SUMOylation

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SPECIALITY HOSPITAL, KOTTAYAM, India; [2]Sch. of Hlth. Sci., PURDUE UNIVERSITY, West Lafayette, IN

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the midbrain substantia nigra, resulting in motor and non-motor symptoms. Currently, no disease-modifying therapy is available for patients with this devastating disorder. While the exact etiology of PD remains elusive, a growing body of evidence suggests that dysfunction in the parkin protein is pivotal in PD. Parkin is an E3 ubiquitin ligase, and its role in maintaining protein homeostasis and mitochondrial quality control positions it as a potential target for treating PD. Additionally, increasing evidence highlights the importance of post-translational modifications (PTM) in regulating protein function and stability. One such modification is the SUMOylation of parkin. However, the potential role of parkin SUMOylation in the pathogenic mechanisms of PD has yet to be explored. We examined the spatiotemporal localization and activity of parkin and its downstream targets after generating PD-mimicking mitochondrial stress in differentiated SH-SY5Y cells, by using a mitochondrial electron transport chain complex 1 inhibitor, 1-methyl-4-phenylpyridinium (MPP^+). Our findings suggest that early mitochondrial stress in PD stimulates cytosol-to-mitochondria translocation of parkin and its activation as a form of damage repair. However, chronic mitochondrial insult observed during prolonged disease conditions yielded mitochondrial dislocation, inactivation, and aggregation of parkin, resulting in the accumulation of parkin substrates, including parkin-interacting substrate (PARIS), which leads to loss of mitochondrial homeostasis through suppression of its biogenesis via peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) repression. Analysis of SUMOylated parkin levels showed an increase after acute stress, which was even more pronounced under chronic stress conditions. Notably, Anacardic acid- a natural compound identified as a SUMOylation inhibitor that primarily targets the SUMO-activating enzyme (SAE/E1)- was able to rescue the cell death induced by chronic stress, possibly by modulating parkin SUMOylation. Our findings suggest that the enhanced SUMOylation of parkin in response to chronic stress may underlie its inactivation and aggregation, and that targeting this PTM could be a potential therapeutic approach to mitigate this loss.

Disclosures: S. Narukkottil: None. **J.R. Cannon:** None. **G. Chandra:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.01/D63

Topic: C.03. Parkinson's Disease

Support: Queen Elizabeth II Graduate Scholarship in Science & Technology
Canadian Institute of Health Research (CIHR) (PJT- 173540)
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Foundation for Parkinson's Research and funding partners listed on the PPMI website.

Title: Applying machine learning to neuroimaging and biofluid markers for identification of Parkinson's Disease and mild cognitive impairment

Authors: *A.-G. DENNIS[1,2], S. MARTIN[3,4], R. CHEN[1,2,4], P. GERRETSEN[1,4], A. P. STRAFELLA[1,2,4];
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Abstract: Background: Since current diagnostic tests for PD and MCI focus on individual biomarkers, misdiagnoses can be frequent. This research evaluated the use of combined neuroimaging and biofluid data as biomarkers for PD and MCI progression. Methods: Using the support vector machine (SVM) and random forest (RF) machine learning techniques, models were created based on neuroimaging and biofluid biomarkers for a subset of PD and healthy subjects (HC) from the Parkinson's Progression Markers Initiative dataset (https://www.ppmi-info.org/). Striatal binding ratios extracted from DaT-SPECT imaging were used as neuroimaging biomarkers. Proteomic concentrations, including beta-amyloid-42 (Aβ42) and phosphorylated-tau-181 (p-tau), derived from cerebrospinal fluid (CSF) represented the biofluid biomarkers. We performed statistical analysis of biomarker and demographic information to determine significant differences. Results: We found that there were statistically significant differences between subjects with PD and HC in SBRs regardless of cognitive status. When differentiating subjects with PD from HC, both SVM and RF techniques perform with high accuracy using DaT-SPECT alone. These techniques did not perform as well when proteomic biomarkers from CSF were used alone. Models combining DaT-SPECT with Aβ42 and/or p-tau tended to have higher performance. No biomarkers performed well when detecting MCI. Conclusions: Diagnostic performance may be improved through combining neuroimaging with biofluid markers to distinguish subjects with PD from HC. This study's next steps involve investigating other techniques and biomarkers that can apply to both PD and MCI.

Disclosures: A. Dennis: None. **S. Martin:** None. **R. Chen:** None. **P. Gerretsen:** None. **A.P. Strafella:** 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.; Canadian Institute of Health Research (CIHR) (PJT-173540).

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.02/D64

Topic: C.03. Parkinson’s Disease

Title: Cognitive and affective profiles in de novo parkinson's disease

Authors: *C. MARSHALL, E. L. STEGEMOLLER;
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Abstract: Parkinson’s disease (PD) is a progressive neurological disorder that primarily affects the substantia nigra region within the basal ganglia and impacts more than ten million people globally. A major challenge in managing PD is addressing a wide spectrum of symptoms. Although motor impairments are the most widely recognizable hallmark of PD, mood disturbances are also common, particularly early in disease progression. In addition, cognitive changes including difficulties with attention, memory, and executive function, frequently co-occur with mood changes. Despite their prevalence, both mood changes and cognitive dysfunction are overlooked, yet they affect quality of life and complicate daily functioning in persons with PD. Early identification and interventions targeting these symptoms are important for developing effective care strategies. The current study evaluates mood and cognition in recently diagnosed, de novo persons with PD (PD-off; n=5) compared to healthy older adults (HOA; n=3), using the Geriatric Depression Scale (GDS), Geriatric Anxiety Scale (GAS), Apathy Evaluation Scale (AES), and the Montreal Cognitive Assessment (MoCA). Demographic information including age, race, gender, years of education, and handedness was also collected. Data collection is currently ongoing. To identify the most sensitive measures for distinguishing mood and cognitive changes in early-stage PD, Mann-Whitney U tests and effect sizes (r) were calculated for each assessment. The GDS showed the largest effect size (r = 0.58), followed by the MoCA (r = 0.37), indicating these two measures may be the most sensitive to early group differences. GAS (r = 0.27) and AES (r = 0.21) showed smaller effects. These findings suggest that GDS and MoCA may be particularly useful in detecting early cognitive and affective changes in PD populations. As participant recruitment continues, it is anticipated that an increased sample size will clarify the observed group differences, which may have important implications for pervasive intervention strategies in early-stage PD.

Disclosures: C. Marshall: None. **E.L. Stegemoller:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.03/E1

Topic: C.03. Parkinson’s Disease

Support: Creative-Pioneering Researchers Program through Seoul National University (800-20240448)
Cooperative Research Program of Basic Medical Science and Clinical

Science from Seoul National University College of Medicine (800-20250266)

Title: Resting state EEG alpha activity predicts cognitive scores in REM sleep behavior disorder

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Abstract: Idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD) is characterized by the loss of atonia during REM sleep, causing dream-enacting behavior. Although iRBD typically occurs without any clear signs of neurodegenerative disorders, a large subset of patients with iRBD eventually develop Parkinson's disease or dementia with Lewy bodies, typically accompanied by cognitive decline. Hence, identifying a biomarker that reflects a neurophysiological state of patients with iRBD could potentially be used to guide diagnosis and therapy. Here, we show that spatially clustered alpha (8-12 Hz) oscillatory activities in the scalp can predict cognitive performance in patients with iRBD. A cohort of 62 patients with iRBD underwent resting-state electroencephalography (rsEEG) recordings and participated in the Montreal Cognitive Assessment (MoCA) tests, a common measure for cognitive function. Spectral analysis of the rsEEG data revealed that overall power and transient bursting parameters of alpha activity negatively correlated with MoCA test scores. These results accounted for potential confounding factors such as the spatial distribution of the electrodes, age, sex, depression, and medication use. This finding was specific for the alpha activity since clustered theta (4-8 Hz) and beta (12-30 Hz) oscillatory activities were not correlated with the cognitive test scores. Thus, these results suggest that decreased clustered resting-state alpha activity can indicate cognitive impairment in iRBD. Our findings emphasize the importance of rsEEG dynamics in cognitive assessment and highlight the potential utility of rsEEG as an early biomarker for cognitive decline in iRBD patients.

Disclosures: R. Angerbauer: None. **A.J. Park:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.04/E2

Topic: C.03. Parkinson's Disease

Title: Rare and damaging mutations in ankyrin repeat domain proteins and their altered expression are found in patients with Parkinson's disease, melanoma, and both diseases

Authors: O. PETERS, C. BINDON, L. WALTON, A. ZIMMEL, ***R. LOGAN**;
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Abstract: Objective and rationale: Parkinson's disease (PD) and melanoma are epidemiologically linked, but the molecular basis for their co-occurrence remains unclear. Ankyrin repeat domain-containing (ANKRD) proteins mediate protein interactions and are involved in pathways relevant to neurodegeneration and cancer. We hypothesized that rare, damaging variants and altered expression of ANKRD genes contribute to the shared pathophysiology of PD and melanoma. Our objectives were to identify rare and damaging variants in ANKRD genes in individuals with PD, melanoma, or both; assess ANKRD gene expression using public transcriptomic datasets; and highlight candidate ANKRD proteins involved in both diseases. **Methods and results:** We analyzed WGS data from 65 individuals with both PD and melanoma using the *All of Us* v8 dataset (Feb 2025 release). Variants with allele frequency (AF) < 0.01 compared to gnomAD v3.1.2 and AF > 0.2 in the dual-diagnosis group were retained using Hail. This ensured the selected SNPs were rare in the general population yet relatively common in the disease group. Among 331 qualifying variants, the ANKRD36 gene ranked sixth in highest mutation count (n = 11). Gene expression was analyzed using Affymetrix Human Genome U133 Plus 2.0 datasets from NCBI GEO. GEO2R was used to reanalyze 21 PD and 77 melanoma datasets with ≥5 samples per group. Genes were considered up- or downregulated if log fold-change was ≥1.0 or ≤-1.0 (adjusted $p < 0.05$) respectively. Genes replicated in ≥2 PD datasets, ≥3 melanoma datasets, and ranked among the top 20 mutated genes in dual-diagnosis patients were prioritized. The following ANKRD genes met this criteria: ANKRD12, ANKRD28, ANKRD34C, ANKRD35, and ANKRD36, suggesting a biological role. **Conclusions:** ANKRD proteins harbor rare, damaging variants and show altered expression in PD, melanoma, and in patients with both. These results support the hypothesis that ankyrin repeat proteins may serve as molecular links between PD and melanoma. Further studies are warranted to clarify these mechanisms and identify potential therapeutic targets.

Disclosures: O. Peters: None. **C. bindon:** None. **L. Walton:** None. **A. Zimmel:** None. **R. Logan:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.05/E3

Topic: C.03. Parkinson's Disease

Title: Pro-saccade abnormalities as a potential biomarker of Parkinson's disease without freezing of gait

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Abstract: Parkinson's disease (PD) is associated with a range of motor deficits, including oculomotor impairments. While anti-saccade tasks consistently reveal increased error rates and prolonged latencies in PD, findings from pro-saccade paradigms have been inconsistent. This variability may, in part, reflect differences in participant samples across studies, specifically whether individuals with or without freezing of gait (FOG), a motor symptom linked to broader sensorimotor integration deficits, were included. To address this, we investigated eye movement characteristics in 15 individuals with PD without FOG and 15 age- and sex-matched neurologically healthy controls (CT). Participants completed fixation, pro-saccade, and anti-saccade tasks. During saccade trials, we analyzed latency, peak velocity, peak acceleration, gain, velocity-to-amplitude ratio, error rate, and coefficient of variation (CV). Fixation stability was assessed while participants passively viewed five naturalistic video clips depicting real-life scenarios; metrics included fixation count, duration and spatial dispersion. To assess task sensitivity, we also compared saccadic parameters before and after video viewing. We hypothesized that individuals with PD without FOG would exhibit subtle but measurable impairments in pro-saccade performance and reduced adaptability following passive visual stimulation. Our findings revealed significant group differences during pro-saccade tasks. Compared to controls, the PD group showed elevated error rates ($p = 0.035$), reduced velocity-to-amplitude ratio ($p = 0.025$), and significantly higher CVs across most saccadic parameters ($p < 0.038$), indicating greater intra-individual variability. Trends toward reduced peak velocity, acceleration, and gain were also observed in the PD group. During fixation tasks, the PD group exhibited increased variability in fixation number, duration, and dispersion. Only the CT group showed significant modulation in saccadic parameters following video viewing, specifically increased peak velocity ($p = 0.035$), acceleration ($p = 0.035$), and gain ($p = 0.007$). The PD group showed no significant changes post-viewing ($p > 0.05$), suggesting reduced adaptability or high baseline variability that may have masked effects. These results underscore the value of pro-saccade metrics in detecting subtle oculomotor abnormalities in PD without FOG. Diminished modulation following passive viewing may reflect impaired sensorimotor adaptability. Our findings highlight the importance of incorporating pro-saccade and fixation paradigms in future investigations of PD-related oculomotor dysfunction.

Disclosures: F.S. Daeinejad: None. **M. Saadat Foumani:** None. **S. Behzadipour:** None. **L. Alibiglou:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

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Program #/Poster #: PSTR113.06/E4

Topic: C.03. Parkinson’s Disease

Support: ASU Edson Initiative for Dementia Care and Solutions

Title: Higher Susceptibility to Parkinson’s Disease Dementia in Asian population with Apolipoprotein ε4 Compared to Caucasians: A Metanalysis Study

Authors: N. AKHTER[1], *K. BHATIA[2];
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Abstract: Clinical studies on Parkinson's disease have indicated a lower or later reported dementia incidence, underscoring the need for long-term observational studies. Genetic predisposition contributes to Parkinson's Disease Dementia (PDD) risk, with APOE alleles implicated in susceptibility; however, associations with APOE polymorphisms remain inconsistent. To derive a clear understanding for clinical studies so far, a meta-analysis was conducted using existing articles from PubMed, Web of Science, Cochrane, Google Scholar, Embase, WanFang, and CNKI databases, including case- control studies published up to January 31, 2025. A total of 27 studies (3115 PD controls and 1338 PDD cases) were included, with pooled OR (ORs) and 95% confidence intervals (CIs) calculated using CMA, Biostat, USA. To assess APOE genotypes and PDD risk, three comparisons were examined: five genotypes vs. ε3/3, ε2+/ε4+ vs. ε3/3, and ε4+ vs. ε4−. The ε3/4 (OR = 1.56, 95% CI: 1.25-1.95); ε4+ vs. ε3/3 (OR = 1.52, 95% CI: 1.20-1.93) and ε4+ vs. ε4- (OR = 1.62, 95% CI: 1.39-1.90) genotypes were associated with an increased PDD risk, while ε2+ showed no significant effect (OR = 1.21, 95% CI: 0.88-1.65, P = 0.23). Carriers of ε4+ had a 1.52-fold higher risk compared to ε3/3, and the ε4+ vs. ε4− comparison revealed a 1.62- fold greater dementia risk in ε4+ carriers. Subgroup analysis by geographical region confirmed ε4+ as a significant risk factor for PDD across Asian, and Caucasians populations with higher susceptibility in Asian populations. Our findings suggest that ε4 allele of the APOE gene is significantly associated with an increased risk of PDD, especially in Asian populations, highlighting the need for further large-scale, long-term studies to clarify genetic susceptibility.

Disclosures: N. Akhter: None. **K. Bhatia:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.07/E5

Topic: C.03. Parkinson's Disease

Support: JSPS KAKENHI Grant Number 21K19718

Title: Levodopa-induced modulation of gait kinematics and muscle synergies in parkinson's disease

Authors: *R. AYDIN[1], H. HAMADA[2], K. KIKUCHI[1], S. SHIMODA[3], Y. KAMEYAMA[4], K. SATO[4], D. KAMIYAMA[4], E. KITAHARA[5], A. YAMASHITA[1], T. SHIMAZU[6], G. OYAMA[7], T. FUJIWARA[4], Q. AN[1];
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Japan; [6]Neurol., Saitama Neuropsychiatric Inst., Saitama, Japan; [7]Saitama Med. Univ. Hosp., Saitama, Japan

Abstract: Gait impairments in Parkinson's disease (PD) are impacted by disrupted neuromuscular coordination and are known to improve after dopaminergic medication. While behavioral differences between OFF (prior to medication) and ON (post medication) states have been well established, the underlying neuromuscular mechanisms such as how joint kinematics and muscle coordination are reorganized after medication remain poorly characterized. This study investigates how levodopa modulates lower-limb joint angles and muscle synergies during gait in patients with PD, assessments conducted approximately 40 - 45 minutes apart in OFF and ON states (before and after levodopa, respectively). Lower-limb joint angles and surface EMG data were collected from 13 PD patients (mean age: 63.2 ± 6.8 years; 9 males; UPRDS Part III: OFF mean = 39.2 ± 12.3; ON mean = 11.6 ± 4.1) during overground walking in both OFF and ON states. Hip, knee, and ankle joint angles were analyzed across gait cycles to extract kinematic metrics, including extension peak angle, time to peak and range of motion (ROM). Four muscle synergies (Synergy 1 to Synergy 4) were extracted using a non-negative matrix factorization and temporal components were evaluated for peak activation, time to peak, and activation duration. Results revealed that during ON state gait, both ROM hip extension (OFF = 26.03º ± 6.7, ON = 36.33º ± 4, p =0.0002) and peak hip extension (OFF = 19.7º ± 8.5, ON = 9.5º ± 9.45, p=0.0012) significantly improved, showing greater range and deeper extension during stance, potentially contributing to enhanced propulsion. Temporal muscle synergy analysis revealed significant differences between medication states, especially in Synergy 2, which temporally aligns with hip extension during mid to end stance phase of the gait cycle. In ON state, Synergy 2 showed a shorter activation time (OFF = 49 ± 11% of gait cycle, ON= 33 ± 11% of gait cycle, p=0.01) and a higher peak activation (OFF = 0.5 ± 0.2, ON =0.7 ± 0.2, p= 0.01). Hence, ON state revealed a more robust and refined activation with higher amplitude but shorter time. These results suggest enhanced and temporally more localized synergy activation in ON compared to OFF state. Notably, improvements in hip extension during ON state were mirrored by changes in Synergy 2, indicating increased activation strength and efficient recruitment timing during mid to late stance phase of gait cycle. Together, findings highlight that dopaminergic medication enhances both joint-level movement and neuromuscular coordination, particularly around the mid to end stance phase. Muscle synergy analysis offers insights into interpreting kinematic changes during ON-to-OFF transition.

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Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.08/E6

Topic: C.03. Parkinson's Disease

Support: NRF of Korea RS-2019-NR040055
KHIDI RS-2021-KH113820
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KDRC RS-2025-02215497

Title: Eye movements during rapid eye movement sleep in RBD patients differ from those in non-RBD patients

Authors: *J. CHOI;
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Abstract: REM sleep behavior disorder (RBD) is a type of parasomnia defined by the absence of normal skeletal muscle atonia, which typically occurs during rapid eye movement (REM) sleep. Recent studies have highlighted a significant association between RBD and specific neurodegenerative diseases, particularly alpha-synucleinopathies such as Parkinson's disease (PD). Abnormalities in saccadic eye movements are frequently observed in patients with alpha-synucleinopathy, including PD and multiple system atrophy. Saccadic movements are not limited to the waking state; they also occur during REM sleep. The resemblance between REM-associated eye movements and waking saccadic movements suggests that saccade abnormalities may also be present in REM sleep in patients with RBD, a prodromal phase of synucleinopathies. This study aims to investigate the differences in eye movement (EM) in RBD patients during REM sleep compared to non-RBD patients. To this end, we analyzed overnight polysomnography (PSG) in patients with RBD and matched them to those without RBD based on age and sex. We calculated the degree and velocity of EM from electro-oculography (EOG) recorded during PSG. Additionally, we assessed the correlations between eye movement and REM sleep without atonia (RWA), as well as the standardized uptake value ratio (SUVr) of FP-CIT PET in patients with RBD. RBD patients exhibited a greater degree of EM and a faster EM velocity than non-RBD patients. EM parameters were correlated with phasic RWA and tonic RWA. Additionally, EM parameters in RBD patients showed a significant relationship with early-phase SUVr in the pons. Notably, EM parameters displayed worsening trends as alpha-synucleinopathy progressed from idiopathic RBD to PD-RBD. Our findings suggest that REM may vary with different disease states. Analyzing EM alongside EOG in RBD patients could provide additional insights into disease progression. The EM results in RBD patients suggest that it is likely influenced by alpha-synuclein in the REM-generating structures of the pons.

Disclosures: J. Choi: None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.09/E7

Topic: C.03. Parkinson's Disease

Title: An epigenome-wide association study to elucidate risk loci in levodopa-induced dyskinesia

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Abstract: Levodopa is the gold-standard therapy for Parkinson's disease (PD). However, a common side effect of chronic levodopa use is the onset of levodopa-induced dyskinesia (LiD), an involuntary movement disorder characterised by chorea, dystonia, and athetosis. The aetiology of LiD remains poorly characterised. Previous work from other groups has identified a genomic component to the development of this disorder, as well as an aberrant transcriptome. Previous work also suggests that levodopa modulates DNA methylation with aberrant methylation profiles reported in the striatum of rats chronically exposed to L-Dopa. However, to our knowledge, the human LiD methylome remains uncharacterised. Leveraging Illumina MethylationEPIC array data and participant metadata from the Parkinson's Progression Markers Initiative (PPMI) dataset, we performed an epigenome-wide association study (EWAS), comparing individuals at three time points: baseline, pre-LiD PD, and LiD onset. This study identifies dynamic DNA methylation changes following the initiation of levodopa therapy and alterations in the methylome observed at LiD onset and development.These findings may suggest an epigenetic component to LiD pathogenesis and may hold potential clinical value, with the development of predictive biomarkers to identify and stratify patients at elevated and/or imminent risk of LiD development.

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Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.10/E8

Topic: C.03. Parkinson's Disease

Title: The role of metabotropic glutamate receptor types 3 and 5 in Parkinson's disease: analysis of GRM3 and GRM5 gene variants

Authors: *M. ALBORGHETTI[1,2], L. DI MENNA[2], I. DE BARTOLO[1,2], M. SPAZIANO[1], L. NORMA[1], F. PONTIERI[1], M. BORRO[1], M. SIMMACO[1], T. ESPOSITO[3,2], A. BERARDELLI[1,2], F. NICOLETTI[1,2], V. BRUNO[1,2], G. BATTAGLIA[1,2]; [1]Univ. Sapienza, Roma, Italy; [2]I.R.C.C.S. Neuromed, Pozzilli, Italy; [3]Genet. and Biophysics CNR, Napoli, Italy

Abstract: mGlu5 and mGlu3 metabotropic glutamate receptors have been implicated in the pathophysiology of motor and non-motor symptoms of Parkinson's disease (PD). In addition, endogenous activation of mGlu3 receptors shape the vulnerability of nigrostriatal neurons in experimental models of parkinsonism in mice and monkeys (Battaglia et al., J. Neurosci., 24, 2004; Masilamoni et al., Brain, 134, 2011; Di Menna et al., Nat. Park. Dis., 11, 2025). Here, we examined the frequency of polymorphic variants of *GRM3* and *GRM5* (the genes encoding mGlu3 and mGlu5 receptors, respectively) in patients affected by PD and healthy controls, and their association with motor and non-motor signs of PD. The study sample included 1050 patients affected by PD (663 males and 387 females, age: 40-89 years) and 838 age/gender-matched healthy controls (428 males and 410 females, age: 19-94 years). DNA was extracted from peripheral blood, and Whole Exome Sequencing analysis allowed a massive and simultaneous genotyping of all the samples. Two *GRM3* haplotypes were significantly associated with PD. The mutated variants were rs1527768 (G>A), rs187993 (G>T), rs274622 (T>C), and rs724226 (G>A) in the first haplotype, and rs1989796 (T>C), rs187993 (G>T), rs274622 (T>C), and rs724226 (G>A) in the second haplotype. These haplotypes also correlated with the occurrence of postural instability, and the severity of non-motor symptoms and cognitive dysfunction. In contrast, two *GRM5* gene haplotypes showed a lower frequency in patients with PD with respect to healthy controls. The mutated variants were rs10765181 (G>A) in the first haplotype and rs973716 (A>G), rs4753486 (C>T), rs10765181 (G>A) in the second haplotype. Case-control analysis also showed a significant association between the rs60954128 polymorphism of *GRM5* and PD. Individual *GRM3* and *GRM5* polymorphisms also correlated with the severity of motor and non-motor symptoms in PD patients. Most of the gene variants identified in the study were associated with a reduced mGlu3 receptor and an increased mGlu5 receptor expression in the human brain and spinal cord, evaluated through the Genotype-Tissue Expression (GTEx) portal. These findings suggest that mGlu3 and mGlu5 receptors might shape the balance between neurodegeneration and neuroprotection in PD and might be targeted by therapeutic intervention.

Disclosures: M. Alborghetti: None. **L. Di menna:** None. **I. De bartolo:** None. **M. spaziano:** None. **L. Norma:** None. **F. Pontieri:** None. **M. Borro:** None. **M. Simmaco:** None. **T. Esposito:** None. **A. Berardelli:** None. **F. Nicoletti:** None. **V. Bruno:** None. **G. Battaglia:** None.

Poster

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Program #/Poster #: PSTR113.11/E9

Topic: C.03. Parkinson's Disease

Support: R01NS129115-02
UM1TR004528

Title: Validation of the Comprehensive Augmented Reality Testing Platform for the Quantification of Postural Instability and Gait Difficulties in Parkinson's Disease

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Abstract: Postural stability and gait difficulty (PIGD) is a cardinal motor symptom of Parkinson's disease (PD), critical for disease diagnosis and subtype classification. Current assessments of PIGD rely on clinical scales lacking objectivity and reliability. Motion capture systems are capable of objective quantification of motor symptoms but are cost prohibitive and lack portability. Augmented reality (AR) headsets hold promise as a single, portable device clinicians can utilize to capture accurate and precise biomechanical measures of performance during PIGD tasks. The Comprehensive Augmented Reality Testing (CART) platform was designed to facilitate assessment and quantification of PD cardinal motor symptoms. Two assessments from the CART platform, stepping in place (SIP) and postural stability (PS), are examined. The aims of this project are to 1.) assess equivalence of CART outcomes compared to gold standard motion capture and 2.) evaluate known group differences using CART outcomes. 63 people with PD and 34 healthy controls (HC) completed SIP and PS assessments. SIP trials were 60 seconds in duration and a double leg on a foam pad PS stance trial was 30 seconds. A clinician wore an AR headset, seated 10 feet away from the participant and recorded RGB and depth images for each assessment. Motion capture was simultaneously collected on a subset of participants (23 PD and 21 HC) for the equivalence analysis. CART outcomes from all participants were used in the group analysis. Captured from the AR headset, RGB images, depth images and camera parameters were used to construct 3D point clouds, which were processed in combination with MediaPipe pose estimation software to construct a 3D human gait model. SIP metrics were calculated using the 3D ankle joint center positions. PS metrics were calculated using the center of mass. CART measures of step count, cadence, and asymmetry were statistically equivalent (within 5%) to motion capture for SIP. Step height and normalized path length (NPL) were underestimated by 10% and 3.8%, respectively. For the PS assessment, sway area measured by CART was statistically equivalent to motion capture. CART outcomes of step height, step height coefficient of variation, and NPL measured statistically significant differences between HC and PD performance during SIP. Furthermore, sway area during the PS assessment detected significant differences between HC and PD. The CART platform provides objective, accurate and quantitative measures of PD motor performance, using a single portable device conducive to clinical integration.

Disclosures: A. Bazyk: None. **E. Zimmerman:** None. **R. Kaya:** None. **C. Waltz:** None. **M. Miller Koop:** None. **A. Rosenfeldt:** None. **J.L. Alberts:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

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Program #/Poster #: PSTR113.12/E10

Topic: C.03. Parkinson's Disease

Support: NIMH Grant R01MH122688
NIMH Grant RF1MH120025
Lundbeck Foundation fellowship R335-2019-2318

Title: Dietary Factors Affect Brain Iron Accumulation and Parkinson's Disease Risk

Authors: *J. AHERN[1], M. E. BOYLE[2], L. P. SUGRUE[3], O. A. ANDREASSEN[4], W. THOMPSON[5], C. FAN[5], R. LOUGHNAN[6];
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Abstract: Iron dysregulation in the brain has been associated with neurodegenerative diseases like Parkinson's Disease (PD). Iron is exclusively absorbed from food; therefore, dietary patterns may impact risk. We seek to understand how modifiable dietary factors are associated with brain iron accumulation (BIA) and PD risk.
Methods: This study included 228,653 UK Biobank participants (30,675 with neuroimaging; 123,303 female; ages 40-83 years). We used records of lifestyle and dietary preferences (144 questions), T2-weighted Magnetic Resonance Imaging (T2-MRI), and electronic health records (EHRs) of neurological diagnoses.
We conducted factor analysis across the preferences records to identify a latent preference space. We performed linear and logistic regression analyses using i) item-level dietary preferences and ii) dietary preference factors to predict a) a BIA score derived from T2-MRI and b) PD diagnosis from EHR.
We performed a two-sample instrumental variable mediation analysis of dietary preference results related to iron accumulation and PD risk to identify dietary factors that were jointly associated with differences in BIA and PD risk, and performed brain-wide, voxelwise imaging analysis of significant factors using T2-MRI to confirm our effects.
Results: Factor analysis of dietary preferences revealed 20 factors that cumulatively explained 49.77% of variance across individual preferences, with prominent factors loading on alcohol and high-sugar questions.
We found a positive association between BIA and the alcohol factor (pFDR=0.0003) and a negative association between BIA and the high-sugar factor (pFDR=0.0007). These factors were found to have opposite effects on PD risk, with the alcohol factor being associated with decreased PD risk (pFDR<1x10-8) and the high-sugar factor being associated with increased PD risk (pFDR<1x10-8).
Instrumental variable mediation analysis of preferences revealed that dietary preferences associated with higher BIA were also associated with lower risk for PD (r=-0.247, p=0.004).
Voxelwise imaging analysis of alcohol and high-sugar factors, using T2w-MRI, confirmed patterns consistent with increased and decreased iron accumulation in motor regions, including basal ganglia and cerebellum, respectively.
Conclusion: Dietary preferences, especially those related to alcohol and sugars, are related to differences in BIA and PD risk. Findings remained robust across factor analysis, mediation analysis, and voxelwise imaging validation, emphasizing the biological relevance of these dietary patterns and offering direction for future investigations into the relationship between diet, BIA, and PD.

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Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

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Program #/Poster #: PSTR113.13/E11

Topic: C.03. Parkinson's Disease

Support: APDA/D07
Secretaría de Ciencia, Humanidades, Tecnología e Innovación

Title: Diverging predictors of cognitive function in Parkinson's disease and healthy aging: The dominance of age versus education

Authors: *A. MORALES DE ARCIA[1], A. E. RUIZ-CONTRERAS[3], S. ALCAUTER[6], A. LÁZARO-FIGUEROA[4], J. ESQUIVIAS[2], E. MORELOS[7], I. ESTRADA-BELLMANN[8], A. BRITO MEDINA[9], M. E. RENTERÍA[10], Y. MATUK PEREZ[9], U. CABALLERO SANCHEZ[5], P. REYES[9], E. MORELOS[9], C. GUERRA GALICIA[9], V. C. OROPEZA[11];
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Abstract: Cognitive performance in Parkinson's disease (PD) and healthy aging is influenced by both neurobiological and socio-demographic factors. This study examined whether the predictors of global cognition differ between individuals with PD and healthy controls, focusing on the relative impact of age and education.
A total of 243 individuals with PD and 102 healthy controls participated. Multiple linear regression analyses were conducted separately for each group. Predictors included chronological age, years of education, emotional symptoms, and disease severity (for PD). The outcome variable was the total score on the Montreal Cognitive Assessment (MoCA).
In the PD group, chronological age emerged as the strongest predictor of cognitive performance (beta = -0.445, p = 0.002), followed by years of education (beta = 0.221, p = 0.002) and disease severity (beta = -0.168, p = 0.004). In the healthy control group, education was the main predictor (beta = 0.428, p = 0.002), while age (beta = -0.186, p = 0.030) and depressive symptoms (beta = -0.312, p = 0.002) also contributed. Both models accounted for over 40 percent of the variance in MoCA scores (adjusted R-squared = 0.413 and 0.432, respectively).

These findings suggest that in healthy aging, cognitive reserve derived from education may buffer age-related decline. In contrast, in PD, neurodegenerative pathology such as oxidative stress, neuroinflammation, and alpha-synuclein accumulation may diminish the protective effect of education, making age the primary driver of cognitive impairment. This interpretation aligns with prior evidence linking PD to accelerated brain aging and reduced compensatory capacity. In summary, education is the strongest cognitive predictor in healthy aging, whereas age dominates in PD. These distinct profiles highlight the importance of tailoring cognitive interventions to the biological context of neurodegeneration.

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Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

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NIMH R01 MH118388
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Title: Machine learning of neural correlates of neuropsychiatric symptoms in prodromal stage and clinical Parkinson's disease

Authors: *D. TAY[1], A. M. BUCH[2], C. M. LISTON[2];
[2]Psychiatry and Brain and Mind Res. Inst., [1]Weill Cornell Medicine/Cornell Univ., New York, NY

Abstract: Parkinson’s disease (PD) is a multi-system neurodegenerative disorder characterized by substantial phenotypic heterogeneity in clinical symptoms, age of onset, and disease progression. While PD is primarily diagnosed based on clinical symptom presentation of cardinal motor signs including bradykinesia, rigidity, and tremor, many individuals also experience profound neuropsychiatric symptoms—including depression, anhedonia, anxiety, cognitive dysfunction, sleep disturbances, and visual deficits—that often emerge in the prodromal stage and profoundly impact quality of life. This phenotypic variability presents significant challenges for understanding the underlying pathophysiological mechanisms and for developing effective, personalized treatments that target both motor and non-motor symptoms. Current therapeutic approaches—such as dopamine replacement, deep brain stimulation, and focused ultrasound

ablation—do not adequately improve neuropsychiatric symptoms. To meet this unmet need, here, we use machine learning to identify neural correlates of neuropsychiatric symptoms in prodromal and clinical PD. Using a large multi-modal dataset from the Parkinson's Progression Markers Initiative (PPMI)—comprising resting-state functional (rsf)MRI and behavioral measures from N=211 individuals with clinical PD (aged 29-85) and N=205 prodromal participants (i.e., with genetic and clinical risk factors, and striatal dopamine deficits)—we identified latent dimensions of whole-brain functional network connectivity that predict individual differences in neuropsychiatric and motor symptoms. We extracted functional connectivity features from rsfMRI data, and applied regularized canonical correlation analysis to predict individual differences in clinical symptoms on the Geriatric Depression Scale (GDS), State-Trait Anxiety Inventory (STAI), MDS-UPDRS, and a composite cognitive score. Our results reveal that both PD and prodromal participants show neural connectivity patterns linked to neuropsychiatric symptoms, with both shared and distinct features between groups. These findings indicate a possible link between dimensional brain-behavior markers and disease prognosis, and highlight potential future avenues for early prediction and detection. In the long term, our project lays the groundwork for more personalized diagnosis, prognostics, and disease-modifying therapeutics.

Disclosures: D. Tay: None. **A.M. Buch:** None. **C.M. Liston:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

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Program #/Poster #: PSTR113.15/E13

Topic: C.03. Parkinson’s Disease

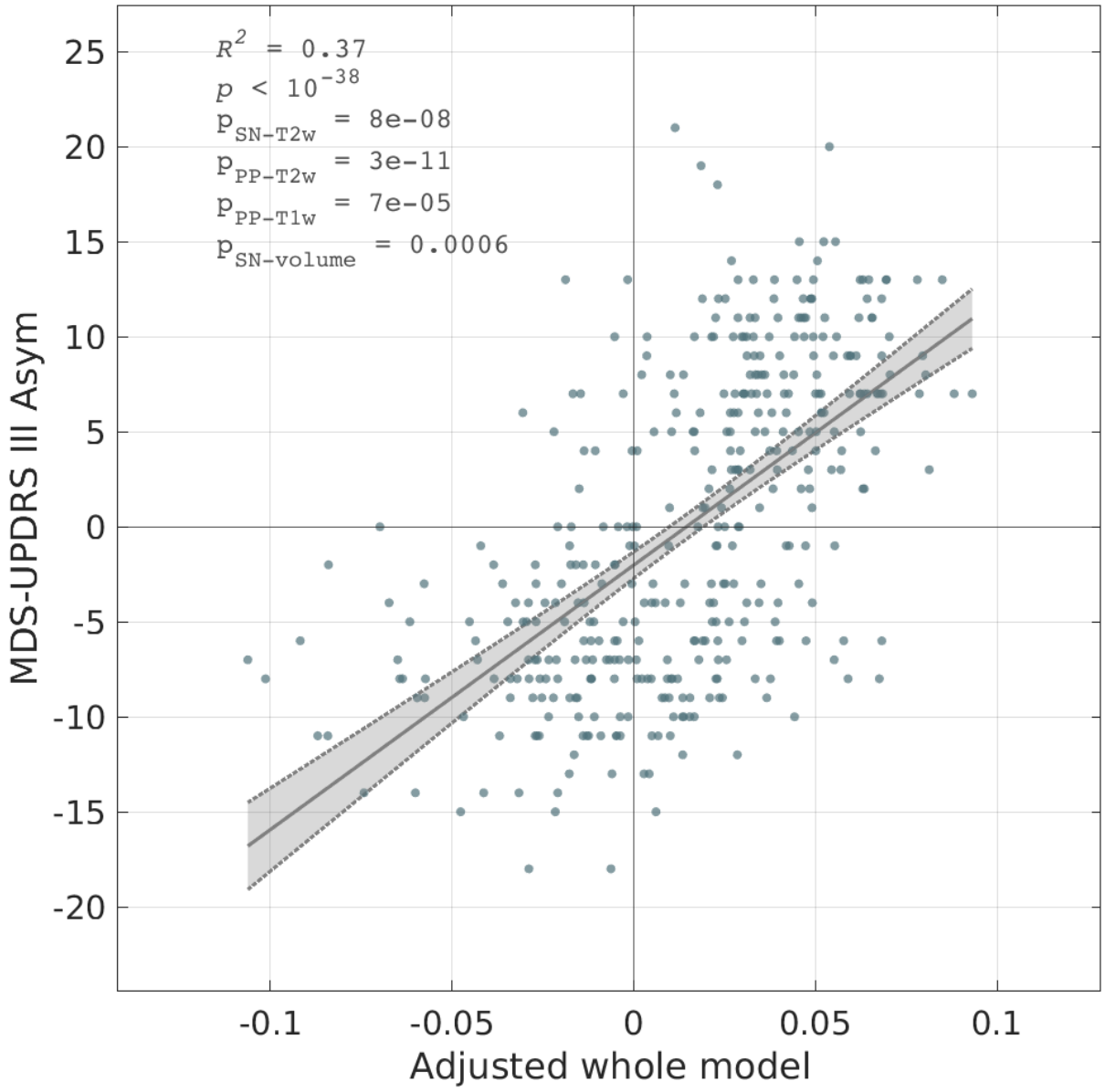
Support: ISF Grant 2449/24

Title: Nigrostriatal structural asymmetries as a biomarker of motor symptom lateralization in Parkinson’s disease

Authors: E. DRORI, ***A. A. MEZER**;
The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Motor symptom asymmetry is a defining feature of Parkinson’s disease (PD), yet the structural correlates of this lateralization remain poorly understood. We analyzed 402 MRI sessions from 157 PD patients in the PPMI database to assess how MRI-derived asymmetries in the substantia nigra (SN) and posterior putamen (PP) explain symptom asymmetry. T1-weighted (T1w), T2-weighted (T2w), and proton density-weighted (PDw) images were harmonized to enable direct comparison of signal intensities. Asymmetry indices were computed for each structure and modality, and their relationship to MDS-UPDRS Part III motor asymmetry (UPDRS3_asym) was assessed. T2w asymmetries in SN and PP were associated with UPDRS3_asym ($R^2 = 0.18$ and 0.22, $p < 10^{-19}$). A combined SN-PP contrast yielded a stronger

association ($R^2 = 0.31$, $p < 10^{-34}$). T1w asymmetry in PP alone was also associated with UPDRS3_asym ($R^2 = 0.26$, $p < 10^{-26}$). A multiple regression model including SN T2w, SN volume, PP T2w, and PP T1w asymmetries best explained symptom lateralization ($R^2 = 0.37$, $p < 10^{-38}$; Fig. 1), with all predictors contributing significantly. Each MRI parameter conveys different information: SN T2w hypointensity on the more affected side likely reflects iron deposition, while PP T2w hyperintensity and T1w hypointensity may reflect gliosis or microstructural disorganization. Interestingly, MRI asymmetries explained variance beyond DaTSCAN-derived dopaminergic measures, suggesting complementary structural information. Finally, results remained robust after accounting for volumetric effects and held in single-visit analyses. These findings position harmonized multi-contrast MRI as a robust and biologically interpretable biomarker of motor asymmetry in PD.



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Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

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Program #/Poster #: PSTR113.16/E14

Topic: C.03. Parkinson's Disease

Support: Olle Engkvist Foundation
Parkinson Research Foundation
Hain foundation

Title: Investigating the impact of mitochondrial genetic risk score for Parkinson's disease investigated in a Swedish case-control cohort

Authors: J. MALMBERG[1], K. ATTERLING BROLIN[2], ***M. SWANBERG**[2];
[1]Translational Neurogenetics Unit, Lunds Univ., Lund, Sweden; [2]Lund Univ., Lund, Sweden

Abstract: Parkinson's disease (PD) is the fastest growing neurodegenerative disorder worldwide and therapies that prevent or slow down PD progression are lacking. PD is manifested by both motor- and non-motor symptoms and the characteristic neuropathology includes intracellular alpha-synuclein aggregates, neurodegeneration of the nigrostriatal pathway and dysfunctional dopamine signaling. A small fraction of patients has monogenic PD, while idiopathic PD is determined by both genetic risk variants and non-genetic risk factors. Interestingly, the biological consequences of monogenic PD, as well as genetic risk variants and non-genetic risk factors converge on mitochondrial dysfunction. In both rodents and humans, around 99% of the genes encoding mitochondrial proteins are located in the nuclear genome. We have in PD mouse models identified increased amounts of gene transcripts encoding mitochondrial proteins involved in oxidative phosphorylation to be associated to PD-like pathology. Genetically determined mitochondrial function defined by a mitochondrial polygenic risk scores (mPRS) is a promising tool to assess PD risk, for clinical stratification and in precision medicine. To assess if variants in nuclear genes encoding mitochondrial proteins affect risk and progression of PD in the Swedish population, we analyse and compare different mPRS in the MPBC cohort with 929 cases and 935 population-based matched controls from southern Sweden. mPRS tested are defined by mitochondrial localization (n=1.136), mitochondrial disorders (n=178), mitochondrial function (n=1.137) and functions in oxidative phosphorylation (n = 124). The latter was reported by Arena *et al* to identify PD with mitochondrial impairment and to be associated to mitochondrial respiration and response to mitochondrial-targeted therapies. In the MPBC, PD-related outcomes and covariates are derived from questionnaires, national registries for medication and diagnosis, and the Swedish PD-registry. We have previously identified potential population-specific association to PD in the MPBC for the *PLPP4* gene and lack of association to PD for the *GBA1 T369M* variant reported to increase PD risk by 80% in other European populations. This makes the MPBC suitable to study population-specific effects. A strength of this study is analyses and comparisons between different mPRS in a population-specific cohort

with extensive registry- and questionnaire-based data. This allows us to determine mitochondrial effects on PD with non-genetic covariates, clinical outcomes and gene-environment interactions.

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Poster

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Location: SDCC Halls B-H

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Program #/Poster #: PSTR113.17/E15

Topic: C.03. Parkinson’s Disease

Support: NeuroMat
Fapesp
Capes

Title: Unraveling gait automaticity decline independent of cognitive decline in Parkinson's disease: a study using the new Parkinson's Affordable Neuro-movement Detection and Analysis (PANDA) system

Authors: *M. E. PIEMONTE[1], A. F. HELENE[2], A. C. ROQUE[3];
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Abstract: Daily mobility often requires walking while multitasking, such as talking or carrying items. This ability relies on automaticity—the nervous system's capacity to coordinate movements with minimal attention—which is impaired in Parkinson's disease (PD). Increased attentional control during gait is crucial to mitigate this impairment. However, as attention is a limited resource, the balance between automaticity and cognitive function affects gait under dual-task (DT) conditions. Aging may also impair both automaticity and cognition, while education contributes to cognitive reserve. Though many studies have explored gait deficiencies under DT in PD, the specific decline in gait automaticity from early to intermediate stages, isolating cognition, education, sex, and aging effects, remains unclear. This study investigated the decline in gait automaticity with disease progression, independent of cognition, age, sex, and education in 114 individuals with PD. Participants were divided into three groups based on Hoehn and Yahr (H&Y) stages, matched for age, sex, education, and cognitive capacity (assessed by the Montreal Cognitive Assessment). They completed three gait tests under two cognitive DT conditions (verbal fluency and regressive counting). The primary variable was the time to complete the tests, and the Gait Performance Index (GPI) was calculated from various gait parameters. The GPI during DT with verbal fluency differentiated the three groups, showing that gait automaticity declines progressively from the early stage of PD, independent of cognitive capacity, age, sex, and education. The GPI, derived from the low-cost, user-friendly PANDA system, may serve as an alternative index for early detection and monitoring of gait automaticity decline in PD in clinical settings.

Disclosures: M.E. Piemonte: None. **A.F. Helene:** None. **A.C. Roque:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

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Program #/Poster #: PSTR113.18/E16

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS R01NS117547

Title: Dynamic Resting-State Functional Connectivity in Parkinson's Disease Participants with Freezing of Gait.

Authors: N. SINGHAL, *V. R. MISHRA;
Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Background: Functional magnetic resonance imaging (fMRI) is a cornerstone for mapping cortico-cortical dynamics across contexts ranging from early development to neurodegenerative disorders. However, traditional analyses often rely on static connectivity measures, which may overlook the brain's dynamic nature. As dynamic fMRI remains an evolving field, novel approaches are reshaping our understanding of time-varying neural activity. Therefore, this study leverages the Co-Activation Pattern (CAP) Toolbox to examine transient neural connectivity in individuals with Parkinson's disease without freezing of gait (PD-nFOG), PD with freezing of gait (PD-FOG), and healthy controls (HC). By analyzing temporal and spatial characteristics of co-activation states, we aim to identify dynamic network alterations associated with disease progression and symptom severity. **Methods**: We utilized a dual-interface preprocessing pipeline with a GUI and CLI to streamline fMRI data preparation. Preprocessing involved fMRI optimal data acquisition, skull-stripping, distortion correction, motion correction with MCFLIRT, and artifact regression. Band-pass filtering and removal of CSF and white matter signals were applied. Images were normalized to the MNI152 template, with regression and smoothing done in SPM. Using the CAP Toolbox, we conducted dynamic analysis by identifying transient co-activation patterns across the brain through k-means clustering. This approach captures recurring spatial patterns of synchronized activity, allowing the extraction of key metrics such as occurrence rate, dwell time, transition probability, and spatial distribution. These metrics were compared across PD-nFOG, PD-FOG, and HC to characterize group differences in dynamic neural connectivity. **Results**: Using CAP analysis, our pilot analysis identified altered dynamic functional connectivity in PD-nFOG and PD-FOG groups compared to HC, especially in high-activity motor regions such as the prefrontal cortex, supplementary motor area, and basal ganglia. These changes reflect disruptions in neural network stability associated with motor symptoms. **Conclusion**: Consistent with our hypothesis, we identified several key regions implicated in PD-FOG with aberrant dynamic functional connectivity when compared to PD-FOG. The correlations between the dynamic shift in states with disease progression and physical therapy scores are currently underway.

Disclosures: N. Singhal: None. **V.R. Mishra:** None.

Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

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Program #/Poster #: PSTR113.19/E17

Topic: C.03. Parkinson's Disease

Support: NIH NIA-R01AG063982
MJFF-022672 Award

Title: Disrupted Brainstem Functional Connectivity and Molecular Signatures in Isolated REM Sleep Behavior Disorder

Authors: *L. HUA[1], K. SINGH[1,2,3], M. GARCIA-GOMAR[4,1], F. HANNANU[1], S. KOLEY[1], A. STEFANI[1,5,6], S. GRIMALDI[1,7], A. VIDENOVIC[6,8], M. BIANCIARDI[1,8];
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Abstract: MOTIVATION: Isolated REM sleep behavior disorder (iRBD) is considered one of the earliest prodromal stages of α-synucleinopathies with high risk of progression to Parkinson's disease. Neuropathological staging suggests that neurodegeneration originates in the brainstem, yet direct evidence of network-level dysfunction at brainstem nuclei level remains elusive due to limited spatial resolution of conventional MRI and lack of precise human brainstem atlas. **METHODS:** We leveraged 7 Tesla resting-state fMRI and our lab recently developed probabilistic Brainstem Navigator atlas of 20 iRBD-relevant brainstem nuclei to examine functional connectivity (FC) alterations in 16 iRBD patients (67.19 ± 5.96, 3F) compared with 17 elderly controls (EC; 64.41 ± 4.15, 4F). Age and sex did not differ significantly between groups. To investigate molecular underpinnings, we performed partial least squares regression (PLS) linking brainstem FC alteration T-map with regional gene expression from the Allen Atlas. **RESULTS and DISCUSSION:** Compared to EC, iRBD patients exhibited significantly reduced FC ($p < 0.005$) among monoaminergic and reticular nuclei (e.g., locus coeruleus, pontine nuclei, reticular formation), which regulate arousal and REM sleep, supporting early dysfunction in iRBD in nuclei orchestrating sleep-wake architecture and vigilance. In contrast, significantly increased FC ($p < 0.005$) in iRBD was found between viscerosensory-motor nuclei and ventral spinal cord, potentially reflecting maladaptive hyperconnectivity leading to metabolic stress and heightened vulnerability, and disinhibition due to loss of cortical inhibitory

influence. Furthermore, spatial organization of FC—as indexed by the correlation between FC strength and Euclidean distance—was preserved in EC (r = -0.288, p = 0.025) but disrupted in iRBD (r = -0.199, p = 0.123), suggesting impaired topographical specificity of intrinsic brainstem networks. Graph-theoretical results confirmed that iRBD patients exhibited decreased global/local efficiency and clustering coefficient, and increased shortest path length. These alterations indicate a shift toward more segregated and fragmented network topology. Finally, the first PLS component explained 34.47% of T-map variance, and gene enrichment highlighted neurofilament bundle assembly alterations—molecular pathways associated with α-synuclein pathology. **CONCLUSION:** Together, these findings provide the first nucleus-level, gene-informed evidence of early-stage brainstem network functional dysfunction in iRBD, identifying potential biomarkers and mechanisms underlying prodromal α-synucleinopathy.

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Poster

PSTR113: Parkinson's Disease Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.20/Web Only

Topic: C.03. Parkinson’s Disease

Support: American Parkinson’s Disease Association through a Diversity in Parkinson’s Disease Research Grant (APDA/D07)
Parkinson’s Genetics Program (GP2)
ALF is a doctoral student of the Programa de Doctorado en Psicología de la Universidad Nacional Autónoma de México and she is a scholarship holder who received a grant scholarship (1222481) from CONACYT for her Psychology PhD studies

Title: A reliable approach for the detection of Mild Cognitive Impairment in Parkinson's Disease from a Mexican cohort

Authors: *A. LÁZARO-FIGUEROA[1,2], A. MORALES DE ARCIA[3], P. REYES[6], I. HERNÁNDEZ-RUIZ[2], G. DE ANDA MOCTEZUMA[2], J. ESQUIVIAS[4], I. ESTRADA-BELLMANN[7,8], N. GANDARILLA MARTINEZ[9], C. GUERRA GALICIA[10], Y. MATUK PEREZ[11,12], E. MORELOS[13], C. PONCE FERNÁNDEZ[14], A. BRITO MEDINA[13], S. ALCAUTER[15], M. E. RENTERIA[16], A. MEDINA-RIVERA[5], A. E. RUIZ-CONTRERAS[2]; [1]Sch. of Psychology, Univ. Nacional Autonoma de Mexico, Mexico, City, Mexico; [2]Lab. de Nuerogenómica Cognitiva. Unidad de Investigación en Psicobiología y Neurociencias, Coord. Psicobiología y Neurociencias, Fac. Psicología. Univ. Nacional Autónoma de México (UNAM), Mexico City, Mexico; [3]Univ. Nacional Autónoma de México, Tuxtla, ; [4]Univ. Nacional Autónoma de México, Querétaro, Mexico; [5]Lab. Internacional de Investigación sobre el Genoma

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Abstract: Mild cognitive impairment (MCI) in individuals with Parkinson's disease (PD) has the potential risk of progression to dementia. One of the most widely used instruments for assessing cognitive status is the Montreal Cognitive Assessment (MoCA). This establishes a cutoff point of <26 points for detecting MCI. However, one of the problems identified is its limited reliability when applied to populations in developing countries, due to the overestimation of individuals with MCI. Another important point is that the assessment of cognitive status is influenced by a person's age (β=.12, p<.001) and education (β=.34, p<.001). Therefore, here we aimed to analyze and identify the prevalence of MCI in Mexican PD patients, controlling for age and education level, using the criteria of the Movement Disorders Society for MCI. We collected 213 controls (μ age 57.4 $\pm$ SD 9.5 years) and 518 PD Patients (μ age 66.7 $\pm$ SD 10.4 years) which were divided according to their age (four etarian groups: 32-49; 50-64; 65-74; 75 or more years) and years of education (four groups: 1-6, 7-9, 10-12,13 or more years). Then, we calculated the mean of the MoCA score from controls, as a function of age and years of education, identifying the cut-off score as -1-SD for identifying MCI of PD patients according to their age and school level. Thus, the prevalence of MCI was 32% for the PD Mexican patients, significantly different from the prevalence of 11% of the control group (p<0.001). These results are more reliable than the prevalence detected if the cutoff point were generalized to <26 points in MoCA (MCI in controls: 55% vs. PD patients: 73%). In conclusion, we propose this method to reliably improve the detection of MCI, avoiding the bias of schooling and age on cognitive performance.

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Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.01/E18

Topic: C.06. Neuromuscular Diseases

Title: Stage-specific mechanisms regulate TDP-43 nuclear body homeostasis

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Abstract: TAR DNA binding protein 43 kDa (TD-43) is a nuclear RNA-binding protein critical for RNA processing and regulation. Protein inclusions containing TDP-43 are a pathological hallmark of amyotrophic lateral sclerosis and frontotemporal dementia. Our previous work revealed that stress induces TDP-43 to form dynamic, liquid droplet-like, cytoprotective condensates in the nucleus, termed TDP-43 nuclear bodies (NBs). We demonstrated that the long noncoding RNA (lncRNA) *NEAT1* is required for initiating TDP-43 NB assembly. Subsequent study showed that heat shock protein (Hsp) 70 is recruited into TDP-43 NBs under stress. Interestingly, Hsp70 exhibits dual functionality: it promotes TDP-43 liquid-liquid phase separation (LLPS) to facilitate NB assembly; meanwhile, it prevents liquid-to-solid phase transition of TDP-43 NBs, thereby, reducing TDP-43 nuclear aggregates during prolonged stress. Mechanistically, Hsp70 interacts with a conserved region of the TDP-43 low complexity domain. The interaction between Hsp70 and TDP-43 enhances LLPS during assembly but limits excessive TDP-43 intermolecular interaction during maintenance, thus suppressing pathological aggregation. Protein post-translational modifications (PTMs) also critically regulates TDP-43 phase separation. Our most recent work revealed that both stress and stress withdrawal induce robust ubiquitination of TDP-43. Strikingly, ubiquitination is specifically required for the prompt disassembly of TDP-43 NBs upon stress release, whereas inhibiting ubiquitination had no significant effect on TDP-43 NB assembly. Our ongoing efforts are to elucidate the molecular mechanisms underlying these distinct regulations. In summary, the series of studies on TDP-43 NB demonstrate that its homeostasis is tightly regulated at multiple levels: *NEAT1* initiates assembly, Hsp70 maintains condensate dynamics, and ubiquitination governs disassembly. Collectively, these findings underscore the importance and need for time-resolved analysis to dissect stage-specific regulations in biomolecular condensates.

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Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.02/E19

Topic: C.06. Neuromuscular Diseases

Title: Induction and dynamics of TDP-43 aggregation in iPSC-derived neurons

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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive loss of motor neurons. One of the hallmarks of ALS is the cytoplasmic mislocalization and aggregation of TDP-43, which has led to ALS being recognized as a proteinopathy. TDP-43 aggregation is getting attention as a novel target for ALS therapeutics. Protein homeostasis is the process of maintaining the balance of functional proteins, and the disturbance of protein homeostasis is believed to contribute to abnormal protein aggregation, including that of TDP-43. To establish a method for inducing endogenous TDP-43 aggregation in induced pluripotent stem cell (iPSC)-derived neurons by disrupting protein homeostasis, we tested various chemical compounds known to influence protein synthesis or degradation. As a results, we successfully induced endogenous TDP-43 aggregation in iPSC-derived motor neurons and cortical neurons.
When iPSC-derived neurons were treated with compounds that disrupt protein homeostasis, TDP-43 puncta were observed to colocalize with G3BP1 in the cytoplasm, and the formation of puncta was more pronounced compared to well-known stimuli such as MG-132 or H_2O_2. The number of puncta increased in a dose-dependent manner with the compounds and in a time-dependent manner with the duration of compound treatment. The puncta disappeared after the removal of the compounds following a few hours of treatment, suggesting that the puncta formation is reversible at this stage. A method to induce more solid TDP-43 aggregates is currently under investigation. This TDP-43 induction model is being utilized to identify molecules capable of inhibiting TDP-43 aggregation. In addition, attempts are also underway to gain insight into its clinical relevance by characterizing cells with TDP-43 aggregation. Furthermore, efforts are ongoing to use this model in combination with astrocytes and microglia co-cultures.
In conclusion, we have established a method to induce endogenous TDP-43 aggregation in iPSC-derived neurons by disrupting protein homeostasis. We are currently using this method to assay compounds and are also attempting to combine it with a neural co-culture system. This method holds promise for studying ALS as a proteinopathy and for advancing drug development.

Disclosures: H. Kobayashi: A. Employment/Salary (full or part-time): FUJIFILM Corporation. **H. Munezane:** A. Employment/Salary (full or part-time): FUJIFILM Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); FUJIFILM Corporation. **S. Endoh-Yamagami:** A. Employment/Salary (full or part-time): FUJIFILM Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); FUJIFILM Corporation.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.03/E20

Topic: C.06. Neuromuscular Diseases

Support: LCF/PR/HA21/52350003
CNS2022-135759

Title: Mislocalized cytoskeletal protein biogenesis within TDP-43 aggregates derails sarcomere organization in human myocytes induced from fibroblasts

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Abstract: A key challenge in the study of amyotrophic lateral sclerosis (ALS) is that the affected cells, mainly human motor neurons and muscle cells, are difficult to isolate and culture. To address this limitation, we evaluated cultured dermal fibroblasts as a potential cellular model for ALS investigations, given their accessibility via minimally invasive biopsies and their capacity to be reprogrammed into ALS relevant cell types, including neurons and muscle cells. Morphological and biochemical analyses of patient-derived fibroblasts revealed prominent cytoplasmic mislocalization and aggregation of TAR DNA-binding protein 43 (TDP-43), along with substantial disruption of F-actin and 4A-alpha-tubulin fibers, indicating compromised cytoskeletal integrity, which are pathological features of the disease. Intriguingly, cytoskeletal fibers partially colocalized with cytoplasmic TDP-43, including within its aggregates, suggesting that TDP-43 may participate in their synthesis or assembly in control cells and contribute to their mislocalization and disorganization in the ALS context. To further investigate these observations, we reprogrammed fibroblasts into induced myocytes (iMCs) via retroviral expression of the muscle lineage determinant MyoD. Consistent with previous findings, control iMCs exhibited TDP 43 not only in the nucleus but also in association with myosin within sarcomeric structures, implying a role in muscle skeletal protein biogenesis, particularly within the sarcomere. Moreover, in patient derived iMCs, myosin colocalized with TDP-43 aggregates while sarcomeres were disrupted, supporting the notion that these aggregates misdirect myosin synthesis and disrupt sarcomere organization. Finally, we investigated whether preventing TDP-43 aggregation could reduce myosin aggregation and restore sarcomere structure. To this aim, we used protein kinase inhibitors, as our previous work demonstrated their ability to restore TDP-43 nuclear localization and promote aggregate clearance. Treatment with these inhibitors rescued TDP-43 distribution and alleviated cytoskeletal defects. Overall, our findings reveal a novel mechanism that may be central to ALS, deepening our understanding of disease pathogenesis and identifying new avenues for therapeutic intervention.

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Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.04/E21

Topic: C.06. Neuromuscular Diseases

Title: Tdp-43 proteinopathy in astrocytes induces cell-autonomous and non-cell autonomous effects in a disease relevant ipsc-derived in vitro model

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Abstract: TDP-43 proteinopathy in astrocytes induces cell-autonomous and non-cell autonomous effects in a disease-relevant iPSC-derived in vitro model Ivan Nyarko-Danquah[1,2], Iqra Pervaiz[1†], Zoe Piccus[1†], Zhonglin Zhao[1], Sean Ryan[1], Dimitry Ofengeim[1], and Francesca Rapino[1] [1] Sanofi, Cambridge, MA, 01701, USA. [2] Howard University, Washington, DC, 20059, USA [†] Employee of Sanofi when this work was undertaken **Abstract:** Transactive response DNA-binding protein (TDP-43), is a highly conserved RNA-binding protein which plays a crucial role in regulating transcription and RNA splicing. Mislocalization and aggregation of TDP-43 in the cytoplasm represent a major pathological hallmark of amyotrophic lateral sclerosis (ALS). Although TDP-43 proteinopathy has extensively been studied in motor neurons, evidence support the contribution of other non-neuronal cells such as astrocytes. Various approaches have been used to model TDP-43 proteinopathy *in vitro.* Here, we engineered a disease-relevant iPSC-derived cell model of TDP-43 proteinopathy in which hTDP-43 is expressed and mislocalized, under a tet-on system, modelling the toxic gain-of-function pathology. We first differentiated these engineered iPSCs into astrocytes and motor neurons in a spinner flask bioreactor using small molecule patterning method, and characterized them to validate the mislocalization, phosphorylation and aggregation of cytoplasmic TDP-43. Using these iPSC-derived astrocytes, we demonstrate the cell-autonomous effect of TDP-43 pathology on astrocyte reactivity and mitochondrial dysregulation. We also show the non-cell autonomous effect of astrocytic TDP-43 proteinopathy using an astrocyte-motor neuron co-culture which revealed diminished neuronal activity and reduced neuronal viability as a result of the TDP-43 proteinopathy in astrocytes. Our results reveal the cell-autonomous as well as the non-cell autonomous role of astrocytes in TDP-43 proteinopathy and indicate that astrocytes contribute to disease progression by assuming a reactive state that directly impairs neuronal activity and viability.

Disclosures: I. Nyarko-Danquah: A. Employment/Salary (full or part-time): Sanofi. **I. Pervaiz:** A. Employment/Salary (full or part-time): Sanofi. **Z. Piccus:** A. Employment/Salary (full or part-time): Sanofi. **T. Zhao:** A. Employment/Salary (full or part-time): Sanofi. **S. Ryan:** A. Employment/Salary (full or part-time): Sanofi. **D. Ofengeim:** A. Employment/Salary (full or part-time): Sanofi. **F. Rapino:** A. Employment/Salary (full or part-time): Sanofi.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.05/E22

Topic: C.06. Neuromuscular Diseases

Support: Motor Neurone Disease Association (MNDA) DNA004

Title: Tdp-43 pathology and autophagy defects modeled and rescued in tbk1 mutant ipsc derived motor neurons

Authors: Z. SIMMONS[1], N. FIORE[1], Y. HAMWI[1], ***C. ABBATE**[2], M. MCMILLAN[1], T. PHILIPS[1], S. HINCKLEY[1];
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Abstract: Nearly all cases of Amyotrophic lateral sclerosis (ALS) are linked to RNA binding protein TAR DNA-binding protein 43 (TDP-43) pathology. Nuclear TDP-43 is a key regulator of cellular RNA metabolism. In ALS, TDP-43 is mis-localized to the cytoplasm where it forms cytoplasmic inclusions. Neuronal TDP-43 nuclear clearing and cytoplasmic aggregation of TDP-43 leads to significant RNA dysregulation and cellular toxicity. A notable example of this is Stathmin-2 (*STMN2)* mis-splicing due to TDP-43 loss-of-function. Restoring TDP-43 dysfunction has proven challenging, as the etiology of TDP-43 dysregulation in ALS is still largely unknown. However, numerous studies associate disruptions of autophagy flux with TDP-43 accumulation and neurodegeneration in both familial and sporadic cases. Genetic mutations in several autophagy related and ALS-causing genes lead to TDP-43 accumulation including Tank binding kinase 1 (*TBK1*). Overall upregulation of autophagy is a widely recognized area of therapeutic potential. To study the potential of autophagy regulation we are uncovering the characteristics of three patient iPSC derived motor neurons harboring individual TBK1 mutations that were provided by the Motor Neurone Disease Association (MNDA). Each of these TBK1 cell lines contain the signature of TDP-43 mislocalization, TDP-43 loss-of-function gene expression including increased STMN2 cryptic expression, and autophagy dysfunction. Using a STMN2 splice switching antisense oligonucleotide (ASO), we were able to restore STMN2 cryptic expression in all TBK1 mutant patient lines. Thus, the TBK1 iPSC lines contain both TDP-43 loss- and gain-of-function characteristics that can be targeted and restored. These cell lines will be valuable models for investigating therapeutic modalities to rescue TDP-43 pathology especially through mechanisms of autophagy.

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Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR114.06/E23

Topic: C.06. Neuromuscular Diseases

Title: Loss-of-function and toxic gain-of-function of TDP43 in an in vitro model of amyotrophic lateral sclerosis

Authors: A. HENRIQUES[1], ***G. CULLEY**[2], V. DE CONTO[2], C. BOTTO[2], L. ROUVIERE[2], P. POINDRON[2], N. CALLIZOT[3];
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Abstract: Amyotrophic lateral sclerosis (ALS) is an adult motor neuron disease characterized by degeneration and loss of upper (motor cortex) and lower (spinal cord and brainstem) motor neurons and muscle denervation. Neurodegeneration of spinal motor neurons and loss of neuromuscular junctions in ALS are caused by complex and multifactorial pathological events, including mitochondrial stress and accumulation of misfolded proteins. Proteinopathy in ALS is progressive over time and across CNS areas. Most ALS patients present with TDP43 aggregates in motor neurons and mutations on TARBP (the gene coding for TDP43) are associated with familial cases of ALS. TDP43 is a protein involved in RNA metabolism, mitochondrial function and axonal transport. TDP43-mediated neurodegeneration is due to loss-of-functions of the protein, due to its phosphorylation and aggregation, but also to toxic gain-of-functions driven by TDP43 neurotoxic species, such as fibrils. Here, we investigated, in separate experiments, the loss-of-function of TDP43, by promoting its mislocalization, and the toxic gain-of-function of TDP43, by applying toxic TDP43 pre-formed fibrils (PFFs), on primary spinal MNs. First, primary spinal MNs were cultured for 14 days and were subjected to excitotoxicity (glutamate, 5 µM for 20 minutes, followed by a wash-out of 24 hours). In a second experiment, we used PFFs of TDP43, generated from human recombinant TDP43 subjected to agitation at 37°C. TDP43-PFFs were applied on primary spinal MNs (on day 14 of culture) for 72 hours and 96 hours. Immunostaining and automated image analysis were applied to investigate neuronal survival, integrity of the neurite network, abnormal cytoplasmic accumulation of TDP43 and markers of autolysosomal vesicles. Our results showed that, when exposed to glutamatergic stress, spinal MNs presented with an early mislocalization of TDP43, followed by an accumulation of hyperphosphorylated TDP43 in the cytoplasm and autolysosomal burden. Neurotoxicity and TDP43 pathology were mitigated in the presence of Riluzole, a FDA-approved drug for the management of ALS. In the second experiment, the application of TDP43-PFFs on healthy spinal MNs lead to a time- and concentration-dependent neurotoxicity, associated with a loss of neurites. Altogether, these findings demonstrate that *in vitro* models of ALS, based on primary spinal MNs, are valuable tools for modelling ALS, as they reproduce the TDP43 loss-of-function, due to its sequestration in the cytoplasm, and the TDP43 toxic gain-of-function that are key features of ALS.

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Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

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Program #/Poster #: PSTR114.07/E24

Topic: C.06. Neuromuscular Diseases

Support: WINGS-LST W2021022
JSPS DC2 202415056

Title: Intracellular Temperature-Dependent Regulation of TDP-43 Condensation: Implications for Amyotrophic Lateral Sclerosis Pathogenesis

Authors: *D. YAMANE[1], M. TAKARADA[2], Y. SUDO[3], T. FUNATSU[4], K. OKABE[2], Y. HORI[3], T. TOMITA[3];
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Abstract: Background: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by selective motor neuron degeneration. A pathological hallmark of ALS is the cytoplasmic accumulation of detergent-insoluble protein inclusions containing TAR DNA-binding protein 43 (TDP-43). Familial ALS is often linked to mutations in the *TARDBP* gene, which encodes TDP-43. Normally localized in the nucleus, TDP-43 forms cytoplasmic condensates, similar to stress granules (SGs), via liquid-liquid phase separation (LLPS). It is well-established that temperature is a crucial modulator of LLPS. Previously, we demonstrated the existence of spontaneous temperature increases within single cells (Okabe et al., Nat. Commun., 2012) and their important role in cellular functions, such as SG formation. Building on this, we hypothesized that intracellular temperature might similarly regulate TDP-43 condensation, offering a novel mechanistic insight into ALS pathogenesis. **Methods:** To investigate TDP-43 condensation, we utilized live imaging of EGFP-tagged TDP-43 in COS7 cells. Condensation was induced by either sodium arsenite (Ars) treatment or localized near-infrared (IR) laser irradiation.**Results:** Ars treatment induced TDP-43 condensation; however, these condensates did not co-localize with conventional SG markers, suggesting distinct structures with potentially shared regulatory mechanisms. Critically, localized IR laser heating specifically induced TDP-43 condensation at the irradiated sites. This effect was abolished when heat-absorbing polymers were introduced into the cells, confirming temperature-dependent regulation. Notably, familial ALS-associated TDP-43 mutants exhibited highly reactive to temperature increases compared to wild-type TDP-43.**Conclusions:** Our findings reveal that TDP-43 condensation is regulated by intracellular temperature, providing a novel mechanism beyond previously studied post-translational modifications such as phosphorylation and ubiquitination. These results suggest that aberrant intracellular temperature fluctuations or dysregulation could directly contribute to pathological TDP-43 aggregation in ALS. Our study offers a novel framework for understanding TDP-43opathy and opens new avenues for therapeutic interventions targeting temperature-dependent protein dynamics in neurodegeneration.

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Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

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Title: Nuclear import defects drive cell cycle dysregulation in neurodegeneration

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Abstract: Neurodegenerative diseases (NDDs) and other age-related disorders have been classically defined by a set of key pathological hallmarks. Two of these hallmarks, cell cycle dysregulation (CCD) and nucleocytoplasmic transport (NCT) defects, have long been debated as being either causal or consequential in the pathology of accelerated aging. Specifically, aberrant cell cycle activation in post-mitotic neurons has been shown to trigger neuronal cell death pathways and cellular senescence. Additionally, NCT has been observed to be progressively dysregulated during aging and in neurodegeneration, where the increased subcellular redistribution of nuclear proteins, such as TAR DNA-Binding Protein-43 (TDP-43), to the cytoplasm is a primary driver of disease. However, the functional significance of NCT defects as either a causal mechanism or consequence of pathology, and how the redistribution of cell cycle machinery contributes to neurodegeneration, remains unclear. Here, we describe that pharmacological inhibition of importin-β nuclear import is capable of perturbing cell cycle machinery both in mitotic neuronal cell lines and post-mitotic primary neurons in vitro. Our NemfR86S mouse model of motor neuron disease, characterized by nuclear import defects, further recapitulates the hallmarks of CCD we observed in mitotic cell lines and in post-mitotic primary neurons in vitro, and in spinal motor neurons in vivo. The observed CCD is consistent with the transcriptional and phenotypical dysregulation commonly associated with neuronal cell death and senescence-like features in NDDs. Together, this evidence suggests that impairment of nuclear import pathways resulting in CCD may be a common driver of pathology in neurodegeneration.

Disclosures: J. Plessis-Belair: None. **T. Russo:** None. **M. Riessland:** None. **R. Sher:** None.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.09/E26

Topic: C.06. Neuromuscular Diseases

Title: High-capacity microfluidic compartmentalized cell cultures for studying axonal regrowth in sporadic ALS iPSC-derived motor neurons

Authors: S. M. LARDELL[1], L. MOLL[1], N. KULESSKAYA[2], A. DOMANSKA[2], H. HUTTUNEN[2], ***P. KARILA**[1], J. PIHL[1];
[1]Cellectricon AB, Mölndal, Sweden; [2]Herantis Pharma Plc, Espoo, Finland

Abstract: Neurological diseases are the leading cause of disability and the second largest cause of death in humans, and despite this, neurology remains to be one of the more failure-prone areas of drug discovery. The complexity of the human brain and limitations in existing in vivo models, as well as challenges associated with the establishment of relevant in vitro models result in a substantial translation gap. However, microfluidic in vitro models have shown promise in regard to the development of human models having improved translational relevance.
Cellectricon has developed a high-capacity compartmentalized microfluidic co-culture plate that enables the establishment and study of complex neurological in vitro models. The plate is comprised of 96 experimental units compliant with American National Standard Institute of the Society for Laboratory Automation and Screening (ANSI/SLAS) standards of a 384-well plate [1]. Each experimental unit is comprised of 3 wells connected by microchannels, allowing for the passage of axons, but not cell bodies or dendrites. The co-culture plate design provides the capability of parallelizing and automating experiments while reducing experimental volumes of cells or compounds. The channel design allows for the separation of axons from dendrites. Moreover, targeted treatment of specific cells, soma or axons can be achieved for extended periods of time by including a hydrodynamic barrier. In addition, the cell compatibility of the plate has been tested with several primary and iPSC-derived neuronal cultures.
As an example of the utility of the co-culture plate, it was used to evaluate the effects of HER-096, a peptide drug developed based on the active site of cerebral dopamine neurotrophic factor (CDNF), on axonal regrowth post-axotomy in motor neuron cultures derived from sporadic ALS iPSCs. While HER-096 is developed as a disease-modifying therapy for Parkinson's disease, the mother molecule CDNF has shown broad neuroprotective and neurorestorative effects in diverse models of neurodegeneration, including rodent models of ALS. The biological mechanisms facilitating functional recovery of injured axons remains poorly understood. In this study, axotomy was successfully performed, and significant axonal regrowth was observed with HER-096 compared to untreated control.
To conclude, Cellectricon's microfluidic compartmentalized co-culture plates enable the establishment and study of complex neurological in vitro models as demonstrated by the characterization of HER-096.
Ref.:
[1] Moll L et al.. ACS Chem Neurosci. 2024 Jan 17;15(2):236-244. doi: 10.1021/acschemneuro.3c00409. PMID: 38150531; PMCID: PMC10797611.

Disclosures: S.M. Lardell: A. Employment/Salary (full or part-time): Cellectricon AB. **L. Moll:** A. Employment/Salary (full or part-time): Cellectricon AB. **N. Kulesskaya:** A. Employment/Salary (full or part-time): Herantis Pharma Plc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual

funds); Herantis Pharma Plc. **A. Domanska:** A. Employment/Salary (full or part-time): Herantis Pharma Plc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Herantis Pharma Plc. **H. Huttunen:** A. Employment/Salary (full or part-time): Herantis Pharma Plc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Herantis Pharma Plc. **P. Karila:** A. Employment/Salary (full or part-time): Cellectricon AB. **J. Pihl:** A. Employment/Salary (full or part-time): Cellectricon AB.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.10/E27

Topic: C.06. Neuromuscular Diseases

Support: T32AG057468

Title: The Role of Aurora B Kinase in the Development of Neuron Dysfunction in ALS/FTD

Authors: *S. MARTIN, J. KUNWAR, A. ALAANI, M.-Y. TSAI, S. T. BRADY;
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affecting upper and lower motor neurons which leads to paralysis and death. Frontotemporal dementia (FTD) is a neurodegenerative disease that affecting frontal and temporal lobes which results in cognitive changes and dementia. ALS and FTD overlap genetically and clinically. The most common genetic risk factor associated with ALS/FTD is Chromosome 9 open reading frame 72 (C9orf72) repeat expansion mutation. Through repeat associated non-AUG translation, the C9orf72 mutation results in formation of five different dipeptide repeat proteins. Nuclear pathologies (changes to nuclear size, shape, and transport) decrease the overall health of the neuron; and these nuclear pathologies are associated with the C9orf72 dipeptide repeat proteins. However, it is unknown how C9orf72 dipeptide repeats contribute to development of nuclear pathologies. Previous studies have implicated kinases in ALS/FTD pathogenesis, raising the possibility that a signaling kinase might play a role in development of nuclear pathologies in C9orf72-associated neurodegeneration. Aurora B kinase is a serine/threonine kinase known to have nuclear localization and functions and may have a cytoplasmic role regulating neurite outgrowth. Our preliminary data demonstrate changes to Aurora B kinase expression levels in primary cortical and motor neurons expressing a subset of the C9orf72 dipeptide repeats. We propose that nuclear pathologies occur through an Aurora B kinase-dependent mechanism and potentially contribute to development of axonal degeneration in C9orf72-associated neurodegeneration. To address this hypothesis, we transfected rat primary cortical and motor neurons with expression plasmids containing the C9orf72 dipeptides. We found that there are changes to Aurora B kinase expression and activity in primary cortical and motor neurons expressing the poly-PR, poly-GR, and poly-PG dipeptides. Treating primary cortical neurons that

were transfected with the dipeptides with an Aurora B kinase inhibitor, AZD-1152, resulted in a decrease in neurite length in cells expressing the poly-PR and poly-PG dipeptides and an increase in neurite length in cells expressing the poly-GR dipeptide, suggesting that Aurora B kinase plays a role in axonal processes. Our findings indicate that alterations in Aurora B kinase may be involved in the development of pathologies in C9orf72-associated ALS/FTD, perhaps establishing a common mechanism of neurodegeneration in ALS/FTD caused by this mutation.

Disclosures: S. Martin: None. **J. Kunwar:** None. **A. Alaani:** None. **M. Tsai:** None. **S.T. Brady:** None.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.11/E28

Topic: C.06. Neuromuscular Diseases

Title: Advancing ALS modeling: High-dimensional insights with CytoTronics' Pixel

Authors: C. BANFILL[1], S. CHINTA[1], P. SURESH[1], S. SUTAR[1], S. PRIME[2], *S. CHITALE[1]; [1]CytoTronics, Boston, MA; [2]Axol Biosci., Cambridge, United Kingdom

Abstract: Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of motor neurons, with diverse genetic mutations contributing to disease onset and progression. Modeling ALS using human iPSC-derived motor neurons provides a promising avenue for understanding disease mechanisms and screening therapeutics. Here, we demonstrate the application of the CytoTronics' Pixel to perform simultaneous, label-free, high-resolution analysis of both structural and functional phenotypes in iPSC-derived motor neurons from healthy and ALS-associated genotypes. Motor neurons derived from human iPSCs (Axol Bioscience) representing healthy control and ALS-linked TDP43, C9ORF72, and SOD1 mutations were cultured for 28 days on Pixel 96-well microplates with poly-D-lysine and vitronectin. Pixel's impedance-based electrical imaging was used to assess cell morphology, health, and attachment every 2 hours, while extracellular neural recordings captured spontaneous activity every 12 hours. Over 20 orthogonal impedance parameters and multiple neural activity metrics were analyzed using the Pixel software suite, including principal component analysis (PCA) for high-dimensional data interpretation. Pixel enabled continuous monitoring of disease-relevant features across genotypes. Electrical imaging revealed distinct morphological signatures, such as altered attachment, clumping, and network formation, in ALS lines compared to controls. PCA of impedance features clearly distinguished disease-associated cultures. Neural recordings captured progressive functional maturation and revealed genotype-specific differences in firing rate, burst characteristics, and network dynamics. ALS-associated neurons showed elevated firing rates and increased bursting dynamics as compared to controls, indicating abnormal excitability. The CytoTronics' Pixel provides a scalable, non-invasive approach to capturing both structural and functional phenotypes in long-term iPSC-derived neuronal cultures.

Combined with disease-relevant models, Pixel enables robust, longitudinal analysis for ALS research, cell line validation, and phenotypic drug screening - offering new insights into neurodegenerative disease mechanisms and therapies.

Disclosures: C. Banfill: A. Employment/Salary (full or part-time): CytoTronics, Inc. **S. Chinta:** A. Employment/Salary (full or part-time): CytoTronics, Inc. **P. Suresh:** A. Employment/Salary (full or part-time): CytoTronics, Inc. **S. Sutar:** A. Employment/Salary (full or part-time): CytoTronics, Inc. **S. Prime:** A. Employment/Salary (full or part-time): Axol Bioscience. **S. Chitale:** A. Employment/Salary (full or part-time): CytoTronics, Inc..

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.12/E29

Topic: C.06. Neuromuscular Diseases

Title: A Human iPSC-derived Motor Neuron Platform: Applications in Drug Discovery and ALS Research

Authors: *T. PHILLIPS, D. LEITE, T. R. ROSENSTOCK, S. THOMSON, N. MIRZA; Sygnature Discovery Ltd, Nottingham, United Kingdom

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by motor neuron loss, muscle atrophy, paralysis, and respiratory failure. The heterogeneous etiology of ALS makes therapeutic development challenging, as highlighted by recent clinical failures and withdrawal of a medicine after initial accelerated approval. Drug Discovery assays utilising human iPSC-derived motor neurons offer a (patho)physiologically relevant tool that might improve probability of success in the clinic. In this work we compared iPSC-derived motor neurons from a healthy donor and an ALS patient with a C9orf72 mutation. Cultures were maintained for 21 days and characterized using the following markers: Islet-1, HB9, ChAT and TUJ1. Functional assays evaluated mitochondrial function, oxidative stress, lysosomal status, and glutamate-induced excitotoxicity. Mitochondrial calcium and membrane potential were assessed with Fluo-3 and TMRE, respectively; oxidative stress via H2DCFDA-AM fluorescence and NRF2 staining; lysosomal status via LAMP1 and p62; and glutamate toxicity via metabolic assays. Readouts were acquired using PHERAstar® and ImageXpress™, with image analysis via MetaXpress™ using AI/ML tools. GraphPad Prism was used for data analysis. Motor neurons were scalable in both 96- and 384-well formats, supporting their suitability for drug discovery screening. By day 21, motor neuron purity reached 85%, based on the expression of selective markers (Islet-1, HB9, ChAT) relative to the total number of DAPI-stained nuclei. C9orf72 ALS-derived motor neurons exhibited a significant 25% reduction in mitochondrial calcium (healthy group: 100 ± 1.75; ALS group: 74.8 ± 4.09; mean ± SEM) and a 12% decrease in mitochondrial membrane potential (healthy group: 100 ± 1.95; ALS group: 88.3 ± 2.32; mean ± SEM), consistent with published findings. No significant changes were observed

in DCF fluorescence; however, NRF2 levels were significantly reduced by 13% (healthy group: 1 ± 0.019; ALS group: 0.92 ± 0.021; mean ± SEM). Lysosomal integrity, assessed via lysosomal markers and p62 staining, remained unchanged. Glutamate exposure induced a concentration-dependent decrease in viability, with IC_{50} values of 204.5 mM (healthy) and 211.7 mM (ALS). Our humanised, scalable platform enables high-content phenotypic profiling of motor neurons, offering a translationally relevant system for application in ALS drug discovery. By faithfully recapitulating patient-specific pathology, this system bridges the translational gap and could support the development of targeted therapeutics for ALS.

Disclosures: T. Phillips: None. **D. Leite:** None. **T.R. Rosenstock:** None. **S. thomson:** None. **N. Mirza:** None.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.13/E30

Topic: C.06. Neuromuscular Diseases

Title: Understanding ALS variants and ion channel expression changes using high throughput automated patch clamp

Authors: N. BRINKWIRTH[1], ***A. R. OBERGRUSSBERGER**[1], N. BECKER[1], Y.-L. LU[2], S. PRIME[3], E. DRAGICEVIC[1], N. FERTIG[1];
[1]Nanion Technologies GmbH, Munich, Germany; [2]Nanion Technologies, Inc., Livingston, NJ; [3]Axol Biosci., Cambridge, United Kingdom

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects spinal motor neurons. Although the pathology of ALS is still poorly understood, several disease phenotypes are recognized to be associate with motor neurons from ALS patients. A lack of human cell models has forced scientists to rely on animal models and cell lines that do not always recapitulate human biology. To support ALS research and drug discovery, Axol has developed an expanded set of ‘ready to ship’ motor neurons. With rapid 10 day to ‘thaw to assay ready’ protocols for axoCell motor neurons are backed with QC and functional QC. The functionally validated cells at maturity display distinct morphological and functional phenotypic differences for the ALS disease phenotypes; C9orf72, SOD1 and TDP43, displaying a variety of sodium channel hyperexcitable firing mechanisms and burst train event modulation between the different phenotypes. In this study we used an unaffected control cell line and ALS variant C9orf72 human stem cell-derived motor neuron type and compared their ion channel expression using high throughput automated patch clamp. Both neuron types were captured on the NPC-384 chips for recording with a success rate of 80 - 90% for R_{Seal} > 400 MΩ. We detected voltage-gated K channels in both cell types, with at least 2 populations of K_V channels displaying different kinetics. Overall, there was a reduction in K_V amplitude in the C9orf72 variant compared with unaffected (677 ± 32 pA/pF, n = 116 for unaffected vs. 375 ± 17 pA/pF, n = 111

for C9orf72). We also observed a marked reduction in the amplitude of voltage-gated Na^+ currents in C9orf72 compared with unaffected (current density was -338 ± 24 pA/pF, n = 121 for unaffected vs -223 ± 14 pA/pF for C9orf72). The V_{half} of activation and inactivation for the Na_V current was unchanged between the two groups and the current was completely blocked by 500 nM TTX. Ligand-gated ion channels responding to glutamate, GABA and glycine were also detected in both groups. Responses to glutamate were similar in amplitude with an EC_{50} value for glutamate of approximately 20 μM for both groups. Current amplitudes and EC_{50} in response to glycine was also similar between the 2 groups (EC_{50} = 45 μM), but current amplitudes in response to GABA were smaller in the C9orf72 cells vs. unaffected (-601 ± 56 pA, n = 39 for unaffected vs. -361 ± 37 pA, n = 28 for C9orf72). The EC_{50} for GABA was identical between the two groups (31 μM). In conclusion, we could detect differences in ion channel currents recorded from unaffected and C9orf72 variant which may underlie differences in excitability of ALS motor neurons compared with their unaffected counterparts.

Disclosures: **N. Brinkwirth:** A. Employment/Salary (full or part-time): Nanion Technologies. **A.R. Obergrussberger:** A. Employment/Salary (full or part-time): Nanion Technologies. **N. Becker:** A. Employment/Salary (full or part-time): Nanion Technologies. **Y. Lu:** A. Employment/Salary (full or part-time): Nanion Technologies. **S. Prime:** A. Employment/Salary (full or part-time): Axol Biosciences. **E. Dragicevic:** A. Employment/Salary (full or part-time): Nanion Technologies. **N. Fertig:** A. Employment/Salary (full or part-time): Nanion Technologies.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.14/E31

Topic: C.06. Neuromuscular Diseases

Support: NIH/R41AG085831
NIH/R41AG084421

Title: Dissecting ALS and FTD Mechanisms Using hiPSC-derived Cortical Neurons, Motor Neurons, Astrocytes, and Microglia

Authors: K.-M. TRAN[1], A. DUONG[2], N. BUTELET[2], V. TRUONG[1], P. WALSH[1], ***W. W. POON**[2,3];
[1]Anatomic Inc., Minneapolis, MN; [2]NeuCyte, Inc., Mountain View, CA; [3]Inst. for Memory Impairments and Neurolog. Disorders, UC Irvine, Irvine, CA

Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), once considered distinct diseases, are now recognized as part of a clinical, genetic, and neuropathological spectrum. ALS is characterized by motor neuron degeneration, while FTD involves cortical atrophy. Genetic studies have revealed overlapping mutations, most notably the

C9ORF72 hexanucleotide repeat expansion, which can lead to ALS, FTD, or both. This overlap underscores the heterogeneity of patient phenotypes and highlights fundamental gaps in our understanding of how specific mutations drive selective neuronal vulnerability. Although protein aggregation is a shared hallmark across neurodegenerative diseases, ALS and FTD differ in the proteins involved, such as TDP-43, SOD1, and C9ORF72-derived dipeptide repeats, each associated with distinct patterns of neuronal loss. To investigate these mechanisms, we generated hiPSC-derived cortical neurons, motor neurons, astrocytes, and microglia from patients carrying distinct ALS/FTD mutations. Bulk RNA sequencing revealed transcriptomic differences across donor genotypes and cell types. In parallel, these cells are being incorporated into isogenic, region-specific 3D microphysiological systems (MPS) to model both cell-autonomous and non-cell-autonomous contributions to neurodegeneration. This platform provides a scalable, human-relevant system to dissect gene-specific vulnerabilities and protective mechanisms, supporting translational efforts to identify novel therapeutic targets for ALS and FTD.

Disclosures: **K. Tran:** A. Employment/Salary (full or part-time): Anatomic, Inc. **A. Duong:** A. Employment/Salary (full or part-time): NeuCyte, Inc. **N. Butelet:** A. Employment/Salary (full or part-time): NeuCyte, Inc. **V. Truong:** A. Employment/Salary (full or part-time): Anatomic, Inc. **P. Walsh:** A. Employment/Salary (full or part-time): Anatomic, Inc. **W.W. Poon:** A. Employment/Salary (full or part-time): NeuCyte, Inc.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.15/E32

Topic: C.06. Neuromuscular Diseases

Title: Modeling ALS Using Patient-Derived iPSCs: A Human-Relevant Platform for Disease Research and Therapeutic Discovery

Authors: *D. KURGANOVA, C. MYERS, B. FRAHER, C. TICAS RODAS, A. MANTEY, K. TUTTIS RODRIGUES, L. AGBOR, N. ECKERT, T. TANAKA;
Elixirgen Scientific, Baltimore, MD

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder marked by the progressive loss of motor neurons in the spinal cord and brain, ultimately leading to muscle weakness, paralysis, and death. Although both genetic and environmental factors are implicated, the exact mechanisms underlying ALS remain poorly understood. A significant challenge in ALS research is the heavy reliance on animal models which often fail to fully capture the complexity and variability of the human disease. Consequently, therapeutic approaches that show promise in these models do not translate effectively to human patients, highlighting a critical gap in disease modeling. Furthermore, clinical trials are limited by the inability to safely access brain and spinal cord tissue from patients, preventing the identification of disease-specific pathways and the stratification of patients based on these pathways. These limitations underscore

the urgent need for more representative human-based models of ALS. To address this gap, Elixirgen Scientific established a Quick-Tissue™ technology that uses patient-derived induced pluripotent stem cells (iPSCs) to generate human-relevant ALS models. Our fast and reproducible transcription factor-mediated differentiation protocol can be applied to iPSCs from both healthy and diseased donors, producing spinal motor neurons. Within just 10 days from the start of differentiation, these neurons exhibit strong expression of a pan-neuronal marker TUBB3 (95%<), a cholinergic neuron marker CHAT (70%<) and a key motor neuron marker HB9 (70%<) as confirmed by immunostaining. Importantly, our sporadic ALS patient-derived motor neurons also replicate a hallmark pathological feature of the disease: TDP-43 mislocalization. Immunofluorescence microscopy demonstrated that in healthy motor neurons, TDP-43 was found preferentially localized to the nucleus, whereas, it showed a clear increase in cytoplasmic localization in motor neurons derived from two sporadic ALS patients ($p<0.0001$, Student's t-test). In addition, one of the two ALS patient derived motor neurons exhibited poor survival on day 7 of in-vitro culture. In conclusion, our patient-specific, iPSC-based platform provides a powerful and scalable tool to more accurately model ALS pathology and accelerate therapeutic discovery.

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Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.16/E33

Topic: C.06. Neuromuscular Diseases

Title: C9orf72 facilitates precursor vesicle trafficking along axons

Authors: *M. TIAN[1], G. KOCHLAMAZASHVILI[2], V. HAUCKE[3];
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Abstract: The proper neuron function largely relies on the efficient cargo transport along the axon because of the extremely polarized morphology. Axonal transport defects have been reported in multiple neurodegenerative diseases. Small GTPase Arl8b plays a crucial role of regulating the transport of precursor vesicles with motor protein Kif1A along axons. However, the regulation of Arl8b-related precursor vesicle transport is still poorly understood. Here we found that an amyotrophic lateral sclerosis (ALS) related protein C9orf72 has direct interaction with Arl8b and acts as a guanine nucleotide exchange factor (GEF) protein to regulate the activity of Arl8b. Furthermore, loss of C9orf72 leads to defects of axonal transport of precursor

vesicles as well as Arl8b related vesicles. This study might reveal a new axonal transport related mechanism in ALS.

Disclosures: M. Tian: None. **G. Kochlamazashvili:** None. **V. Haucke:** None.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR114.17/E34

Topic: C.06. Neuromuscular Diseases

Title: Modeling, Phenotyping, and Screening in ALS and FTD using High-Density Microelectrode Arrays

Authors: M. HRUSKA-PLOCHAN[1], E. GUELLA[1], S. RONCHI[1], ***M. OBIEN**[2];
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Abstract: Human neural models of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are essential for advancing research of these fatal neurodegenerative disorders. The advent of iPSC-derived neural systems, from neuronal monocultures to brain and spinal cord organoids, has enabled discoveries that were previously impossible due to the limited availability of live patient CNS tissue, the human-specific RNA-binding of TDP-43, cross-species barriers, and the general inadequacy of animal models of these diseases. To fully leverage these complex human-derived neural networks, understanding their functional properties, and how these are altered in disease, is a prerequisite. This need is further underscored by recent NIH and FDA policy shifts that prioritize human-based research models, such as organoids and tissue-on-chip platforms, over traditional animal models. As biological research enters this new era, deciphering the functional dynamics of these advanced systems is more important than ever. In this study we applied our next-generation high-density microelectrode arrays (HD-MEAs), which enable real-time, label-free, and non-invasive electrophysiological recordings with unmatched spatial resolution, allowing to fully characterize and exploit the complexity of these *in vitro* neural cultures. The MaxTwo multiwell HD-MEA platform, featuring 26,400 electrodes per well, captures activity across entire networks, individual neurons, and subcellular compartments, including axonal arbors. Using this system, we profiled disease-specific activity in ALS (TDP-43 M337V, Q331K) and FTD (GRN KO) models. The platform's ultra-dense coverage and industry-leading signal-to-noise ratio (SNR) enabled consistent detection of disease phenotypes with minimal sample replicates. ALS cultures exhibited reduced spontaneous and network activity, while GRN KO neurons displayed pronounced hyperactivity and irregular oscillations, phenotypes that would likely be missed by low-density MEAs due to signal averaging and sparse spatial coverage. To probe subcellular alterations, we applied our revolutionary AxonTracking assay to extract metrics such as conduction velocity, latency, axonal length, and branching by tracing action potential propagation. GRN KO neurons exhibited significantly shorter, less-

branched axons, suggesting that their hyperactivity may represent a compensatory response to structural deficits.

Disclosures: **M. Hruska-Plochan:** A. Employment/Salary (full or part-time): MaxWell Biosystems. **E. Guella:** A. Employment/Salary (full or part-time): MaxWell Biosystems. **S. Ronchi:** A. Employment/Salary (full or part-time): MaxWell Biosystems. **M. Obien:** A. Employment/Salary (full or part-time): MaxWell Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MaxWell Biosystems.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.18/E35

Topic: C.06. Neuromuscular Diseases

Title: Identification of neuronal subtype-specific splice variants in iPSC-derived cell models of ALS and FTD

Authors: A. VETELEANU[1], H. GARNETT[1], M. GAMPERL[2], S. SALIC-HAINZL[2], T. BUERCKSTUEMMER[2], T. BROWN[1], A. TURNER[1], B. NEWMAN[1], K. ELLIS[1], K. FIRTH[1], O. DOVEY[1], G. MASTROGIOVANNI[1], W. BERNARD[1], ***T. OOSTERVEEN**[1];
[1]bit.bio, Cambridge, United Kingdom; [2]bit.bio Vienna, bit.bio, Vienna, Austria

Abstract: Familial and sporadic cases of amyotrophic lateral sclerosis (ALS) are characterised by the premature degeneration of upper and lower motor neurons. Most of these patients have inclusions of the TDP-43 protein independent of the aetiology. TDP-43 is a nucleic acid-binding protein and is involved in gene regulation and the processing of RNA. Mutations in TARDBP, encoding TDP-43, can cause its age-related aggregation and nuclear depletion, leading to pathogenic alternative mRNA splicing. Remarkably, TDP-43 mutations such as M337V cause either ALS or frontotemporal dementia (FTD) even within the same family, implying that TDP-43 might have cell type dependent transcript targets and risk factors.
To discover neuron-specific TDP-43 transcript targets, we used a bulk RNA-sequencing approach to identify splice variants in our ioGlutamatergic and ioMotor Neurons carrying the heterozygous or homozygous M337V mutation in TARDBP. We used the MAJIQ software package to compare the splice variants of TDP-43 WT/WT, TDP-43 M337V/WT and TDP-43 M337V/M337V ioGlutamatergic and ioMotor Neurons at different culturing time points (day 11, day 21 and day 30). Since ALS and FTD are age-related neurodegenerative diseases, we included day 30 samples of ioGlutamatergic and ioMotor Neurons carrying wild-type TDP-43 or the TDP-43 homozygous mutation treated with the recently published neddylation inhibitor MLN4924, reported to induce hallmarks of cellular aging.
Comparative analysis of wild-type versus TDP-43 mutant cells revealed splice variants both unique to, and shared between, ioGlutamatergic and ioMotor Neurons. At day 30 of the neuronal

cultures, we identified 5 to 25 different splicing events when comparing wild-type to TDP-43 mutant cells. Many of the genes have been previously implicated in ALS and FTD or have been shown to undergo alternative splicing in ALS patients, and include for example SETD5, PRUNE2, CALD1 and DPP6. Treatment of TDP-43 mutant cells with MLN4924 resulted in the induction of genes associated with aging, as identified by the Digital Aging Atlas, and led to distinct splicing events compared to the untreated cells, suggesting an interaction between the TDP-43 mutation and age-related stress. Thus, our bulk RNA-sequencing data, which we are currently validating, demonstrate that our iPSC-derived ALS/FTD cell models provide a platform to delineate TDP-43 function and identify cell specific target transcripts of TDP-43, and are valuable tools to study ALS/FTD and screen for drugs that can modulate the progression of these devastating diseases.

Disclosures: **A. Veteleanu:** A. Employment/Salary (full or part-time): bit.bio. **H. Garnett:** A. Employment/Salary (full or part-time): bit.bio. **M. Gamperl:** A. Employment/Salary (full or part-time): bit.bio. **S. Salic-Hainzl:** A. Employment/Salary (full or part-time): bit.bio. **T. Buerckstuemmer:** A. Employment/Salary (full or part-time): bit.bio. **T. Brown:** 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. Ellis:** A. Employment/Salary (full or part-time): bit.bio. **K. Firth:** A. Employment/Salary (full or part-time): bit.bio. **O. Dovey:** A. Employment/Salary (full or part-time): bit.bio. **G. Mastrogiovanni:** A. Employment/Salary (full or part-time): bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time): bit.bio. **T. Oosterveen:** A. Employment/Salary (full or part-time): bit.bio.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.19/E36

Topic: C.06. Neuromuscular Diseases

Support: JSPS KAKENHI Grant Number JP23K18178
JST SPRING Grant Number JPMJSP2108

Title: The regulation of intracellular temperature-mediated TDP-43 dynamics by TMEM106B, a risk factor for frontotemporal lobar degeneration

Authors: *T. YOSHIKI[1], D. YAMANE[1], K. OKABE[2], Y. HORI[1], T. TOMITA[1];
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Abstract: Frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP) is characterized by abnormal accumulation of TAR DNA/RNA-binding protein 43 kDa (TDP-43) in patient brains. TDP-43 normally localizes to the nucleus; however, in patients, it forms solid,

amyloid-like fibrils in the cytoplasm of neurons. Since point mutations in *TARDBP* gene, encoding TDP-43, linked to familial FTLD-TDP cause amino acid substitutions to promote the aggregation, understanding the molecular mechanisms of TDP-43 aggregation is crucial to elucidate the pathogenesis.Genome-wide association studies of FTLD-TDP patients revealed the increased expression of Transmembrane protein 106B (TMEM106B), a type II transmembrane protein involved in lysosomal function, as a risk factor. However, the precise mechanisms whereby TMEM106B contributes to the pathogenesis of FTLD-TDP remain unclear.We have investigated the role of intracellular temperature in the dynamics of TDP-43 and the pathogenesis of FTLD-TDP (Yamane et al., accompanying presentation). Local cytoplasmic heating using an infrared (IR) laser induced the condensation of TDP-43 with reduced mobility and solid-like behavior that are reminiscent of pathological TDP-43 aggregation.We then induced the TDP-43 condensation by IR laser in the TMEM106B-overexpressing COS7 cells and found that the formation of TDP-43 condensation was significantly accelerated. We also found that the average intracellular temperature of the TMEM106B-overexpressing COS7 cell was about 1°C higher than that of control COS7 cells. Intriguingly, the accelerated condensation of TDP-43 was suppressed by reducing culture temperature by 1 °C. These results indicate that the overexpression of TMEM106B increased the intracellular temperature, resulting in promotion of amyloid-like TDP-43 condensation. This provides novel insights into how TMEM106B contributes to TDP-43 pathology in FTLD-TDP. In the future, we will further investigate the role of TMEM106B in TDP-43 pathology in vivo and elucidate the mechanisms of TMEM106B-induced elevated intracellular temperature.

Disclosures: T. Yoshiki: None. **D. Yamane:** None. **K. Okabe:** None. **Y. Hori:** None. **T. Tomita:** None.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR114.20/E37

Topic: C.06. Neuromuscular Diseases

Support: Target ALS Foundation: 1RF1NS127407
Target ALS Foundation: BB-2024-C1-L3

Title: Assessment of neuronal stimulator of interferon genes (STING) pathway activation in iPSC models of amyotrophic lateral sclerosis

Authors: I. FLESSAS, C. MARQUES, A. H. HELD, *B. WAINGER;
Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Amyotrophic lateral sclerosis (ALS) is a rapidly progressing and fatal neurodegenerative disease of the motor nervous system. Approximately 10% of ALS cases occur within families (fALS), such as the C9*orf*72 intronic repeat expansion, whereas the remaining

90% are characterized as sporadic ALS (sALS). Increasing evidence implicates neuroinflammatory pathways, including the stimulator of interferon genes (STING) pathway, in ALS pathogenesis. STING activation drives type I interferon (IFN-I) responses and may be triggered by DNA damage observed in ALS. We previously identified neuronal activation of the STING pathway in both fALS and sALS postmortem tissues, and in human iPSC-derived cortical and motor neurons from C9orf72 and TDP-43 mutant fALS patients. We found that both the canonical (cytoplasmic dsDNA sensing) and noncanonical (damaged nuclear DNA sensing) STING pathway interferon responses were upregulated in fALS patient iPSC-derived cortical neurons. Here we extend this work to determine whether the STING activation observed in postmortem sALS tissues is also recapitulated in human iPSC-derived neurons from sALS patients. We derive NGN2 neurons from sALS iPSC lines using established methods in our lab. We utilize immunostaining, gene expression, and protein analyses to examine cell-autonomous STING activation. We also evaluate the downstream interferon responses specific to STING using immunostaining and qRT-PCR. We perform experiments to assess STING activation at early and later time points of iPSC neuron culture. Finally, we determine whether sALS neurons are more sensitive to previously identified inducers of STING activation, including DNA damage and TDP-43 knockdown. The results of these studies will help evaluate the use and required complexity of sALS iPSC-based disease models.

Disclosures: I. Flessas: None. **C. Marques:** None. **A.H. Held:** None. **B. Wainger:** None.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.21/E38

Topic: C.06. Neuromuscular Diseases

Title: Tdp-43 modulates autophagy via ug-rich sequence in the mouse ulk1 3'utr

Authors: *R. MIYAZAKI[1], K. MATSUKAWA[2], T. IWATSUBO[2], T. HASHIMOTO[1,2]; [1]Dept. of Degenerative Neurolog. Dis., Natl. Inst. of Neuroscience, Natl. Ctr. of Neurol. and Psychiatry, Kodaira City, Tokyo, Japan; [2]Dept. of Neuropathology, Grad. Sch. of Medicine, The Univ. of Tokyo, Bunkyo-Ku, Tokyo, Japan

Abstract: TAR DNA-binding protein 43 kDa (TDP-43) is an RNA-binding protein identified as a major component of ubiquitin-positive inclusions that accumulate in the affected neurons of patients with amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Although TDP-43 pathology is associated with neuronal cell death, the molecular mechanisms underlying TDP-43-mediated neurotoxicity remain elusive. In a *Drosophila* model overexpressing human wild-type TDP-43 in compound eyes, we observed progressive retinal degeneration accompanied by a significant upregulation of the autophagy-related gene *Atg1*. Here, we present a novel mechanism by which TDP-43 regulates *Ulk1*, a mammalian homologue of *Atg1*.We first examined the interaction between TDP-43 and *Ulk1* mRNA in mouse

neuroblastoma Neuro-2a (N2a) cells and found that TDP-43 directly binds to *Ulk1* mRNA through its RNA recognition motif. Knockdown of *Tardbp* in N2a cells resulted in a significant reduction in both *Ulk1* mRNA and protein expression. Furthermore, treatment with the transcription inhibitor actinomycin D following knockdown of *Tardbp* in N2a cells resulted in a significant decrease in *Ulk1* mRNA levels, suggesting that TDP-43 regulates Ulk1 expression by binding to and stabilizing its mRNA.TDP-43 is preferentially known to interact with *UG-rich* sequence. We established monoclonal N2a cell lines (Δ*UG* mutant N2a cells) lacking multiple *UG-rich* sequence in the 3'-untranslated region (3'UTR) of the *Ulk1* gene using the CRISPR-Cas9 system. Knockdown of *Tardbp* in Δ*UG* mutant N2a cells showed an attenuated downregulation of Ulk1 protein and did not reduce the expression of *Ulk1* mRNA.Since Ulk1 is a key component of the Ulk1 complex that initiates macroautophagy, we investigated whether TDP-43 modulates autophagic activity through Ulk1 expression. In wild-type N2a cells, knockdown of *Tardbp* significantly decreased the LC3-II/LC3-I ratio, which serves as an indicator of autophagy induction, along with decreased Ulk1 protein levels under starvation conditions and treatment with the autophagy inhibitor bafilomycin A1.In contrast, in human neuroblastoma SH-SY5Y cells, which lack a *UG-rich* sequence in the 3'UTR of the human *ULK1* gene, knockdown of *TARDBP* had no effect on *ULK1* mRNA or protein expression.These findings demonstrate that a *UG-rich* sequence in the mouse *Ulk1* 3'UTR is essential for TDP-43-dependent binding and stabilization of *Ulk1* mRNA, thereby regulating its expression and downstream macroautophagic activity. Our study reveals a novel post-transcriptional mechanism of autophagy modulation by TDP-43 and highlights species-specific differences in this pathway.

Disclosures: R. Miyazaki: None. **K. Matsukawa:** None. **T. Iwatsubo:** None. **T. Hashimoto:** None.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.22/E39

Topic: C.06. Neuromuscular Diseases

Support: RO1NS126191

Title: Investigating the role of Stathmin2 Phosphorylation Sites in DLK-Dependent Degradation

Authors: *C. LATHRUM[1], D. SUMMERS[2];
[1]Integrated Biol., Univerity of Iowa, Iowa City, IA; [2]Integrated Biol., Univ. of Iowa, Iowa City, IA

Abstract: Neurodegenerative diseases are a major problem in the United States today accounting for around 800 billion dollars in health care costs and severely impacting quality of life for millions of people. Though the mechanisms of neurodegenerative diseases such as Alzheimer's or Amyotrophic Lateral Sclerosis (ALS) are relatively unknown, one of the main contributing

factors is axonal degeneration. Loss of the axon severs connections between neurons, and in some instances causes death of the neuron itself. Axon degeneration is regulated by various pathways including the dual leucine zipper kinase (DLK) mitogen-activated protein kinase (MAPK) pathway. This cascade is responsible for the degradation of Stathmin2 (Stmn2), an axon maintenance protein. Previous work identified that preventing phosphorylation at serine's 62 and 73 within Stmn2 can mitigate DLK dependent degradation of Stmn2. When this occurs, Stmn2 becomes axon protective within embryonic (E13.5) mouse dorsal root ganglion (DRG) neurons. We have characterized axonal trafficking of this neuroprotective Stmn2 protein to ascertain how phosphorylation affects co-migration with partners on the same vesicle. To take this work a step further we are characterizing other phosphorylation sites within Stmn2 by generating individual amino acid phosphorylation dead and phosphomimic substitutions. From here we have examined whether any of these mutants are axon protective. Initial results indicate that these mutants do not confer protection at the level of the Ser62/73 double mutant. Our results indicate that the duplicate phosphorylation sites for DLK degradation allow for this pathway to target Stmn2 at multiple locations for degradation to occur. Stmn2 mRNA splicing is uniquely regulated in primates highlighting potential specific-specific modes of controlling Stmn2. For this we have developed an iPSC based system to analyze the effects of Stmn2 phosphorylation in human sensory neurons. This work uncovers new mechanisms controlling Stmn2 function with important implications for protecting the nervous system.

Disclosures: C. Lathrum: None. **D. Summers:** None.

Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.23/E40

Topic: C.06. Neuromuscular Diseases

Title: Investigating aberrant neuronal excitability in amyotrophic lateral sclerosis and frontotemporal dementia using human iPSC-derived neurons

Authors: *C. GOLDRICK[1,2], G. NEVES[3], F. RICCIO[3], J. BURRONE[3], I. LIEBERAM[2]; [2]Ctr. for Gene Therapy and Regenerative Med., [3]Ctr. for Developmental Neurobio., [1]King's Col. London, London, United Kingdom

Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are progressive neurodegenerative diseases for which there are no effective treatments. The diseases are diverse in their clinical presentations, with ALS primarily causing motor deficits and FTD disrupting cognitive function. Interestingly, mounting evidence in recent years has uncovered links between the two diseases and provided new insight into shared aspects of their pathologies. This growing evidence of shared features between ALS and FTD as well as the prevalence of comorbidity, suggests that there may be common neurodegenerative pathways involved in the development of this disease spectrum. Among the most common drivers of ALS and FTD are

hexanucleotide repeat expansions in C9Orf72 (C9Orf72-RE), and mutations in the TARDBP gene, both of which result in the formation of pathological TDP-43 protein aggregates in the late stages of ALS and FTD. In both cases, expression of excitability-related genes or proteins is disrupted, resulting in abnormal cellular excitability. However, the underlying disease mechanism is not well understood. In this study, we aim to investigate neuronal excitability in ALS and FTD and characterise any abnormalities. To this end, glutamatergic CNS cortical-like neurons were derived from human patient-derived iPSCs harbouring C9Orf72-RE or TARDBP mutations. Using whole-cell patch clamp electrophysiological recordings and optogenetic stimulation-based approaches, intrinsic neuronal excitability and homeostatic plasticity at the axon initial segment (AIS) were characterised in our model. Preliminary results suggest that while intrinsic excitability properties remain largely unchanged across genotypes, activity-dependent homeostatic plasticity at the AIS is impaired in C9Orf72-RE mutant models. Following the delivery of optogenetic stimuli to channelrhodopsin-expressing neurons, healthy control neurons exhibit AIS shortening following optogenetic stimulation, whereas C9Orf72-RE neurons lack this adaptive mechanism indicating a hypoexcitable disease phenotype. Similar experiments with TARDBP mutant neurons are ongoing. Future work will include RNA sequencing of optogenetically-stimulated and unstimulated cultures to determine what may be driving this abnormality on a transcriptional level, as well as multi electrode array analysis to examine excitability at the network level. Such findings may further reveal how aberrant excitability is disrupted on a molecular level in ALS and FTD, and inform novel therapeutic strategies aimed at normalizing neural activity.

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Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

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Program #/Poster #: PSTR114.24/Web Only

Topic: C.06. Neuromuscular Diseases

Support: Roche unconditional gran
Ministery of Health PNRR Grant PNRR-POC-2023-12377653
Ministery of Health Ricerca Corrente

Title: Time-dependent SMN2 splicing modulation reveals ciliary gene dysregulation as a novel therapeutic target in SMA spinal cord organoids

Authors: *S. CORTI[1], A. D'ANGELO[2], F. BEATRICE[1], M. MIOTTO[4], S. LODATO[5], F. RIZZO[1], G. P. COMI[3], L. OTTOBONI[1];
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Abstract: Spinal muscular atrophy (SMA) is a devastating genetic neurodegenerative disorder caused by motor neuron loss due to deficient survival motor neuron (SMN) protein. Although SMN-restoring therapies show clinical promise, their effectiveness declines with treatment delay, revealing critical knowledge gaps regarding disease mechanisms and optimal intervention timing.Using patient-derived spinal cord organoids in a novel Matrigel-free system, we uncovered widespread ciliary gene dysregulation as a previously unrecognized component of SMA pathogenesis. Our organoid model recapitulated key disease features, including altered GABAergic neuron morphology, increased astrogliosis, and impaired network activity as measured by multielectrode array recordings.Treatment with RO7021707, a Risdiplam-like SMN2 splicing modifier, demonstrated maximal therapeutic efficacy when initiated at day 45 of differentiation—a timing that corresponded with peak SMN protein restoration and functional recovery. RNA sequencing analysis revealed significant downregulation of essential ciliary genes, including structural components and transition zone proteins, which were substantially restored following treatment. Single-cell transcriptomics identified cell-type-specific therapeutic responses, with cholinergic neurons exhibiting the most pronounced gene expression changes. Across treatment timepoints, we consistently observed upregulation of 3 genes and downregulation of 43 genes, with significant enrichment in ribosomal organization and oxidative phosphorylation pathways.These findings establish ciliary dysfunction as a novel pathogenic mechanism in SMA and demonstrate that precise timing of SMN restoration is critical for achieving optimal therapeutic outcomes. Our results provide new mechanistic insights into the effects of treatment timing and identify ciliary function as a potential therapeutic target for SMA intervention.

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Poster

PSTR114: ALS and Motor Neuron Diseases: *In Vitro* Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.25/E41

Topic: C.06. Neuromuscular Diseases

Title: Smn levels in ipsc-derived motor neurons from sma siblings with discordant clinical presentation

Authors: *T. J. A. MENSA[1], S. L. COOK[2], H. H. NOMA[1], N. VIDAL FOLCH[2], C. STOUT[2], M. C. JAHNKE[1], S. HRSTKA[1], L. KIRKEBY[3], L. HASADSRI[2], D. SELCEN[1], N. P. STAFF[1]; [1]Neurol., [2]Lab. Med. & Pathology, [3]Ctr. for Regenerative Med., Mayo Clin., Rochester, MN

Abstract: Spinal muscular atrophy (SMA) is a neurodegenerative disease caused by the homozygous loss of the *Survival Motor Neuron 1* (*SMN1*) gene. Its nearly identical paralog, *SMN2*, has a single nucleotide substitution (C>T) in exon 7, leading to alternative splicing. As a result, approximately 90% of *SMN2* transcripts lack exon 7, producing an unstable protein that is

rapidly degraded. There is an inverse relationship between *SMN2* copy number and disease severity, as *SMN2* is the primary genetic modifier of SMA. Only a few other modifiers have been reported. However, rare cases of phenotypic discordance among siblings with identical *SMN2* copy numbers suggest the involvement of additional SMN-independent genetic modifiers. We identified a sibling pair with discordant clinical presentation. As like other reported cases, the siblings we report here have significant clinical discordance, high copy number of *SMN2*, and phenotypic variability associated with sex. We performed ddPCR deletion/duplication analysis to confirm that both siblings have a homozygous deletion of *SMN1* and four copies of *SMN2*. Sanger sequencing full gene analysis of *SMN2* revealed no modifying variants in either sibling. We next evaluated SMN levels in patient-specific induced pluripotent stem cell-derived motor neurons (iPSC-derived MNs) collected from these siblings. Western blot analysis showed that iPSC-derived MNs from both siblings expressed similar levels of SMN protein, which were statistically significantly higher than that observed in a Type I SMA patient. Future studies include in-vitro characterization of the patient-specific iPSC-derived MNs collected from the reported discordant siblings. SMA-specific iPSC-derived MNs are reported to have decreased survivability in culture and decreased neurite outgrowth. Our preliminary data demonstrate reduced neurite outgrowth in MNs from a Type I SMA patient compared to those from a carrier control. Future studies also include comparative transcriptomic and proteomic analysis as the siblings reported here are an apt model for the discovery of SMN-independent modifiers.

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Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.01/E42

Topic: D.04. Brain Injury and Trauma

Support: NHMRC grant 2019011
NHMRC grant 2041019

Title: Cellular analysis of the superior colliculus following lesions of the primary visual cortex in marmosets

Authors: M. H. CHONG[1], M. G. ROSA[1], ***N. ATAPOUR**[2];
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Abstract: Unilateral damage to the primary visual cortex (V1) causes profound loss of vision. Our previous studies in marmoset monkeys show pronounced degenerative and regenerative changes in the lateral geniculate nucleus (LGN) after V1 lesions, including changes in the neurochemistry of neurons and formation of new projections to the middle temporal area. To

better understand V1 lesion-induced structural changes in this species, we assessed the superior colliculus (SC), a layered midbrain structure which also receives direct inputs from both the retina and V1 but only sends indirect projections to V1. Despite significant neuronal loss and volume reduction in LGN in the same animals (n=4), V1 lesion did not affect SC volume or neuronal density within 37-56 months. Comparing SC volumes on the same side of a V1 lesion with the contralateral SC and non-lesioned cases showed no significant difference [~17-22 mm^3, One-way ANOVA; F (2, 9) = 1.88, $p = 0.21$]. Furthermore, there was no correlation between the amount of post-lesion LGN shrinkage and SC volume (Simple linear regression, $R^2 = 0.002$). Neuronal density, estimated by stereological sampling in the SC layers that are recipient of visual inputs [*stratum griseum superficiale* (SGS), *stratum opticum* (SO)], showed no significant change relative to the opposite side SC or control animals [SGS: ~ 50-60×10^3/mm^3, F(2, 43) = 0.38, $p = 0.69$; SO: ~ 30-40×10^3/mm^3, F(2, 43) = 3.54, $p = 0.04$]. We also investigated the expression of orthodenticle homeobox 2 protein (Otx2), a transsynaptic retinal protein, known to regulate plasticity in the visual system. In control animals, a clear decreasing gradient of neuronal density across the dorsoventral axis of SC was observed, with SGS and SO having the highest mean neuronal density. Estimates of average density of $Otx2^+$ neurons in SC were similar between lesioned (either in neonatal period or adulthood) and control cases (SGS: ~30-45×10^3/mm^3, SO: ~20-24×10^3/mm^3, $p>0.05$). These results demonstrate that secondary loss of neurons and volume changes do not occur in the superficial layers of the SC, in contrast with the LGN. The widespread connectivity of SC with structures other than V1 may protect it from detectable degeneration and volume loss, possibly aiding in the residual vision.

Disclosures: M.H. Chong: None. **M.G. Rosa:** None. **N. Atapour:** None.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

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Program #/Poster #: PSTR115.02/E43

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

Support: NIH Grant BRAIN R01NS110564
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NIH Grant T32 MH119168

Title: A histological exploration of in vivo cellular responses to stiff and flexible electrode implants

Authors: *S. NARAYANAN[1], V. DHAWAN[1], B. WU[1], D. SHI[1], T. CUI[2];
[1]Bioengineering, [2]Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Rationale: Penetrating neural microelectrode arrays (MEAs) enable high-resolution communication with neurons in vivo, but chronic use is limited by recording degradation and

rising stimulation thresholds. Some of these issues are linked to brain tissue immune responses. Recently there has been interest in device stiffness and flexibility as a contributor to the immune response but the molecular signaling mechanism is not well understood. **Objective:** To investigate how device stiffness influences the foreign body response, we implanted stiff silicon-based and flexible polyimide-based MEAs of similar geometry into the mouse striatum for 4 weeks (n=4/group). We performed immunohistochemistry for glia (Iba-1, GFAP), mechanosensing (Piezo1), and neurons (NeuN). **Methods & Results:** First, we measured average signal intensity as a function of distance from the probe. Iba-1, GFAP, and Piezo1 were elevated near all implants, with significantly higher Iba-1 and Piezo1 expression near stiff probes. Across stiff-implant images, total Piezo1 expression correlated strongly with Iba-1 and GFAP, suggesting that stiffer implants elicit a stronger glial response via mechanosensing mechanisms. Second, using intensity thresholding and CellPose, we quantified marker expression within microglia, astrocytes, and neurons. Iba-1 and GFAP intensity within microglia and astrocytes respectively rose with proximity to the implant and were higher overall around stiff probes, indicating increased microglial and astrocyte activation. Piezo1 expression within all three cell types was also elevated near the probes and declined with distance. Interestingly, glial activation extended beyond regions of high Piezo1, suggesting downstream signaling mechanisms for activation further from the implant. Piezo1 was significantly elevated in microglia near stiff implants compared to flexible, very slightly elevated in astrocytes, and unchanged in neurons. This suggests the stiffness-induced response is primarily microglial. Finally, preliminary nuclear morphology analysis shows decreased circularity near stiff probes, suggesting nuclear deformation and potential transcriptional changes that impact cell function.

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Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

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Program #/Poster #: PSTR115.03/E44

Topic: D.04. Brain Injury and Trauma

Support: NIH R44MH131514
NSF CAREER 1943906
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NIH R01NS115707

Title: In vivo microglia calcium dynamics in response to intracortical microelectrode injury

Authors: *V. SINGH, A. KOLLAR, N. AIZEZI, K. C. STIEGER, T. D. KOZAI; Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Microglia are brain-resident macrophages responsible for inflammatory responses, synaptic pruning, and regulation of neural activity. Microglial calcium (Ca^{2+}) has been shown to elevate in acute injury models like focal laser ablation and ischemic stroke. However, very few studies have explored microglial Ca^{2+} dynamics in the context of chronic injury, and how they evolve over time. As a potent second messenger, Ca^{2+} can provide insights into microglial activity that extend beyond what can be inferred from morphology alone. We hypothesized microglia Ca^{2+} to increase in frequency and duration over time after injury. To investigate this, we tracked microglial Ca^{2+} activity in a transgenic mice model expressing cytoplasmic tdTomato and GCaMP6f in microglia, enabling simultaneous visualization of morphology and Ca^{2+} transients via in vivo two-photon imaging. Following intracortical microelectrode implantation, we observed a significant increase in the mean duration of Ca^{2+} transients from 3 hrs to 3 days post-injury (dpi) (2.05 ± 0.29s vs. 2.65 ± 0.77 s, $p = 0.0268$), while event count and peak intensity remained unchanged. Assessing the spatial bins relative to the electrode site, we found a significantly higher event count in microglia located 150-200 µm from the electrode at 3 hrs vs. 3 dpi (16.27 ± 8.84 vs. 11.73 ± 1.25, $p = 0.0212$). At 3 dpi, microglia within 50 µm of the electrode showed significantly higher peak intensity (0.354 ± 0.075 dF/F vs. 0.29 ± 0.07 dF/F, $p = 0.038$). Additionally, between 50-100 µm from the electrode, there was a significant increase in mean event duration (2.58 ± 0.14 s vs. 2.11 ± 0.419 s, $p = 0.0079$) and mean signal intensity (0.408 ± 0.325 dF/F·s vs. 0.2569 ± 0.2146 dF/F·s, $p = 0.0079$). Within 150-200 µm, mean signal intensity was also elevated (0.414 ± 0.325 dF/F·s vs. 0.197 ± 0.0656 dF/F·s, $p = 0.0135$). We also analyzed morphological features of individual microglia in relation to their Ca^{2+} dynamics. The ramification index, a measure of microglia ramification (1) versus amoeboid (0) state, showed a positive correlation with event count ($R^2 = 0.176$, $p < 0.0001$), event duration ($R^2 = 0.116$, $p < 0.0001$), and mean signal intensity ($R^2 = 0.068$, $p < 0.001$). In contrast, the directionality and transitional indices, which quantify the polarization of microglial processes toward the injury site, showed no significant correlations with activity. Overall, these findings demonstrate that microglia calcium activity increases in response to chronic injury. Further analyses are needed to characterize specific microglia calcium dynamics to functional states that may not be evident from morphology alone.

Disclosures: V. Singh: None. **A. Kollar:** None. **N. Aizezi:** None. **K.C. Stieger:** None. **T.D. Kozai:** None.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.04/E45

Topic: D.04. Brain Injury and Trauma

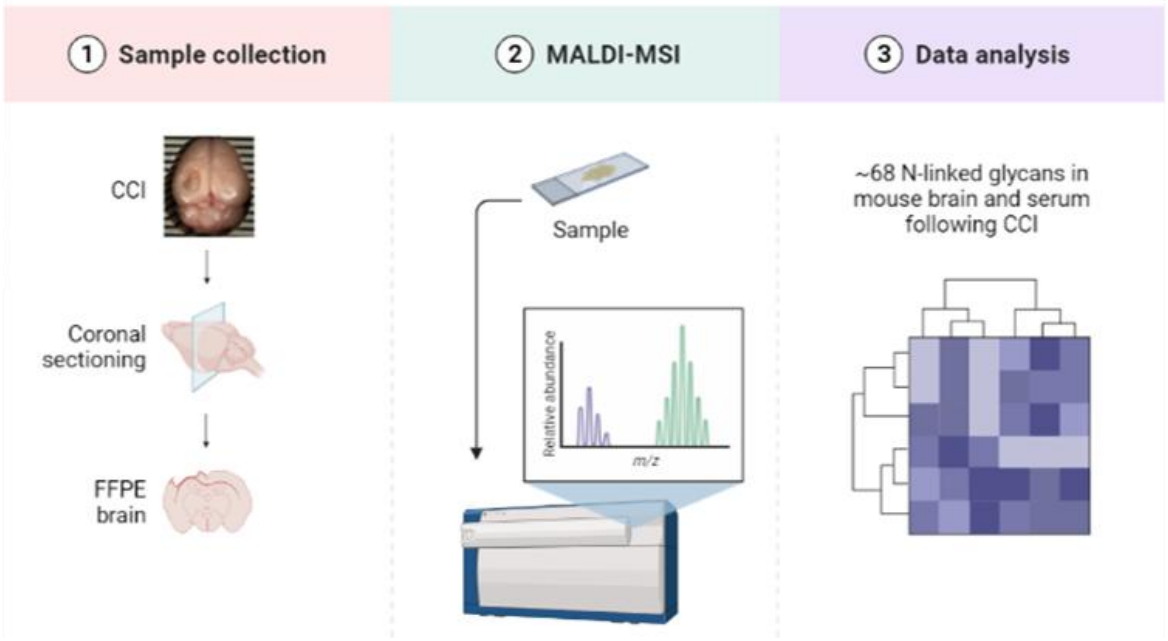
Support: NIH Grant R56NS124707
KSCHIRT 22-1A
KSCHIRT 24-2

NIH Grant R35NS133593
NIH grant R01AG066653

Title: Spatial mapping of the brain glycome in a rodent model of traumatic brain injury

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Abstract: N-linked glycosylation is a complex co- and post-translational process that connects metabolism to cellular signaling, with N-glycosylated proteins being critical for maintenance of the central nervous system and proper brain function. These include processes that are disrupted following traumatic brain injury (TBI) such as inflammation, neurogenesis, synaptic function, and memory formation. Despite contributing to these critical biological functions, the role of N-glycans in the dysfunction accompanying TBI is relatively unexplored. TBI results from the sudden transmission of an external force to the head, inducing both acute and chronic metabolic changes that contribute to injury severity and outcome. TBI heterogeneity requires approaches that allow mapping of regional molecular and metabolic change. Here, matrix assisted laser disposition ionization mass spectroscopy imaging (MALDI-MSI) was used to spatially profile the location and distribution of multiple N-linked glycan species in mice from 6 hours to 28 days following a cortical contusion injury (CCI). Our findings reveal that CCI induces dynamic changes in N-glycan expression across various regions of the brain, resulting in the temporal and spatial reduction in a majority of N-linked glycans across the brain. Together, these data show for the first time the complete profiling of N-glycomic changes in a well-characterized rodent model of neurotrauma. The data represent a pioneering step in defining how glycoprotein change may contribute to TBI progression.



Disclosures: D.A. Andres: None. **L. Wu:** None. **L. Young:** None. **M.S. Gentry:** 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.; Maze Therapeutics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Maze Therapeutics, Valerion Therapeutics, Ionis Pharmaceuticals. F. Consulting Fees (e.g., advisory boards); Chelsea's Hope, Glut1-deficiency syndrome, and the adult polyglucosan body disease foundation. **R. Sun:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Maze Therapeutics. F. Consulting Fees (e.g., advisory boards); Little Warrior Foundation.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.05/E46

Topic: D.04. Brain Injury and Trauma

Support: VA Grant

Title: Non-invasive MRI Reveals Chronic Brain Dysregulation Following Blast-Induced mTBI in Mice

Authors: *I. PATHAK[1], B. OSBURN[1], T. KELTY[3], M. PARIKH[3], T. MONY[1], L. LEE[1], T. ROLD[4], J. CUI[5], C. JOHNSON[2], S. RECTOR[1], M. M. THAKKAR[6], Z. GU[7], J. SMITH[1], L. MA[8];
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Abstract: **Introduction.** Mild traumatic brain injury (mTBI) is a leading cause of long-term disability in Veterans, with neuroinflammation as a key but poorly understood contributor. This study uses magnetic resonance imaging (MRI) and spectroscopy (MRS) to characterize a blast-induced mTBI mouse model at the chronic stage, examining outcomes based on injury severity and sex. **Methods.** **Blast exposure**: Adult male and female mice (n = 42) were subjected to single (1x) or double (2x) low-intensity blast (LIB) exposures using a standardized 350-gram Composition C-4 explosive at a 1-meter height. Sham controls underwent identical handling without blast exposure. **Imaging:** Mice (n = 5 per group) underwent in vivo 7T MRI using a cryoprobe under 1.5% isoflurane anesthesia. Field homogeneity was optimized with B_0 shimming. Anatomical references were acquired via T2-weighted imaging. Cerebral blood flow (CBF) was quantified using arterial spin labeling (ASL). Diffusion tensor imaging (DTI) with multi-shot EPI (b = 1250 s/mm², 30 directions) assessed microstructural integrity. ^{1}H-MRS (PRESS sequence) with voxel-based shimming and water suppression was used to quantify metabolites in the cortex, hippocampus, and thalamus. **Behavioral testing:** All mice were

evaluated using the Open Field test and the LightSpot test by an automated home-cage monitoring system to assess locomotor activity and anxiety-like responses. A separate cohort of males (n = 12) was tested using the Novel Object Location Task (NOLT) at ZT12 to assess spatial memory. **Results.** At 7 months post-injury, female mice in the 2x group exhibited significantly reduced CBF in the hippocampus and cortex ($p < 0.01$ vs. sham; $p < 0.05$ vs. 1x), along with decreased mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in the cortex ($p < 0.01$ vs. sham; $p < 0.05$, 1x vs. sham). MRS revealed elevated cortical total creatine (tCr) ($p < 0.05$, 2x vs. sham) and decreased phosphocholine (PCho) ($p < 0.05$, 1x vs. sham). In males, cortical and hippocampal CBF was modestly reduced in the 2x group but did not reach statistical significance compared to other groups. However, males in the 2x group showed significantly reduced DTI-based quantitative anisotropy (QA) ($p < 0.05$ vs. sham), increased taurine ($p < 0.05$ vs. sham), and elevated tCho in both LIB groups ($p < 0.05$ vs. sham) in the cortex and hippocampus. Males also showed a significantly lower NOLT index in both LIB groups ($p < 0.05$ vs. sham), indicating impaired spatial memory. **Conclusion.** This study demonstrates persistent, sex-specific brain dysregulation following blast-induced mTBI. Repeated blast exposure led to more severe chronic effects compared to a single exposure.

Disclosures: I. Pathak: None. **B. Osburn:** None. **T. Kelty:** None. **M. Parikh:** None. **T. Mony:** None. **L. Lee:** None. **T. Rold:** None. **J. Cui:** None. **C. Johnson:** None. **S. Rector:** None. **M.M. Thakkar:** None. **Z. Gu:** None. **J. Smith:** None. **L. Ma:** None.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.06/E47

Topic: D.04. Brain Injury and Trauma

Support: NIH NINDS RF1NS1380

Title: Traumatic Brain Injury Causes Neurovascular Uncoupling and Alters Network Function in a Rodent Model of the Development of Alzheimer's Disease and Related Dementias.

Authors: *P. R. TERRITO[1], S. A. PERSOHN[2], A. JULLIENNE[3], D. V. AGOSTON[5], J. YAN[4], A. OBENAUS[6];
[1]Indiana Univ. Sch. of Med., Indinanapolis, IN; [2]Stark Neurosci., Indiana Univ., Fishers, IN; [3]Div. of Biomed. Sci., [4]Univ. of California, Riverside, Riverside, CA; [5]APG, USUHS, B2036, Bethesda, MD; [6]Biomed. Sci., Univ. of California Riverside, Riverside, CA

Abstract: Emerging evidence suggests that traumatic brain injury (TBI) is a significant risk factor in developing Alzheimer's disease and related dementias (ADRD). Understanding the role of age, sex, and genetic risk factors may enable earlier identification of at-risk individuals and identifying evidence-based treatments. To facilitate standardization, the NIH/NINDS TBI-ADRD consortium was funded to develop and optimize methods to evaluate the role of TBI in

ADRD development and progression. Using translational neuroimaging, and advanced image processing methods, we assessed the impact of closed-head TBI on neurovascular dysregulation and network remodeling. Eight-month-old C57BL6/J mice were exposed to single closed head injury (CHI) over the left mid-brain. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) scans were acquired, at various days post injury (DPI), registered to the Paxinos-Franklin Brain Atlas, extracted, normalized to corpus callosum, and neurovascular uncoupling, and metabolic covariance analysis was performed across sex, strain, and DPI. In 8-month-old mice, CHI resulted in a significant neurovascular uncoupling at 30 and 60DPI. These changes exhibited sex-based differences as well as lateralization, indicative of coup and contrecoup brain injury. Injury patterns between 30 and 60DPI were also sexually dimorphic, with females showing a greater number of perturbed brain regions. Connectomic modeling of sham-treated mice revealed no change in network characteristics at 30 or 60DPI. By contrast, CHI in females showed elevation in degree, positive, negative connection strengths, and clustering coefficient at 30DPI, which was lost by 60DPI. These data indicate that CHI results in neurovascular dysregulation, which is sexually dimorphic and connectomic modeling indicated network remodeling post CHI TBI.
Funding: NIH NINDS RF1NS1380

Disclosures: P.R. Territo: None. **S.A. Persohn:** None. **A. Jullienne:** None. **D.V. Agoston:** None. **J. Yan:** None. **A. Obenaus:** None.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.07/E48

Topic: D.04. Brain Injury and Trauma

Support: NHMRC GNT2010763
CIHR FRN191316

Title: Biomarker and behavioural profiles following a pre-clinical model of stress and intimate partner violence-brain injury.

Authors: *J. BRAND[1], J. T. ALLEN[3], S. J. MCDONALD[4], J. GAWRYLUK[1], B. R. CHRISTIE[2], S. R. SHULTZ[5];
[2]Div. of Med. Sci., [1]Univ. of Victoria, Victoria, BC, Canada; [3]Neurosci., Univ. of Victoria & Vancouver Island Univ., Victoria, BC, Canada; [4]Monash Univ., Melbourne, ; [5]Dept. of Neurosci., Monash Univ., Melbourne, Australia

Abstract: Intimate partner violence (IPV) primarily affects women, and upwards of 90% of IPV survivors experience brain injury (BI). IPV-BI is unique compared to other traumatic brain injury (TBI) as survivors experience a combination of mild TBI (mTBI), non-fatal strangulation (NFS), and stress which likely exacerbates injury deficits compared to injuries in isolation. Using a

novel rat model of IPV-BI, we previously found that mTBI+NFS exacerbated behavioural deficits and neuroinflammation compared to isolated injuries. The purpose of this study was to investigate how stress may further influence IPV-BI outcomes. It was hypothesized that rats exposed to stress + IPV-BI would have worse behavioural deficits and an altered pathophysiological profile compared to IPV-BI in isolation. Young-adult female rats were grouped based on 1) Stress via predator odor (i.e., fox odour 2,5- dihydro-2,4,5-Trimethylthiazoline; TMT) or sham and 2) IPV-BI or sham. Immediately after the stress exposure, rats were administered an IPV-BI (i.e., mTBI + NFS) or sham injury and assigned to either a 2h or 7d recovery in order to characterize the temporal profile of neuropathophysiology and blood biomarkers of inflammation. The 7d recovery rats also underwent a series of behaviour tests to assess motor function, cognition, as well as anxiety-like behaviours. Analysis of brain and blood are ongoing; however, preliminary results indicate that exposure to an acute stressor prior to IPV-BI worsens behavioural deficits and supports the notion that stress in an important modifying factor in IPV-BI.

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Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.08/E49

Topic: D.04. Brain Injury and Trauma

Support: Bloomberg Ophthalmology Foundation

Title: Traumatic brain injury triggers retinal remodeling: morphological alterations in ipRGCs in a murine model

Authors: M. TERZIC[1], B. CSUBAK[2], ***M. A. SMITH**[1];
[2]Pharmaceut. Sci., [1]Northeast Ohio Med. Univ., Rootstown, OH

Abstract: Purpose: Circadian rhythm disruptions are frequently reported in the acute phase following concussion and moderate traumatic brain injury (TBI), including altered sleep architecture, diminished nocturnal melatonin secretion, and dysregulated clock gene expression. While multiple brain regions may contribute to these disruptions, accumulating evidence suggests that the retina—specifically melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs)—may represent an early and vulnerable node in this pathophysiological cascade. Given their critical role in circadian photoentrainment, ipRGCs are a promising target for elucidating non-image-forming visual system pathology post-TBI. Although overt degeneration of ipRGC is controversial in neurodegenerative diseases, their structural and functional integrity, potential contribution to circadian dysfunction and other symptoms following TBI remains largely unexplored. **Methods:** We employed immunohistochemistry and

high-resolution confocal microscopy to assess ipRGC morphology and retinorecipient brain projections at acute and subacute timepoints following a single, non-repetitive controlled cortical impact (CCI) in adult C57BL/6 mice. Morphometric analysis using Neurolucida 360 quantified dendritic field area, branching complexity, and total cable length. Projection site integrity was evaluated using markers of gliosis and synaptic integrity. **Results:** One week post-CCI, ipRGCs exhibited significant dendritic retraction, reduced arbor complexity, and smaller dendritic fields, despite unchanged soma density within the ganglion cell layer. These morphological deficits suggest early post-traumatic remodeling of the ipRGC network, which may impair circadian signal transmission to central pacemaker structures. **Conclusions:** Our findings indicate that ipRGCs undergo early dendritic pathology following TBI, potentially contributing to the circadian and sleep-wake disturbances observed in patients. Given the anatomical accessibility and cellular simplicity of the anterior visual system, ipRGCs may serve as a sensitive and tractable model for investigating mechanisms of axonopathy and neuroplasticity in the context of diffuse brain injury.

Disclosures: M. Terzic: None. **B. Csubak:** None. **M.A. Smith:** None.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.09/E50

Topic: D.04. Brain Injury and Trauma

Support: NIH NINDS 1RF1NS1380

Title: Phenotyping an adult mouse model of concussion-induced Alzheimer's disease and related dementias

Authors: *A. JULLIENNE[1], J. YAN[1], M. BRIGHT[2], S. PERSOHN[2], H. PHAN[1], I. KURUP[1], D. V. AGOSTON[3], P. R. TERRITO[2], A. OBENAUS[1];
[1]Univ. of California, Riverside, Riverside, CA; [2]Stark Neurosci. Res. Inst., Indiana Univ., Indianapolis, IN; [3]APG, USUHS, B2036, Bethesda, MD

Abstract: Background: Traumatic brain injury (TBI) is a risk factor for developing Alzheimer's disease (AD) and related dementias (ADRD). We have previously demonstrated that a closed head injury (CHI) can initiate progressive AD-like symptomatology, including cognitive decline, brain atrophy, blood-brain barrier alteration and neuronal loss in juvenile mice. Our goal was to characterize a new concussion model to assess if TBI can lead to ADRD in adult mice. We also sought to validate the model across two research sites to ensure rigor and reproducibility. Methods: Eight- and twelve-month-old C57BL/6J mice of both sexes were subjected to CHI and longitudinally monitored for 60 days post-injury (dpi) using Magnetic Resonance Imaging (MRI) and 18F-Fluorodeoxyglucose Positron Emission Tomography (PET). At 60 dpi, blood was collected and plasma prepared from sham (anesthesia only) and CHI mice, vessel painting was

performed to assess cerebrovascular morphology, followed by ex vivo diffusion MRI to assess changes in brain morphology. Results: Mice with CHI induced by personnel from both sites showed similar cerebral blood flow and T2 MRI signatures. No overt parenchymal bleeding or edema were detected at 1, 7, 30 or 60 dpi on MRI. We found no significant alteration of vessel density or vessel length in CHI mice compared to Shams at 60 dpi. Brain glucose metabolism was altered in a sex-specific manner and neurovascular coupling (NVC) was altered in a region dependent manner at 30 and 60 dpi, particularly in females, in cortical and hippocampal regions. Summary: We demonstrate reproducibility between the two experimental sites and found significant dynamic and progressive alterations in NVC that exhibit similarities to vascular dysfunction as observed in other AD or AD risk models. Conclusion: A single CHI in adult mice can alter vascular and metabolic function, similar to what is observed in human TBI patients with accelerated progression to ADRD. Funding: NIH NINDS 1RF1NS1380 (AO/PT)

Disclosures: A. Jullienne: None. **J. Yan:** None. **M. Bright:** None. **S. Persohn:** None. **H. Phan:** None. **I. Kurup:** None. **D.V. Agoston:** None. **P.R. Territo:** None. **A. Obenaus:** None.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.10/E51

Topic: D.04. Brain Injury and Trauma

Support: NIH NINDS RF1NS1380

Title: Tbi adrd: modeling the role of age at traumatic brain injury in the development of alzheimer's disease and related dementias data processing pipeline.

Authors: *S. PERSOHN[1], K. ELDRIDGE[1,2], A. JULLIENNE[3], P. R. TERRITO[5], D. V. AGOSTON[6], J. YAN[4], A. OBENAUS[7];
[1]Indiana Univ., Indianapolis, IN; [2]Indiana Univ., Indiana University, IN; [3]Div. of Biomed. Sci., [4]Univ. of California, Riverside, Riverside, CA; [5]Med., Indiana Univ. Sch. of Med., Indinanapolis, IN; [6]APG, USUHS, B2036, Bethesda, MD; [7]Biomed. Sci., Univ. of California Riverside, Riverside, CA

Abstract: Emerging evidence suggests that traumatic brain injury (TBI) is a contributing risk factor for Alzheimer's disease (AD) and related dementias (ADRD). Risk factors such as sex, genetic predispositions, including the APOE genotype, are known to increase the risk of developing ADRD. Understanding these disease trajectories and their intersections may enable earlier identification of at-risk individuals. The goal of our program is development of translationally relevant disease models that recapitulate human disease and standardization across research sites, where TBI induces ADRD progression. The study will utilize MODEL-AD mouse models: B6, B6.APOEε4/ε4, B6.APOEε4/ε4.hAβ, and B6.APOEε4/ε4.hAβ.MAPT at 17D, 8M, and 12M of age. Mice will undergo single (sCHI) or repeated (rCHI) closed head

injuries. Longitudinal neuroimaging will be performed using multi-modal MRI (T1W, T2W, SWI, PWI, DTI) and PET (18F-FDG, 18F-AV45) scans accompanied with behavior. Neurovascular uncoupling analysis will be performed on the 18F-FDG and PWI data to analyze the changes across models, ages, and sidedness. Post-mortem immunopathology, blood and tissue biomarkers will be collected to align with clinical translational endpoints. A preliminary study performed across two research sites in mice at 8M demonstrated high reproducibility on MRI estimates of cerebral blood flow and tissue relaxation (T2) measures with significant differences between sham and sCHI. Neurovascular and metabolic uncoupling at 30- and 60-days post-injury exhibited sex-based differences as well as lateralization (sidedness). Plasma biomarker and postmortem immunopathology across the lifespan are underway to elucidate cell and molecular phenotypes. The UCR/IU TBI-ADRD consortium has developed a comprehensive workflow with detailed SOPs, procedures, and model systems that will be leveraged to characterize the role of TBI induced ADRD progression. Funding: NIH NINDS RF1NS1380

Disclosures: S. Persohn: None. **K. Eldridge:** None. **A. Jullienne:** None. **P.R. Territo:** None. **D.V. Agoston:** None. **J. Yan:** None. **A. Obenaus:** None.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.11/E52

Topic: D.04. Brain Injury and Trauma

Title: Temporal profiling of plasma extracellular vesicles identifies enolase-2 as a TBI severity biomarker in mice

Authors: B. KRISHNAMACHARY[1], D. LECCA[1], Y. LI[1], Z. LEI[1], H. LI[1], L. WEI[1], Y. YANG[2], *J. WU[3];
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Abstract: Traumatic brain injury (TBI) remains a major clinical and research challenge, with a lack of reliable biomarkers available to accurately assess injury severity and progression, thereby limiting our understanding of the dynamic pathophysiological changes following injury. Circulating extracellular vesicles (EVs) have emerged as critical mediators of intercellular communication and may carry molecular signatures reflective of injury severity. Alterations of EVs cargo may reflect the state of glial cells and neurons during TBI. However, the role of EVs in TBI pathogenesis and their potential to differentiate injury severity remain incompletely understood. This study aimed to characterize the proteomic profile of plasma EVs following TBI and to investigate their cellular origin and functional impact. Using a controlled cortical impact (CCI) model in young adult male C57BL/6 mice, mild, moderate, or severe TBI was induced by cortical deformation depths with 3.5 m/s. Plasma samples were collected at day 1 post-injury for

mild and moderate groups, and at days 1, 7, and 30 for severe injury. Plasma EVs were isolated via differential ultracentrifugation, and tissue EVs *via* size exclusion chromatography. Western blot confirmed canonical EV markers. Proteomic analysis *via* the Olink Mouse Exploratory Panel revealed a significant injury-dependent elevation of enolase-2 (Eno2) in plasma EVs, with western blot confirming increased Eno2 levels in severe TBI at all time points. In contrast, Eno2 in tissue-derived EVs decreased in days 7 and 30, indicating possible redistribution or cellular release dynamics. Magnetic bead-based immunocapture of EVs from astrocytes (GLAST), microglia (CD11b), and neurons (L1CAM) identified astrocyte-derived EVs as the primary source of circulating Eno2 after TBI. Using CD63-GFPf/f/Cx3cr1-Cre mice, microglia-derived CD63+ EVs progressively increased during days 7 and 31, indicating sustained microglial activation over time. Astrocyte-derived EVs (CD63-GFPf/f/Aldh1l1-Cre) showed a modest rise at day 7 and a pronounced increase on day 30, suggesting delayed astrocytic EV possibly associated with prolonged astrocyte activation. Functionally, EVs from injured mice induced a dose-dependent increase in the pro-inflammatory cytokine CXCL2 secretion in cultured primary microglia, involving EVs in secondary injury-associated neuroinflammation. Taken together, this study demonstrates that levels of Eno-2 in circulating EVs increase in an injury severity-dependent manner, suggesting that EV-associated Eno-2 may serve as a potential biomarker involved in the pathological and recovery processes following head trauma.

Disclosures: B. Krishnamachary: None. **D. Lecca:** None. **Y. Li:** None. **Z. Lei:** None. **H. Li:** None. **L. Wei:** None. **Y. Yang:** None. **J. Wu:** None.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.12/E53

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

Support: U.S. Dept. of Veterans Affairs I01 BX006251

Title: Neurite degeneration in perilesional cortex after traumatic brain injury

Authors: *S. WON, D. OGUT, R. ATLURI, R. A. SWANSON;
Neurol., UCSF & SFVAHC, San Francisco, CA

Abstract: The mechanical insult of focal TBI triggers the release of intracellular proteins and blood products. These factors induce astrogliosis, microglial activation, and leukocyte infiltration. Microglia/macrophage activation following TBI contributes to neuronal injury through the release of cytokines, proteases and reactive oxygen species. In a recent study, we demonstrated that neurites (axons and dendrites) were much more vulnerable than neuronal cell bodies to neuroinflammatory injury induced by LPS or S100b injected into mouse cortex. The neurite degeneration resulted from microglial activation and superoxide release, leading to formation of neuritic cofilactin rods. Here we investigated whether this mechanism contributes to

neurite degeneration following TBI, using a controlled cortical impact model in YFP-overexpressing mouse. All outcome measures were from n = 4-6 mice of both sexes age 3.5 - 5.5 months, with image analysis done by investigators blinded to the experimental conditions. We examined an area of 500 - 2000 um from the TBI lesion edge. Within this area there was no detectable loss of neuronal cell bodies, but there was a loss of YFP-labeled neurites beginning 6 hrs after TBI and increasing to reach 80% loss by 24 hours. These neurites were projections from the deeper layers of cortex, not from the lesioned area itself. The neurite loss was confirmed by a parallel decline in neurofilament-H immunoreactive processes and by silver staining. Neurons in this area also exhibited cofilactin rod formation and oxidative stress, and Sholl analysis confirmed microglial activation 6 hr through 72 hr. These observations suggest that microglial/macrophage activation causes neurite loss far out of proportion to neuronal loss in peri-lesional cortex through a mechanism involving oxidative stress and cofilactin rod formation. Ongoing studies are assessing whether this neurite loss scan be reduced by blocking microglial/macrophage activation with a hexokinase-2 inhibitor.

Disclosures: S. Won: None. **D. Ogut:** None. **R. Atluri:** None. **R.A. Swanson:** None.

Poster

PSTR115: Brain Injury: Animal Models: Biomarkers and Histology

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Program #/Poster #: PSTR115.13/E54

Topic: D.04. Brain Injury and Trauma

Support: MDO intramural USU grant: MDO-70-12756
Military Traumatic Brain Injury Initiative (MTBI2) Graduate Fellowship Award; HJF Award Number: 313884-10.01-67330

Title: Investigating Glymphatic Function and Neurological Deficits as a result of Traumatic Brain Injury.

Authors: *C. M. BOUSLOG;
Uniformed Services Univ. of the Hlth. Sci., Silver Spring, MD

Abstract: Abstract: Traumatic brain injuries (TBI) are a global concern and have long-term detrimental effects months to years after the initial injury itself. Research has shown that the consequences of TBI differ with altered severity, but the extent and mechanism of it’s impact is still unknown. TBI often results in progressive cognitive decline and balance/gait instability which may be attributed to glymphatic exchange dysfunction. The glymphatic system is a waste clearance mechanism which facilitates CSF and interstitial fluid exchange via a network of fluid traveling in the perivascular space along penetrating arteries. Deficits to the glymphatic system can affect the brain’s ability to maintain homeostasis needed for motor coordination and memory and has been implicated in neurodegenerative disorders such as Alzheimer’s disease. There is an urgent need for research on the effects of TBI on glymphatic functionality to identify therapeutic

targets. To evaluate the effect of varying severities of TBI on behavior and glymphatic function, we established a mild, moderate and severe TBI (impact depth, Z = 1, 1.5 or 2.0 mm respectively at 2.0mm lateral, and 2.0mm posterior to bregma) injury model in mice using an open head controlled-cortical impact TBI. Seven days post-TBI, all TBI mice exhibited impairments in balance/gait stability, displaying significantly more slips compared to Sham, with the moderate TBI showing the greatest number of slips (P=0.001). Balance impairments were positively correlated with injury severity (R2=0.2002, P=0.0011, F(1,48) =12.03). Contextual, but not cue, fear memory recall, as determined by fear conditioning testing, was also significantly impaired in female, but not male, TBI mice. Moderate TBI (CCI=1.5mm) mice displayed a trending reduction in pulsatility of penetrating arteries, which correlates with beam walk slips, (R2=0.2653, P=0.5162, F(1,4) =1.44), tying driving forces of the glymphatic system to behavioral deficits. Understanding changes to glymphatic exchange as a function of injury severity will help to elucidate potential therapeutic targets with a goal to mitigate post-TBI neurocognitive trajectory by restoring glymphatic functionality.

Disclosures: C.M. Bouslog: None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.01/E55

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Defitech Foundation
Onward Medical
RESTORE network
Wings for Life Foundation
Digital Research Alliance of Canada
Natural Sciences and Engineering Research Council
Canadian Institutes of Health Research

Title: The molecular mechanism of hypotension-induced heart disease after spinal cord injury

Authors: *J. SORIANO;
École Polytechnique Fédérale de Lausanne, Geneva, Switzerland

Abstract: Individuals with spinal cord injury (SCI) are at increased risk of myocardial infarction, heart failure, and arrhythmogenic potential. Although maladaptation of cardiac structure and function following SCI is well-established, it remains unknown how these changes predispose the heart to a four-fold increased risk of heart disease. Here, we establish a preclinical model of chronic SCI in which invasive assessments of cardiac structure and function are coupled to rigorous evaluations of myocardial infarction, arrhythmogenic potential, and heart failure. We then leveraged single-nucleus RNA sequencing (snRNA-seq) of left ventricular

tissue to investigate the mechanisms by which SCI and the subsequent persistent hypotensive state lead to increased risk for heart disease. Our results indicate that hypotensive episodes following SCI trigger severe cardiac ischemia resulting in cardiac remodeling, which can be prevented with epidural electrical stimulation (EES) targeting the hemodynamic hotspot. These findings establish a mechanistic link between hypotensive episodes after SCI and heart disease and highlight the therapeutic potential of EES.

Disclosures: J. Soriano: None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.02/E56

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Horizon Europe (HORIZON); Call: HORIZON-MSCA-2021-DN-01; Project: 101073374 — ReWire
Christopher & Dana Reeve Foundation: Neuroprosthetic system to manage lower urinary tract dysfunction after spinal cord injury

Title: Restoring the lower urinary tract function after spinal cord injury using epidural electrical stimulation

Authors: *V. NGUYEN[1,2,3], L. MAHE[1,2,3], R. HUDELLE[1,2,3], J. SORIANO[1,2,3], A. Y. TEO[1,2,3], M. GAUTIER[1,2,3], S. A. KOMI[2], F. FALLEGGER[2], N. HANKOV[1,2,3], L. ASBOTH[1,2,3], R. DEMESMAEKER[1,2,3], C. KATHE[4], T. H. HUTSON[5], N. D. JAMES[1,2,3], Q. BARRAUD[1,2,3], M. MILANO[1,2,3], N. REGAZZI[1,2,3], I. DEWANY[1,2,3], A. DE COUCY[1,2,3], V. PEREZ PUCHALT[1,2,3], S. P. LACOUR[2], J. SQUAIR[1,2,3], J. BLOCH[1,2,3], G. COURTINE[1,2,3];
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Abstract: Spinal cord injury (SCI) disrupts descending supraspinal control lower urinary tract function, causing detrusor overactivity and detrusor-sphincter dyssynergia. Here, we developed a neuroprosthetic strategy using epidural electrical stimulation (EES) to modulate spinal circuits regulating lower urinary tract function. By combining retrograde trans-synaptic tracing with in vivo functional mapping, we identified “urodynamic hotspots” corresponding to parasympathetic detrusor and somatic sphincter control, respectively. We engineered stimulation protocols targeting these regions to re-establish the reciprocal detrusor-sphincter activity necessary for voiding and to suppress detrusor overactivity during storage in rodent models of SCI. Single-cell RNA sequencing and cell type specific ablations revealed a neuronal architecture spanning the

spinal cord and brainstem responsible for the restoration of lower urinary tract functions. These results define the requirements for EES-mediated lower urinary tract recovery and support targeted neuromodulation as a promising avenue for restoring autonomic function after SCI.

Disclosures: V. Nguyen: None. **L. Mahe:** None. **R. Hudelle:** None. **J. Soriano:** None. **A.Y. Teo:** None. **M. Gautier:** None. **S.A. Komi:** None. **F. Fallegger:** None. **N. Hankov:** None. **L. Asboth:** None. **R. Demesmaeker:** None. **C. Kathe:** None. **T.H. Hutson:** None. **N.D. James:** None. **Q. Barraud:** None. **M. Milano:** None. **N. Regazzi:** None. **I. Dewany:** None. **A. de Coucy:** None. **V. Perez Puchalt:** None. **S.P. Lacour:** None. **J. Squair:** None. **J. Bloch:** None. **G. Courtine:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.03/E57

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Swiss National Science Foundation (SNSF)

Title: The molecular logic of spinal cord regeneration across evolution

Authors: *A. Y. TEO[1], N. REGAZZI[2], J. SORIANO[2], C. KATHE[3], T. H. HUTSON[4], M. GAUTIER[2], A. DE COUCY[2], G. ZHOU[2], S. L. CETO[5], C.-F. V. LATCHOUMANE[2], C. G. BECKER[6], T. BECKER[6], M. M. SOUSA[7], Z. HE[8], B. L. SCHNEIDER[9], E. BEZARD[10], Q. BARRAUD[2], J. BLOCH[2], M. A. ANDERSON[2], G. COURTINE[2], J. SQUAIR[2];
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Abstract: Unravelling how certain vertebrates regenerate the injured spinal cord remains one of the most challenging and potentially transformative pursuits in medicine. In this study, we present a single-cell transcriptomic atlas encompassing six regenerative and non-regenerative models of spinal cord injury, ranging from zebrafish to nonhuman primates. Using this atlas, we dissect the evolutionary conservation and divergence of molecular mechanisms that underlie spontaneous spinal cord repair. Regenerative species consistently form a tripartite barrier that limits immune cell entry and protects intact neural tissue, while activating ancient, intrinsic neuronal growth pathways to regenerate damaged axons. Importantly, we demonstrate that these

regenerative mechanisms can be reactivated in non-regenerating species, effectively recapitulating evolutionarily conserved molecular programs that repair spinal cord injury and restore neurological function.

Disclosures: A.Y. Teo: None. **N. Regazzi:** None. **J. Soriano:** None. **C. Kathe:** None. **T.H. Hutson:** None. **M. Gautier:** None. **A. de Coucy:** None. **G. Zhou:** None. **S.L. Ceto:** None. **C.V. Latchoumane:** None. **C.G. Becker:** None. **T. Becker:** None. **M.M. Sousa:** None. **Z. He:** None. **B.L. Schneider:** None. **E. Bezard:** None. **Q. Barraud:** None. **J. Bloch:** None. **M.A. Anderson:** None. **G. Courtine:** None. **J. Squair:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.04/E58

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Wings for Life Project Grant - Elucidating mechanisms underlying functional repair following spatiotemporal stimulation of the injured cervical spinal cord
Swiss National Science Foundation (310030_185214) - Targeted amplification of the motor recovery engram following spinal cord injury

Title: Neuronal architectures underlying recovery of arm and hand function after cervical spinal cord injury

Authors: *I. DEWANY[1,2,3], V. PEREZ PUCHALT[1,2,3], E. BODIN[1], R. SADRY[1], A. TEO[1,2,3], F. QUATTROCIOCCHI[1,2,3], N. CHO[1], M. GAUTIER[1,2,3], K. GALAN[1,2,3], A. PHILIPPIDES[1,2,3], C. KATHE[4], T. H. HUTSON[5], F. MERLOS[1,2,3], Q. BARRAUD[1,2,3], J. BLOCH[1,2,3,6], J. SQUAIR[1,2,3,6], N. D. JAMES[1,2,3], G. COURTINE[1,2,3,6];
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Abstract: The circuit-level mechanisms underlying the natural recovery of upper-limb function after cervical spinal cord injury (SCI) remain poorly understood. Equally unclear is whether neuromodulation therapies that augment this recovery target the same mechanisms. Here we unravel the intricacies of natural and targeted circuit reorganization following cervical spinal cord injury (SCI) by identifying the neuronal subpopulations that orchestrate spontaneous and neuromodulation-induced recovery. To enhance our understanding of the neuronal architectures key to functional repair, we first examined changes in neuronal activity patterns associated with

spontaneous recovery by conducting advanced 3D imaging of whole mouse brains. Unbiased, large-scale statistical analyses of these data identified a single brain region that was directly connected to the cervical spinal cord and displayed alterations in neuronal activity correlated to upper-limb functional repair. We next utilized snRNA-sequencing and cell type prioritization to identify recovery-organizing neuronal subpopulations embedded in the cervical spinal cord. To confirm their contribution to functional repair, we selectively ablated each of our identified nodes individually; finding that natural recovery of upper limb function failed to occur in all cases. Finally, through the use of intersectional virus-mediated tract tracing, we demonstrate dense connectivity between each of these individual nodes, thus exposing a complete neuronal architecture that dramatically reorganizes following cervical SCI and becomes essential to regain upper limb function. This enhanced understanding of natural repair pathways could ultimately be combined with our cervical spinal cord stimulation paradigms to maximize recovery of upper limb functions.

Disclosures: I. Dewany: None. **V. Perez Puchalt:** None. **E. Bodin:** None. **R. Sadry:** None. **A. Teo:** None. **F. Quattrociocchi:** None. **N. Cho:** None. **M. Gautier:** None. **K. Galan:** None. **A. Philippides:** None. **C. Kathe:** None. **T.H. Hutson:** None. **F. Merlos:** None. **Q. Barraud:** None. **J. Bloch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Onward Medical. F. Consulting Fees (e.g., advisory boards); Onward Medical. **J. Squair:** None. **N.D. James:** None. **G. Courtine:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Onward Medical. F. Consulting Fees (e.g., advisory boards); Onward Medical.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.05/F1

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Swiss National Science Foundation (SNSF)
Wings for Life
ONWARD Medical

Title: Mechanisms underlying improvements in response to externally applied electrical stimulation of the spinal cord

Authors: *V. PEREZ PUCHALT[1,2,3], I. DEWANY[1,2,3], R. SADRY[1], M. BOSS[1], F. QUATTROCIOCCHI[1,2,3], E. FERNÁNDEZ-LAVADO[2], A. PHILIPPIDES[1,2,3], A. TEO[1,2,3], M. GAUTIER[1,2,3], C. KATHE[4], T. H. HUTSON[5], F. MERLOS[1,2,3], V. AURELI[1,2,3], A. ALASHQAR[6,7], A. ROWALD[6,7], H. LORACH[1,2,3], Q. BARRAUD[1,2,3], S. P. LACOUR[2], J. BLOCH[1,2,3,8], J. SQUAIR[1,2,3,8], N. D. JAMES[1,2,3], G. COURTINE[1,2,3,8];
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Abstract: Electrical stimulation of the spinal cord applied during rehabilitation has enhanced upper and lower limb function in numerous preclinical models, from rodents to primates, as well as a number of clinical studies. Stimulation of the spinal cord can be achieved using non-invasive methodologies, whereby electrical current is delivered to the spinal cord through surface electrodes (ARC^{EX} Therapy). However, the mechanisms responsible for neurological recovery in response to this therapy remain poorly understood. To fill this knowledge gap, we studied the neural pathways that are directly recruited by ARC^{EX}, and the subsequent modulation of the neuronal subpopulations mediating the observed neurological recovery in response to this therapy. To deliver ARC^{EX} in mice, we developed a soft, wearable device embedded with electrodes that target the cervical spinal cord of mice. The wearable device enhanced mechanical and electrical properties and ensured consistent electrode placement, improving the reproducibility and robustness of stimulation. We then used a judicious combination of anatomical, molecular and causal methodologies to investigate the mechanisms of ARC^{EX}. Dorsal rhizotomies revealed that ARC^{EX} relies on sensory afferents to provoke muscle activation. In-situ hybridisation exposed the specific sensory neurons that were most transcriptionally activated by ARC^{EX}. Monosynaptic viral tracing revealed a strong connection between these sensory neurons and a specific neuronal subpopulation within the spinal cord that have previously been identified as essential to promote neurological recovery after SCI. Using a newly designed neurorobotic platform for mice, we quantified the effect of ARC^{EX} Therapy on upper limb motor recovery limbs and demonstrated that these effects were lost in the absence of this specific population of neurons. These results provide a framework to improve the efficacy of non-invasive spinal cord stimulation methodologies.

Disclosures: V. Perez Puchalt: None. **I. Dewany:** None. **R. Sadry:** None. **M. Boss:** None. **F. Quattrociocchi:** None. **E. Fernández-Lavado:** None. **A. Philippides:** None. **A. Teo:** None. **M. Gautier:** None. **C. Kathe:** None. **T.H. Hutson:** None. **F. Merlos:** None. **V. Aureli:** None. **A. Alashqar:** None. **A. Rowald:** None. **H. Lorach:** None. **Q. Barraud:** None. **S.P. Lacour:** None. **J. Bloch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Onward Medical. F. Consulting Fees (e.g., advisory boards); Onward Medical. **J. Squair:** None. **N.D. James:** None. **G. Courtine:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Onward Medical. F. Consulting Fees (e.g., advisory boards); Onward Medical.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.06/F2

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Swiss National Science Foundation

Title: A spatial transcriptomic atlas of human spinal cord injury

Authors: *M. GAUTIER[1], M. A. ANDERSON[3], A. TEO[4], Q. BARRAUD[5], J. BLOCH[6], B. K. KWON[7], G. COURTINE[8], J. SQUAIR[2];
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Abstract: The cellular and molecular complexity of spinal cord injury (SCI) remains a major barrier to the development of effective treatments, especially in human patients where tissue accessibility is limited. Building on the *Tabulae Paralytica*, which defined conserved and divergent mechanisms of injury response in the mouse spinal cord, we now present a spatial transcriptomic mapping of the human lesion site. We profiled both the lesion epicenter and caudal segments of SCI donors across a range of clinical severities (ASIA scores A to D) and time points post-injury, from acute (10 days post injury) to chronic stages (170 days post injury). This dataset enables new insight into the spatial organization of the human injury response. We identify shifts in cellular composition that mirror key trajectories previously described in experimental models, revealing conserved aspects of injury evolution. Furthermore, our data uncover progressive remodeling of the lesion microenvironment, including sustained disruption of the blood-brain barrier, recapitulating hallmarks observed in animal models. This study offers a new resource to investigate the human spinal cord injury microenvironment at spatial and molecular resolution.

Disclosures: M. Gautier: None. **M.A. Anderson:** None. **A. Teo:** None. **Q. Barraud:** None. **J. Bloch:** None. **B.K. Kwon:** None. **G. Courtine:** None. **J. Squair:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.07/F3

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Defitech foundation
Onward medical
RESTORE network
Wings for Life Foundation
Compute Canada
Natural Sciences and Engineering Research Council
the Canadian Institutes of Health Research

Title: The neuronal architecture of autonomic dysreflexia

Authors: *R. HUDELLE;
École Polytechnique Fédérale De Lausanne, Geneva, Switzerland

Abstract: Autonomic dysreflexia is a life-threatening condition after spinal cord injury (SCI), marked by uncontrolled hypertensive episodes triggered by sensory stimuli. Despite its clinical significance, the neuronal mechanisms driving this condition have remained poorly understood, impeding therapeutic progress. This study elucidates the de novo neuronal architecture that emerges post-SCI and underlies autonomic dysreflexia. Through longitudinal mapping in preclinical models, we expose the circuit topology and dynamics responsible for these hypertensive spikes. Then, we identify a competing neuronal architecture activated by epidural electrical stimulation of the lower thoracic spinal cord, which activates local Vsx2 neurons in an adversarial competition for synaptic control. This mechanistic insight enabled the design of a targeted intervention that reorganizes the dysreflexia circuitry, effectively silencing its maladaptive projections and reversing the condition in mice, rats, and humans with SCI. These findings resolve longstanding questions about autonomic dysreflexia's neuronal basis and establish a foundation for mechanism-based therapies to mitigate this debilitating complication of SCI.

Disclosures: R. Hudelle: None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.08/F4

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Wings for Life
Swiss National Science Foundation
Promobilia Foundation
Onassis Foundation
Swiss Government Excellence Scholarships Program
Chinese Scholarship Council
ALARME Foundation

Title: Regeneration to restore upper-limb functions after paralysis

Authors: *A. LASKARATOS[1,2,3], G. ZHOU[4,5], V. AURELI[4,2,6], A. DE COUCY[4,2], J. SORIANO[4,3], R. HUDELLE[4,2], A. TEO[4,3], I. DEWANY[4,3], N. REGAZZI[4,2], A. COLLOMB-CLERC[4,3], M. GAUTIER[4,3], N. D. JAMES[4,2], Z. HE[7], B. L. SCHNEIDER[3], M. V. SOFRONIEW[8], Q. BARRAUD[4,2,3], J. BLOCH[4,2,3,6], J. SQUAIR[4,2,3,6], G. COURTINE[4,2,3,6], M. A. ANDERSON[4,2,3];
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Abstract: Cervical spinal cord injury (SCI) often leads to permanent upper-limb paralysis with devastating consequences. Indeed, restoration of arm and hand function is the number one priority of people with SCI. Our goal is to biologically repair the injured cervical spinal cord by regenerating axons from neurons above the lesion to their natural target regions below it, thereby re-establishing communication between the brain and the spinal segments controlling arm and hand movements. We developed, and functionally characterized, a unilateral cervical hemi-crush SCI rodent model. We verified that certain molecularly characterized neurons in the cervical spinal cord are essential for recovery of upper limb function following cervical SCI. Using a gene therapy approach, we are investigating the ability to regrow the axons of these neurons to their natural target regions in the cervical spinal cord to restore upper limb function. Ultimately, we aim to develop a regenerative strategy to enhance functional recovery in the most severe cases of cervical SCI.

Disclosures: A. Laskaratos: None. **G. Zhou:** None. **V. Aureli:** None. **A. de Coucy:** None. **J. Soriano:** None. **R. Hudelle:** None. **A. Teo:** None. **I. Dewany:** None. **N. Regazzi:** None. **A. Collomb-Clerc:** None. **M. Gautier:** None. **N.D. James:** None. **Z. He:** None. **B.L. Schneider:** None. **M.V. Sofroniew:** None. **Q. Barraud:** None. **J. Bloch:** None. **J. Squair:** None. **G. Courtine:** None. **M.A. Anderson:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR116.09/F5

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Promobilia
the Swiss National Science Foundation

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the ALARME Foundation
Dr. Miriam and Sheldon G. Adelson Medical Foundation
Wings for Life
Friedrich Flick Förderungsstiftung through Wings for Life

Title: Defining the requirements for biological repair and restoration of neurological function across severity, age, and time following spinal cord injury

Authors: *A. DE COUCY[1], A. TEO[2], A. LASKARATOS[2], Q. BARRAUD[2], M. GAUTIER[2], V. AURELI[2], B. L. SCHNEIDER[3], Z. HE[4], J. BLOCH[2], M. V. SOFRONIEW[5], J. SQUAIR[2], G. COURTINE[2], M. A. ANDERSON[2];
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Abstract: Spinal cord injury (SCI) disrupts neural pathways, resulting in permanent neurological deficits. Despite much progress, there is no clinically approved therapy to repair the injured human spinal cord. Our research has identified essential mechanisms for regenerating axons across anatomically complete SCI: (i) activating dormant neuronal growth programs above the injury, (ii) creating a growth-permissive environment within the core of the injury, and (iii) guiding axons below the injury using chemoattractive growth factors. Using gene therapy approaches to target specific neuronal populations and direct them to their natural target region in the lumbar spinal cord restores walking following anatomically complete SCI. However, clinical translation is challenged by biological variability, including differences in age, injury severity, as well as time post-injury. These factors dictate which mechanisms must be combined to mediate meaningful neurological recovery. Translating these findings into effective therapies requires understanding which biological mechanisms must be targeted to repair increasingly severe SCIs and how early these mechanisms must be deployed to target progressively longer timepoints post-injury in both young and aged subjects. Understanding how injury properties and patient-specific factors influence repair is crucial for developing effective, personalized therapies for human SCI.

Disclosures: A. de Coucy: None. **A. Teo:** None. **A. Laskaratos:** None. **Q. Barraud:** None. **M. Gautier:** None. **V. Aureli:** None. **B.L. Schneider:** None. **Z. He:** None. **J. Bloch:** None. **M.V. Sofroniew:** None. **J. Squair:** None. **G. Courtine:** None. **M.A. Anderson:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.10/F6

Topic: D.05. Spinal Cord Injury and Plasticity

Support: NIH: R01NS122888
PVA: P0579366
UH3NS106899
VA: I01RX002245
DoD: SC150298

Title: Impact of SCI on kidney function

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Abstract: Autonomic dysfunction, including urinary issues (involving bladder and kidney, and disorders with the cardiovascular system) are common following spinal cord injury (SCI). Together, these are among the leading issues that impact quality of life in the SCI population. However, few studies have investigated kidney health and function following SCI. Kidneys help regulate blood pressure and electrolyte balance, on top of filtering blood and urine production. It has been previously established that SCI can alter key water/solute balance biomarkers in the kidney, such as vasopressin, atrial natriuretic peptide, aquaporins, and epithelial sodium channels. SCI patients have a higher risk of developing chronic kidney disease (CKD), further increasing cardiovascular disease and potentially causing a cascade of events that increase mortality (e.g. electrolyte imbalance, increased risk of infections, waste buildup, etc.). This current study aimed to investigate the effect of a high thoracic (T3) SCI on kidney function following acute (2- and 7-days post injury) and chronic (6-weeks post-injury) in male rats. We have found that the presence of hematuria following injury, in addition to blood/urine infiltration in the kidney is one potential cause and indication for kidney dysfunction in the acute phase of SCI. Additionally, other biomarkers for fibrosis have been found in the chronic phase of SCI which likely increases chances of developing CKD. This project has strong translational potential since the kidneys are impacted after human SCI, demonstrated by the increased incidence in chronic kidney disease in the SCI population.

Disclosures: J. Gumbel: None. **J. Davis:** None. **E. Iorio:** None. **C. Omondi:** None. **A.R. Ferguson:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.11/F7

Topic: D.05. Spinal Cord Injury and Plasticity

Support: NIH R01NS081040
Buoniconti Fund to Cure Paralysis

Title: The role of IL-1 signaling in fibrotic scar formation after spinal cord injury

Authors: ***B. KANG**[1], C. FEHLBERG[1], J. K. LEE[2], D. JOHN[1];
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Abstract: Following spinal cord injury (SCI), a fibrotic scar forms at the lesion site, which is known to inhibit neural regeneration. This scar is primarily composed of perivascular fibroblasts and extracellular matrix (ECM) proteins such as fibronectin and collagen. However, the molecular mechanisms by which fibroblasts are activated to secrete ECM after SCI are poorly understood. In this study, we used Col1a2-CreER mice for conditional deletion of interleukin-1 receptor1 (IL-1R1) and expression of tdTomato specifically in fibroblasts to investigate the role of IL-1 signaling fibrotic scar formation after SCI. Col1a2-ILR1-tdTom mice (or wildtype controls) received a moderate mid-thoracic contusive SCI. At 4 weeks after injury, the injury site was processed for histological analysis. Conditional deletion of IL-1R1 resulted in a significant reduction in fibrotic scar size and fibronectin deposition at 28 days post-injury. Notably, this reduction occurred without altering the total number of perivascular fibroblasts. Our results suggest that ILR1 signaling contributes to ECM deposition by activated fibroblasts in the fibrotic scar after SCI.

Disclosures: B. Kang: None. **C. Fehlberg:** None. **J.K. Lee:** None. **D. John:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.12/F8

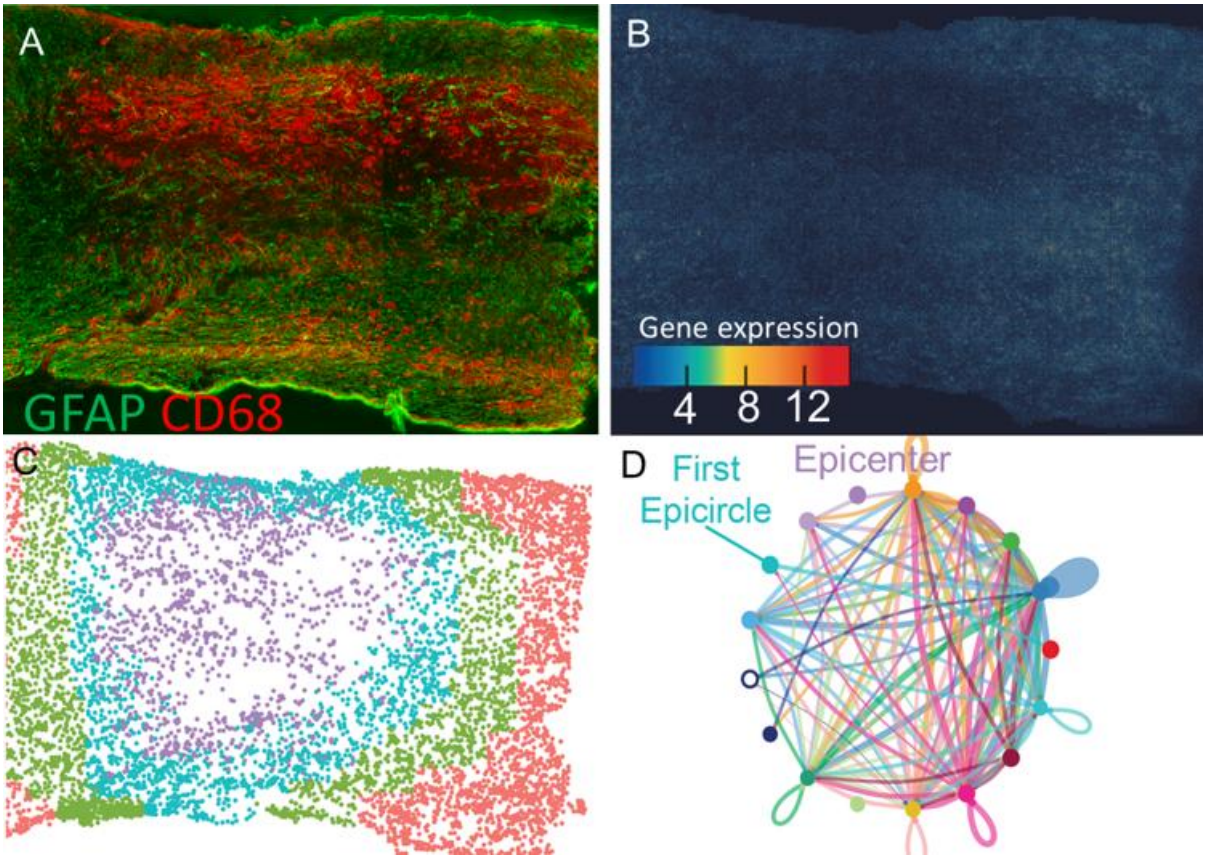
Topic: D.05. Spinal Cord Injury and Plasticity

Title: Understanding Cell-to-cell interactions after spinal cord injury using spatial transcriptomics

Authors: ***H. J. KIM**[1], A. CANFIELD[1], J. LIU[2], E. WANG[1], C. LONDONO[1], B. ZHENG[1];
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Abstract: Understanding the dynamic injury environment following spinal cord injury (SCI) is essential for developing effective therapies. The injury site is highly complex and varies depending on the type and severity of injury. In animal research, different surgical models are used to study SCI. For example, the dorsal hemisection model is well-suited for studying axon regeneration, while the contusion model more closely resembles human SCI pathology. Cell-to-cell interactions originating from the injury epicenter play a critical role in shaping recovery outcomes by transmitting injury-related signals across tissues. To investigate spatially resolved gene expression changes in different SCI models, we applied Stereo-seq, a subcellular spatial transcriptomics technology, to both dorsal hemisection and contusion injuries. This approach enables segmentation of the tissue based on proximity to the injury site and allows us to analyze distance-dependent cell-cell interactions. By capturing high-resolution gene expression patterns

across diverse cell types, this method provides key insights into the molecular mechanisms underlying SCI and offers a powerful framework for understanding how injury type influences the repair response.



(A) Immunostaning of astrocytes (GFAP) and immune cells (CD68)(B) Gene expression in Bin 1 (C) Region segmentation of injury epicenter and 2 epicircles(D) Cell-to-cell interaction within and between regions

Disclosures: H.J. Kim: None. **A. Canfield:** None. **J. Liu:** None. **E. Wang:** None. **C. Londono:** None. **B. Zheng:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.13/F9

Topic: D.05. Spinal Cord Injury and Plasticity

Support: DST SERB SPG/2021/003851

Title: Intermittent theta burst stimulation and Iron oxide nanoparticles drives molecular recovery in spinal cord injured rats: A TMT 11plex LC-MS/MS based proteomics study

Authors: *G. SHARMA[1], S. BANDYOPADHYAY[2], G. HARIPRASAD[3], K. KOCHHAR[1], S. JAIN[4];
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Abstract: Spinal cord injury(SCI) often results in severe motor deficits and loss of mobility. Intermittent theta burst stimulation (iTBS) is a form of transcranial magnetic stimulation (TMS) that has demonstrated potential in enhancing motor recovery, though its underlying mechanisms remain unclear. This study aimed to evaluate the site-specific effects of iTBS, applied to a)motor cortex(MC), b)spinal cord (SC), or c)both MC SC, and to investigate the mechanisms involved. To enhance the precision and efficacy of iTBS, superparamagnetic iron oxide nanoparticles (IONPs) were administered at the lesion site, potentially enabling targeted neuromodulation. Adult male Wistar rats (n= 120) were randomly divided into 10 groups: control; sham SCI; SCI; SCI+sham stimulation(SS); SCI+ iTBS (MC); SCI + iTBS (SC); SCI + iTBS (MC+SC); SCI+ IONPs; SCI + SS + IONPS; SCI + iTBS(MC +SC) + IONPS. Following a complete T13 SCI, rats received iTBS targeting the MC and/or SC. Functional assessments including electrophysiology, locomotor scoring, and bladder function were performed pre and post-intervention. Spinal cord tissue was collected for quantitative proteomics experiment using the Tandem Mass Tag (TMT) 11-plex labeling method. Rats receiving either iTBS (MC) alone or iTBS along with IONPs implantation exhibited improved locomotor function compared to the sham stimulation group. Electrophysiological evaluations revealed enhanced cortical excitability in the iTBS (MC) ($p<0.0001$) and combined iTBS + IONPs ($p=0.0016$) treatment groups. Specifically, motor thresholds were significantly lowered in these groups, indicating more responsive neural networks. LC-MS/MS proteomic analysis identified 638 differentially expressed proteins (DEPs) out of 4059 total proteins when compared across control, SCI, iTBS(MC+SC) and iTBS+ IONPs groups. Gene ontology enrichment analysis linked these DEPs to axon regeneration, neuron projection regeneration, and regulation of cell death. Pathway enrichment analysis revealed key pathways, including coagulation and complement cascades and Ras signaling. ELISA results further confirmed that the intervention groups exhibited changes in the MAPK signaling pathway, consistent with the MS/MS findings. In conclusion, both iTBS alone and in combination with nanoparticles proved effective, resulting in enhanced neural conduction, increased axonal regeneration, reduced inflammation & tissue damage, and improved neuroplasticity at the lesion site in acute spinal cord injury.

Disclosures: G. Sharma: None. **S. Bandyopadhyay:** None. **G. Hariprasad:** None. **K. Kochhar:** None. **S. Jain:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.14/F10

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Reorganization of vascular zonation after spinal cord injury

Authors: *T. CAMEJO[1], Y. WANG[1], C. FEHLBERG[1], S. MOHITE[1], B. KANG[1], J. K. LEE[2], P. TSOULFAS[3];
[2]The Miami Project to Cure Paralysis, [3]Neurosurg. and The Miami Project, [1]Univ. of Miami, Miami, FL

Abstract: Spinal cord injury is a devasting condition that affects 20.6 million people globally. A disrupted vasculature prevents functional recovery after spinal cord injury. The initial trauma that leads to blood vessel rupture and endothelial cell death is eventually followed by vascular remodeling. However, it is not known how the vascular zonation, or the gradual change in endothelial cell types, functions, and molecular features along the arteriovenous axis, is remodeled after spinal cord injury. We investigated the distinct responses of arteries, veins, and capillaries following spinal cord injury. We analyzed tissue from the injury site that were either uninjured or at 14 and 28 days after T8 contusive spinal cord injury in C57BL/6 mice. The tissue was cleared using iDISCO, immunolabeled for smooth muscle alpha-2 actin (ACTA2) as an arterial marker, von Willebrand Factor (vWF) as a venous marker, and podocalyxin (PODX) as an endothelial cell marker, and imaged with lightsheet microscopy. Three dimensional architectural changes in the vascular zonation were analyzed with Imaris software. We found that vWF was visibly upregulated after injury. In addition, capillaries became highly disorganized forming a dense, mesh-like network in the dorsal region and to a lesser extent in the ventral region,resembling the typical density seen in white matter. Arterial branches at the lesion site were reduced and the remaining branches oriented themselves toward the lesion core. In conclusion, spinal cord injury induces reorganization of the vascular zonation pattern that may provide insight into how vascular changes contribute to the pathology around the injury site.

Disclosures: T. Camejo: None. **Y. Wang:** None. **C. Fehlberg:** None. **S. Mohite:** None. **B. Kang:** None. **J.K. Lee:** None. **P. Tsoulfas:** None.

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PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR116.15/F11

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation 1000927

Title: Identifying the descending fiber pathways that drive secondary tissue loss after spinal cord injury

Authors: *A. TREVINO, N. KOBAYASHI, V. BALENTINE, J. W. GRAU;
Texas A&M Univ., College Station, TX

Abstract: Prior work has shown that pain (nociceptive) stimulation after a spinal cord injury (SCI) leads to the expansion of hemorrhage, undermines locomotor recovery, and induces a rise in blood pressure/flow (Turtle, 2019, Exp Neurol, 311,115; Fauss, 2021, Front Sys Neurosci,15). A pharmacological transection at T2 using lidocaine, which blocks communication with the brain, blocked the adverse effects of nociceptive stimulation in a SCI model (Davis, 2020, J Neurotrauma, 37,1729). Additionally, a complete transection blocked the adverse effects as well (Reynolds, 2019, Front Sys Neurosci,13). These experiments led to the development that the brain is mediating the nociceptive-induced adverse effects in a SCI model but the underlying pathway is unknown. The dorsolateral funiculus (DLF) contains major descending pain pathways which makes it an ideal therapeutic target. Previous studies have shown that descending serotonergic fibers through the DLF regulate the development of maladaptive plasticity and neuropathic pain, an effect linked to a loss of GABA-dependent inhibition (Huang, 2018, *Exp Neurol, 306*.105). The current study examined whether the DLF mediates the nociceptive-induced adverse effects in a SCI model. Male Sprague-Dawley rats received a moderate T12 contusion injury then 18 hours later animals were assessed for hindlimb locomotor function. Immediately following they received bilateral DLF lesions or a sham laminectomy procedure at T2. Animals were allowed to recover for 6 hours then blood pressure and hindlimb locomotor was assessed before animals received pain treatment. Animals received noxious electrical stimulation or the control procedure for 6 minutes. Blood pressure and hindlimb locomotor function was assessed immediately after pain treatment and every hour for three hours. A 1-cm portion of the spinal cord encompassing the site of injury was collected and assayed for hemoglobin using a Drabkin assay. Preliminary results suggest that animals that received a bilateral DLF lesion seem to have an initial deficit in locomotor recovery following noxious stimulation but exhibit improved recovery in comparison to the animals that received the sham procedure. Cellular assays are being conducted to assess hemorrhage and cell death.

Disclosures: A. Trevino: None. **N. Kobayashi:** None. **V. Balentine:** None. **J.W. Grau:** None.

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PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

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Program #/Poster #: PSTR116.16/F12

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Neilsen Foundation Grant 1000927

Title: Stress and Systemic Factors Mediate Pain-Induced Tissue Loss in Spinal Cord Injuries (SCI)

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Psychology & Brain Sci., Texas A&M Univ., College Station, TX

Abstract: In recent studies, we have observed that the exogenous administration of norepinephrine, a catecholamine predominantly produced by the adrenal medulla, can adversely impact locomotion following spinal cord injuries (Strain et al., 2021, J Neurotrauma, 38). Furthermore, evidence has been gathered indicating that peripheral nociceptive stimulation exacerbates hemorrhage and adversely affects recovery (Turtle et al., 2017, J Neurotrauma, 34) and that this effect is brain-dependent (Reynolds et al., 2019, Front Sys Neurosci, 13). We hypothesized that brain systems may drive tissue loss after SCI by engaging a systemic stress response, activating the pituitary-adrenal axis. To explore the potential role of the sympathetic system in pain-induced secondary tissue loss after SCI, male rats were subjected to a moderate thoracic (T11-12) contusion injury with either concurrent adrenalectomy (ADX) or sham surgery. After 24 hours, they were exposed to noxious electrical stimulation for six minutes or no stimulation. Subsequently, their locomotor performance was assessed, and a segment of their spinal cord containing the injury was collected post-mortem, along with serum samples. In the absence of pain, there was little difference observed between the ADX and sham groups. The ADX group demonstrated a protective effect against nociception, characterized by reduced locomotor deficits, decreased hemorrhage, and lower cell death markers. The results suggest a systemic factor, tied to the adrenal glands, contributes to secondary tissue loss. To explore this possibility, a second experiment was conducted wherein contused rats received noxious stimulation or nothing. Three hours later, their serum was collected. Other contused rats then received an infusion of serum a day after injury. Rats that received serum from a pain subject had a larger locomotor deficit than those that received serum from a rat without noxious stimulation. Serum infusion did not, however, drive additional hemorrhage at the site of injury.

Disclosures: C.T. Phinney: None. **R. Elejalde:** None. **A. Awalt:** None. **J.W. Grau:** None.

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Program #/Poster #: PSTR116.17/F13

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Electrical changes in DRG neurons after spinal cord injury and implications for neuropathic pain

Authors: *C. ADAM[1], R. STINGEL[2], M. CHEN[3], J. CRODIAN[5], R. SHI[4];
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Abstract: Spinal cord injury (SCI) affects millions worldwide. Survivors are burdened with conditions including neuropathic pain, paralysis, and catastrophic motor deficits. Pain after SCI is one of the most detrimental side effects, often rated worse than motor deficits by patients, and

arises from overactive pain signaling to the brain. Key cells involved in producing neuropathic pain are neurons in the dorsal root ganglia (DRG), which relay sensory information from the peripheral nervous system to the spinal cord. While the initial damage in SCI mostly affects the spinal cord, within 24 hours after the initial injury, inflammation and reactive species spread to the DRG, chemically damaging DRG neurons and rendering DRG cells hypersensitive to stimulus and hyperactive. This sensitization increases pain signals that contribute substantially to neuropathic pain. However, greater understanding of the sensitization process, especially at acute timepoints after injury, is needed to design effective pain management strategies. The signals relayed by DRG, like those of any neuron, involve ion currents and voltage spikes that that propagate through the cell. Electrical properties of these signals dictate how cells respond to stimulus, and whether the cell is more likely to spontaneously fire a false pain signal. Therefore, to understand mechanisms of pain hypersensitization, and how cells might be primed for hypersensitivity after SCI, it is necessary to quantify how the electrical properties of DRG neurons change in the acute phase after SCI and compare changes throughout the spine. In this study, SCI was administered *via* an impact hammer applied to thoracic vertebra 10 (T10) of male Sprague Dawley® rats. DRG cells were isolated 24 hours after SCI from different portions of the spine. Whole cell patch clamp was used to measure the electrical properties of individual DRG neurons, action potentials, and currents. Cell resistance and capacitance, reversal potentials, and signal shape properties were altered by SCI, but the nature of these alterations differed between spinal levels. These results demonstrate that this combined *in vivo* and *in vitro* platform offers a straightforward means to study pain hypersensitization after SCI at the single-cell level and shed light on how the electrical properties of DRG signals change in the acute phase after SCI. Such quantification offers insight into early changes priming DRG neurons for pain sensitivity and thereby how pain signal propagation and attenuation are altered by SCI, offering new insights into how neuropathic pain arises with implications for pain treatment.

Disclosures: C. Adam: None. **R. Stingel:** None. **M. chen:** None. **J. Crodian:** None. **R. Shi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuro Vigor.

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PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

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Topic: D.05. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation
National Institutes of Health (NIH) grants

Title: Differential Mechanisms of At-Level and Below-Level Neuropathic Pain Following Spinal Cord Injury

Authors: *K. SATO[1], J.-B. TIAN[2], Z. WU[1], Q. YANG[1];
[1]The Univ. of Texas Med. Br., Galveston, TX; [2]Integrative Biol. and pharmacology, UT Hlth. Sci. Ctr. At Houston, Houston, TX

Abstract: Spinal cord injury (SCI)-induced persistent neuropathic pain is one of the most common and debilitating consequences of SCI, with at-level pain being particularly challenging due to the lack of effective clinical treatments compared to below-level pain. Neuropathic pain following SCI involves complex mechanisms, including ion channel dysfunction, excitotoxicity, and altered neuronal plasticity, all of which contribute to the maintenance and exacerbation of pain. We hypothesize that distinct cellular and molecular mechanisms underlie at-level and below-level SCI-induced pain. In this study, we employed unbiased RNA sequencing (RNA-Seq) to identify potential pain-associated genes at the lesion site. Subsequently, we used qRT-PCR to compare the expression levels of these pain-associated genes in the below-level (L4-L5) spinal cord and corresponding dorsal root ganglia (DRG). Our findings revealed a significant decrease in the expression of pain-associated genes at the lesion site, whereas their expression remained relatively unchanged in the below-level spinal cord and DRG (L4-L5). These genes include glutamatergic receptors, opioid receptors, and ion channels. Our results provide novel insights into the molecular mechanisms underlying SCI-induced neuropathic pain and highlight potential therapeutic targets, particularly for managing at-level SCI pain.

Disclosures: K. Sato: None. **J. Tian:** None. **Z. Wu:** None. **Q. Yang:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

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Program #/Poster #: PSTR116.19/F15

Topic: D.05. Spinal Cord Injury and Plasticity

Support: JP24ym0126118
JP24bm1223008

Title: Clinical-grade human iPSC-derived neural stem/progenitor cell transplantation promotes functional recovery in chronic cervical spinal cord injury with in vitro and in vivo transcriptomic profiling

Authors: *R. OGAKI[1], N. NAGOSHI[2], M. SHINOZAKI[4], J. KOHYAMA[5], H. OKANO[3], M. NAKAMURA[6];
[1]Dept. of Orthopaedic Surgery, Keio Univ. Sch. of Med., Shinjuku-ku, Japan; [2]Dept. of Orthopaedic Surgery, Keio Univ. Sch. of Med., Tokyo, Japan; [3]Keio Univ. Sch. of Med., Kanagawa, Japan; [4]Dept. of Physiol., Keio University, Regenerative Med. Res. Ctr., Kawasaki-shi, Kanagawa, Japan; [5]Dept. of Sch. of Human Sci., Waseda Univ., Tokyo, Japan; [6]Keio Univ., Tokyo, Japan

Abstract: [Introduction]Approximately 95% of spinal cord injury (SCI) patients are in the chronic phase, where neural regeneration is severely hindered by intramedullary scarring and cavitation. Additionally, over 60% of SCIs occur in the cervical region. In this study, we investigated the therapeutic potential of clinical-grade human iPSC-derived neural stem/progenitor cell (hiPSC-NS/PC) in chronic cervical SCI.**[Methods]**We used clinical-grade hiPSC-NS/PC derived from HLA-homozygous peripheral blood iPSC with a high propensity for glial differentiation. Single-cell RNA sequencing was performed immediately after thawing and at day 28 of terminal differentiation in vitro. For in vivo studies, we transplanted hiPSC-NS/PC into the lesion site of immunodeficient rats with chronic cervical contusive SCI at 6 weeks post-injury. The control group received PBS injections. Motor evoked potentials (MEPs), the Irvine, Beatties, and Bresnahan test, one-handed grip strength test, horizontal ladder test, and kinematic analysis of reaching behavior were conducted for functional assessments. Diphtheria toxin (DT) was used for selective ablation of grafted cells. Histological assessments included neural tracing with biotinylated dextran amine, glycoprotein-deleted rabies virus, and wheat germ agglutinin, along with in vivo single-nucleus RNA sequencing at 12 weeks post-transplantation.**[Results]**Twelve weeks after transplantation, hiPSC-NS/PC exhibited robust engraftment and migration, differentiating into all three neural lineages, with abundant glial cells. The grafted cells displayed spinal cord- and ventral-specific regional identity and differentiated into functionally relevant subtypes, including V2a interneurons. Tracing studies and electron microscopy revealed direct synaptic connections between host corticospinal tract (CST) axons and grafted cells, as well as between grafted cells and host motor neurons. Graft-derived oligodendrocytes contributed to remyelination of host axons. MEPs showed significantly increased amplitudes and shortened latencies, while behavioral tests demonstrated significant functional recovery. Selective ablation of grafted hiPSC-NS/PC by DT resulted in significant functional decline, suggesting a direct contribution of the transplanted cells to functional improvement.**[Conclusion]**Clinical-grade hiPSC-NS/PC engrafted, integrated, and differentiated appropriately within the chronic cervical SCI environment, forming direct functional synaptic connections with host motor circuits, including the CST, thereby contributing to electrophysiological and behavioral recovery.

Disclosures: R. Ogaki: None. **N. Nagoshi:** None. **M. Shinozaki:** None. **J. Kohyama:** None. **H. Okano:** None. **M. Nakamura:** None.

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Topic: D.05. Spinal Cord Injury and Plasticity

Support: USAMRAA HT9425-25-1-0376

Title: Activated fibroblasts by IFNGR1 exaggerates the histopathology and functional deficits after spinal cord injury

Authors: Y. ZHENG[1], H. XUE[1], Y. LIU[3], H. ZHOU[4], X. XIA[2], ***Q. L. CAO**[5];
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[4]Neurol., Florida Intl. Univ., Port St Lucie, FL; [5]Florida Intl. Univ., Port St. Lucie,, FL

Abstract: Following traumatic spinal cord injury (SCI), a fibrotic scar forms in the injury core, representing a major physical and chemical barrier to neural regeneration and functional recovery. However, the molecular mechanisms regulating fibrotic scar formation remain largely unknown, particularly its role in SCI pathophysiology during the acute phase. In this study, we first genetically tracked fibrotic scar formation after a clinically relevant C5 contusion injury using an inducible platelet-derived growth factor receptor β (PDGFRβ+) reporter mouse line. We then examined the role of interferon-gamma (IFN-γ) signaling in fibrotic scarring and its impact on anatomical and functional outcomes following SCI using the inducible conditional knockout (cKO) mice, in which interferon-gamma receptor 1 (IFNGR1) is deleted in PDGFRβ+ cells after tamoxifen administration. Our results showed that tamoxifen-induced tdTomato (tdT) expression in PDGFRβ+ reporter mice labeled both fibroblasts and pericytes in the uninjured spinal cord. Genetically labeled fibroblasts were activated at the injury border by 3 days post-injury (dpi), migrated into the injury core and proliferated by 7 dpi, and persisted in the non-neural injury core from 14 dpi onward. IFNGR1 expression was upregulated in activated fibroblasts near the injury center starting at 3 dpi. Furthermore, IFNGR1 cKO in PDGFRβ+ cells significantly reduced fibroblast proliferation, total fibroblast numbers, and the deposition of fibronectin, collagens, and chondroitin sulfate proteoglycans (CSPGs), thereby limiting fibrotic scar formation at 7 dpi. Notably, reduced fibrotic scarring in IFNGR1 cKO mice was associated with decreased blood-spinal cord barrier (BSCB) leakage, neuroinflammation, and injury size. Importantly, IFNGR1 cKO also led to reduced fibrotic scarring and improved anatomical outcomes at 56 dpi, the chronic phase of SCI. Moreover, forelimb functional recovery was significantly improved in IFNGR1 cKO mice compared to controls from 7 to 56 dpi. These findings indicate that IFNGR1 signaling plays a crucial role in regulating fibrotic scar formation and suggest that targeting this pathway could be a novel therapeutic strategy to mitigate fibrotic scarring and improve anatomical and functional recovery following SCI.

Disclosures: Y. Zheng: None. **H. Xue:** None. **Y. Liu:** None. **H. Zhou:** None. **X. Xia:** None. **Q.L. Cao:** None.

Poster

PSTR116: Spinal Cord Injury: Molecular and Cellular Mechanisms

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Topic: D.05. Spinal Cord Injury and Plasticity

Support: DOH01-C38330GG
DOH01-C39068GG

Title: Plexin-b1 safeguards agility of astrocyte processes and glial alignment to facilitate wound corralling and axon pathfinding after spinal cord injury

Authors: ***H. NI**[1], M. ESTILL[2], D. HALAWANI[3], R. H. FRIEDEL[4], H. ZOU[2];
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Abstract: Spatial organization of glial cells is instrumental for neural repair after CNS injury. In response to stimuli, reactive astrocytes extend hypertrophied processes to corral the wound and confine debris and inflammatory cells in lesion core. How they protect the long arborized processes from physical damage is unclear. It is also not understood how reactive astrocytes steer clear of colliding cells and build a glial bridge to guide axon pathfinding across lesion site after spinal cord injury (SCI). Here, we unveiled a previously unappreciated role of guidance receptor Plexin-B1 in conferring plasticity to astrocytic processes, which is crucial for safeguarding membrane integrity and astrocyte alignment. Plexin-B1 ablation resulted in shedding of astrocytic processes, detected by live cell imaging with fluorescent probes. Sluggish extension and withdrawal of astrocyte processes in the absence of Plexin-B1 also compromised contact-dependent avoidance, leading to misaligned astrocytes and misguided axons in vitro and in vivo. Mice with conditional deletion of Plexin-B1 in astrocytes fared worse in axonal regeneration and functional recovery after SCI, with disorganzied glial barrier, enlarged lesion, inflammatory spillover, and dysregulated activation profiles and signaling communication between injury-activated astrocytes and microglia. Taken together, the agility and membrane integrity of astrocyte processes conferred by Plexin-B1 ensure proper astroglial reactivity and spatial alignment to facilitate neural repair in response to SCI.

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Program #/Poster #: PSTR116.22/G2

Topic: F.04. Voluntary Movements

Support: NIH Grant R01NS136711
New York State Department of Health Spinal Cord Injury Research Board C39067GM

Title: Ephrin signaling limits axon remodeling after corticospinal tract injury

Authors: ***N. SERRADJ**[1], F. MARINO[2], R. GARN[3], R. TAYLOR[4], C. SIPPER[2], A. M. SLOAN[5], E. R. HOLLIS[2];

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Abstract: The corticospinal tract (CST) is the principal pathway mediating voluntary movements in humans, and therefore a critical target for reparative strategies for neural injury and disease. Ephrin signaling shapes the developing corticospinal tract, preventing aberrant projections to the superficial dorsal horn and midline crossing that would otherwise drive mirrored limb movements (Serradj et al., 2014). As the spinal cord completes post-natal development, ephrinB3 expression expands throughout much of the gray and white matter (Omoto et al., 2011). This expression persists into adulthood, and complete knockout models have implicated ephrinB3-EphA4 signaling in restricted axonal growth after SCI (Goldshmit et al., 2004; Duffy et al., 2012); however, the axon guidance defects exhibited in constitutive *ephrinB3* or *EphA4* knockout mice complicate the interpretation of these results and prevent the assessment of corticospinal function. Using conditional deletion of *EphA4* from adult motor cortex (right side), we have found enhanced corticospinal axon collateral growth after contralateral corticospinal injury at the medullary pyramids (left pyramidotomy). Mice with *EphA4* deletion exhibited greater recovery of right forelimb function on the corticospinal-dependent, precision isometric pull task. However, after second ipsilateral pyramidotomy (right pyramid) to disrupt all corticospinal connections, improved performance in *EphA4* deleted mice persisted, implicating a role for supraspinal remodeling. Using Cre-dependent diphtheria-mediated ablation of red nucleus neurons, we found that functional recovery was dependent on rubrospinal projections. Our data provide new insight into how circuit plasticity throughout the descending motor axis can support the recovery of precise forelimb control and provide a target for therapeutical intervention after central nervous system injury and disease.

Disclosures: N. Serradj: None. **F. Marino:** None. **R. Garn:** None. **R. Taylor:** None. **C. Sipper:** None. **A.M. Sloan:** None. **E.R. Hollis:** None.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.01/G3

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Contract 75N95024D00038

Title: In vivo PK, side effect profile, and analgesic efficacy of clinically used compounds in male and female rats demonstrating the established approach of the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP) to profile potential novel analgesics.

Authors: E. DUGAN[1], B. STANFIELD[2], M. URBAN[1], D. P. BUDAC[3], C. CONRAD[4], V. BRINGS[5], S. A. WOLLER[6], S. IYENGAR[7], M. A. VARNEY[8], *E. LEAHY[8], **T. HANANIA**[1]; [1]Behavioral Pharmacol., [2]PsychoGenics, Inc., Paramus, NJ; [3]PsychoGenics Inc., Paramus, NJ;

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Abstract: In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), we evaluated oxycodone and sumatriptan through the established tiered approach used to profile potential novel analgesics. First, pharmacokinetic (PK) studies were conducted to guide dosing, route of administration, and to determine the time course, supporting subsequent efficacy studies. Adult male (n=7) and female (n=7) Sprague Dawley rats were used in the PK studies for each arm. Next, the modified Irwin (n=4 male and 4 female rats) and rotarod tests (n=10 male and 10 female rats) were conducted to evaluate potential neurologic, physiologic, and motor effects that may impact outcome measures in the pain models. Following side effect profile assessment, analgesic efficacy was evaluated in the plantar incision and L5/L6 spinal nerve ligation (SNL) models. For both models 10 male and 10 female rats were used in each treatment arm. The rat plantar incision model is an established model of acute post-operative pain induced by incision of the skin and the plantaris muscle (Brennan et al. 1996). The model is characterized by transient hind paw tactile allodynia and spontaneous guarding behaviors. SNL is a model of peripheral neuropathic pain resulting from chronic nerve compression in which tactile and cold allodynia are produced (Kim and Chung, 1992). All experiments were conducted in a blinded manner. Power analysis was used to determine the group sizes for the various assays. Following pharmacokinetic study recommendations, side effect profile and efficacy studies showed that rats administered oxycodone displayed reduced locomotor activity, sedation, exophthalmos, and increased pupil size in a dose-dependent manner as well as reductions in rotarod performance. Oxycodone improved mechanical allodynia and spontaneous guarding behaviors in the plantar incision model and mechanical and cold allodynia in the SNL model. In side effect profile studies, sumatriptan did not show observable behaviors or impairments on rotarod performance. In efficacy studies, sumatriptan provided minimal improvements on acute mechanical allodynia in the plantar incision and SNL models but did not show efficacy in guarding behavior in the plantar incision model or cold allodynia in the SNL model. The results of these studies of clinically used compounds within the PSPP program demonstrate the validation of the models and endpoints described and highlight the goal of providing a robust platform to accelerate the discovery and preclinical development of non-opioid, non-addictive treatments for pain

Disclosures: E. Dugan: A. Employment/Salary (full or part-time): PsychoGenics Inc. **B. Stanfield:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **M. Urban:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **D.P. Budac:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **C. Conrad:** A. Employment/Salary (full or part-time): NIH/NINDS. **V. Brings:** A. Employment/Salary (full or part-time): NIH/NINDS. **S.A. Woller:** A. Employment/Salary (full or part-time): NIH/NINDS. **S. Iyengar:** A. Employment/Salary (full or part-time): NIH/NINDS. **M.A. Varney:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **E. Leahy:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **T. Hanania:** A. Employment/Salary (full or part-time): PsychoGenics Inc.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.02/G4

Topic: E.01. Somatosensation – Pain and Itch

Support: Grant #2024/03983-0, São Paulo Research Foundation - Brazil (FAPESP)
Finance Code 001, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brazil (CAPES)

Title: Social Psychogenic Stress: a novel neurobehavioral paradigm for studying persistent pain and anxiety, lacking depressive-like behavior

Authors: *A. S. MACHADO, A. VAN LEEUWEN, C. HERRERA TAMBELI, C. PARADA; Dept. of Functional and Structural Biol., State Univ. of Campinas (UNICAMP), Campinas, Brazil

Abstract: Background and Aims: Chronic stress is a key factor in the development and maintenance of chronic pain conditions where psychogenic factors are prominent. Social stress paradigms, such as Social Defeat Stress (SDS), are widely used to study stress-induced behavioral changes. Here, we present an adaptation of the SDS, termed Social Psychogenic Stress (SPS), specifically designed to amplify psychological threat while minimizing physical aggression. This refinement emphasizes the psychogenic components of chronic social stress, offering a novel preclinical tool to investigate mechanisms underlying stress-induced pain chronification and anxiety. **Methods:** Male C57BL/6J mice (targets; n = 15) were subjected to a 10-day SPS protocol conducted in the home cages of different unfamiliar adult SWISS mice (aggressors; n = 15), previously screened for high territorial and aggressive behavior. Each day, target mice were confined for 2 hours inside an adapted mouse trap placed within the home cage of a different SWISS aggressor, allowing naturalistic threatening behaviors with minimal physical contact. Subsequently, targets remained in an adapted hamster cage within the same aggressor's cage for 24 hours, maintaining continuous psychosocial stress. Controls (n=12) were kept in similar cages without aggressor exposure. Mechanical hypersensitivity was assessed via the von Frey test at baseline, and on days 2 and 14 post-SPS. Depressive-like behavior was evaluated through a social interaction test on days 1 and 13 post-SPS. Anxiety-like behavior was measured using the open field test on days 3 and 15 post-SPS. Data were analyzed using two-way ANOVA followed by Sidak's multiple comparison test comparing SPS vs control groups. Protocol approved by the Ethics Committee for Animal Research of the University of Campinas (6407-1/2024). **Results:** SPS induced significant and persistent mechanical hypersensitivity, with reduced paw withdrawal thresholds at both 2 and 14 days post-stress ($p<0.0001$; $p=0.0001$). SPS mice also exhibited anxiety-like behaviors: reduced locomotor activity (distance, velocity, and time moving - all $p<0.03$) on day 3, and decreased center time on day 15 ($p=0.0140$). Notably, SPS did not induce depressive-like social avoidance at either time point. **Conclusion:** The SPS paradigm is a valuable platform for investigating the neurobehavioral mechanisms linking chronic psychosocial stress to persistent pain and anxiety, without inducing depressive-like behavior. Ongoing studies aim to elucidate the roles of endocannabinoid and limbic dopaminergic systems in these processes.

Disclosures: A.S. Machado: None. **A. van Leeuwen:** None. **C. Herrera Tambeli:** None. **C. Parada:** None.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.03/G5

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH contract 75N95024D00038

Title: Development of an In Vivo Electrophysiology Assay for Identifying Novel Analgesics by Evaluating Wide Dynamic Range (WDR) Neuron Activity in the Rat Spinal Nerve Ligation (SNL) Model

Authors: S. ZHONG[1], H. LI[2], D. P. BUDAC[3], M. A. VARNEY[4], S. A. WOLLER[5], S. IYENGAR[6], C. CONRAD[7], V. BRINGS[8], ***A. GHAVAMI**[2];
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Abstract: In the development of new pain therapies, the recording of activity in wide dynamic range (WDR) neurons of the dorsal horn serves as a powerful technique for investigating the effects of analgesic drugs on pain-induced hyperexcitability. This method provides a direct measure of neuronal activity, independent of confounding factors such as sedation or alterations in locomotor behavior. Therefore, it offers a complementary and valuable approach for elucidating pain mechanisms and assessing the pharmacological efficacy of analgesics. The objective of this study was to assess the effects of the clinically effective analgesic gabapentin (100mg/kg, PO) on both spontaneous hyperexcitability and Von Frey-evoked (V.F) responses of WDR neurons in the L5 and L6 spinal nerve ligation (SNL) rat model of neuropathic pain. A total of 56 Sprague Dawley rats (28 per sex) were obtained from Envigo, weighting 200-250 each. Neuropathic pain was induced through tight ligation of the L5 and L6 spinal nerves. Fourteen days after surgery, rats with consistent ipsilateral paw withdrawal thresholds (PWTs) of ≤3.0 g in V.F filament testing were selected for electrophysiological recordings. Under urethane anesthesia, a limited laminectomy exposed the L4-L6 segments of the spinal cord for WDR neuron recording. Gabapentin levels in plasma and brain tissue were measured to correlate recording with drug exposure. The electrophysiological data produced by this *in vivo* assay clearly demonstrated the efficacy of gabapentin in the SNL pain model when compared to saline group (Control). Gabapentin attenuated the increase in spontaneous activities of WDR neurons induced by spinal SNL surgery in both sexes. Gabapentin also significantly decreased the WDR neuronal responses evoked by V.F and brush stimulation. Gabapentin plasma concentration levels at various time points during recording, as well as in the brains after recording, confirmed

that gabapentin reached optimal levels. These results demonstrate that gabapentin significantly attenuated spontaneous neuronal hyperactivity and reduced WDR neuron responses to both V.F and brush stimulation. These findings validate the use of this electrophysiological approach as a robust screening tool for evaluating the efficacy of novel analgesic compounds.

Disclosures: **S. Zhong:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **H. Li:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **D.P. Budac:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **M.A. Varney:** A. Employment/Salary (full or part-time): PsychoGenics Inc. **S.A. Woller:** A. Employment/Salary (full or part-time): NIH/NINDS. **S. Iyengar:** A. Employment/Salary (full or part-time): NIH/NINDS. **C. Conrad:** A. Employment/Salary (full or part-time): NIH/NINDS. **V. Brings:** A. Employment/Salary (full or part-time): NIH/NINDS. **A. Ghavami:** A. Employment/Salary (full or part-time): PsychoGenics Inc.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.04/G6

Topic: E.01. Somatosensation – Pain and Itch

Title: Development and Validation of a Topical Capsaicin-Induced Thermal and Cold Allodynia Model in Rhesus Monkeys with Oral Gabapentin Intervention

Authors: C. DUAN[1], J. WEI[1], M. CHEN[1], D. LIU[1], G. GAO[2], S. LI[3], X. FENG[4], *K. ZHANG[3]; [1]Anhui Deze Preclinical Res. Labs. Inc., Xuancheng, Anhui, China; [2]Anhui Deze Lab. Animal (NHP) Labs. Inc., Xuancheng, Anhi, China; [3]New Vision World LLC, Aliso Viejo, CA; [4]Changchun Zhuoyi Biol. Co. Ltd., Changchun, China

Abstract: Preclinical models using non-human primates (NHPs) offer valuable translational insights for pain research. In this study, we developed and validated a conscious rhesus monkey model to assess tail-withdrawal reflexes in response to thermal and cold stimuli and explored pharmacologic modulation using oral gabapentin and potential intrathecal drug delivery. Tail reflexes were measured in awake rhesus macaques restrained in a primate chair. Tails were immersed in water at three temperatures: non-noxious cold (2 °C), non-noxious warm (42 °C), and acutely noxious heat (55 °C). Tail-withdrawal latency was recorded under each condition to establish baseline sensitivity. A maximum latency of 20 seconds was assigned if no withdrawal occurred within that time. A capsaicin-based model was then used to induce both cold and thermal allodynia. For pharmacologic intervention, gabapentin was administered orally, and its analgesic effects were evaluated in both the 55 °C noxious heat condition and the capsaicin-induced allodynia models at 42 °C. Cerebrospinal fluid (CSF) was also collected via transdermal lumbar puncture to facilitate future intrathecal drug administration. A novel analgesic compound may be tested via this route. Prior to capsaicin application, tails remained immersed for the full 20 seconds in the non-noxious conditions. Withdrawal latencies were significantly reduced to <5

seconds in the noxious condition (55 °C), or following induction of allodynia in 42 °C conditions. Oral gabapentin temporarily reversed allodynia, significantly increasing withdrawal latencies in both noxious and sensitized non-noxious settings. This study establishes a robust and reproducible conscious rhesus model for evaluating both thermal and cold allodynia, offering a valuable platform for testing analgesic therapies. Capsaicin sensitization effectively models neuropathic pain states, while systemic and intrathecal drug delivery routes enable translationally relevant pain modulation studies. This approach may accelerate the development of targeted treatments for neuropathic and inflammatory pain conditions.

Disclosures: **C. Duan:** A. Employment/Salary (full or part-time): Anhui Deze Preclinical Research Laboratories Inc. **J. Wei:** A. Employment/Salary (full or part-time): Anhui Deze Preclinical Research Laboratories Inc. **M. Chen:** A. Employment/Salary (full or part-time): Anhui Deze Preclinical Research Laboratories Inc. **D. Liu:** A. Employment/Salary (full or part-time): Anhui Deze Preclinical Research Laboratories Inc. **G. Gao:** A. Employment/Salary (full or part-time): Anhui Deze Lab Animal (NHP) Laboratories Inc.. **S. Li:** None. **X. Feng:** None. **K. Zhang:** A. Employment/Salary (full or part-time): New Vision World LLC.

Poster

PSTR117: Preclinical Pain Models and Measurements

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Program #/Poster #: PSTR117.05/G7

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH/NINDS R61NS123758
NIH/NINDS R33NS123758

Title: A multivariate index to quantify fibromyalgia-like phenotypes in rodents: utility for drug screening and model validation

Authors: *L. F. FERRARI, A. WILKINSON, N. TAYLOR;
Anesthesiol., Univ. of Utah, Salt Lake City, UT

Abstract: Fibromyalgia syndrome (FMS) is a chronic condition marked by widespread pain, fatigue, and cognitive impairment. Despite its prevalence and impact, current FDA-approved treatments offer limited relief, and translational gaps persist between preclinical and clinical findings. A key limitation is the lack of animal models and analytical tools that capture the FMS's multidimensional nature. To address this, we developed a statistical tool, the Fibromyalgia Analog Model (FAM) index, that integrates core behavioral features of FMS to validate models and evaluate drug efficacy in a manner aligned with human clinical outcomes. The index combines six behavioral domains, nociceptive thresholds (on hind paws, gastrocnemius muscles, face), depression-, anxiety-, and fatigue-like behaviors (detected by forced swim test, elevated zero maze, and home cage monitoring, respectively), into a single value (F). Scores (z), derived from the behavior results, are applied to the equation F =

$0.410xRZ_{paw}+0.618xRZ_{mus}+0.429xRZ_{VF}+0.455xZ_{FST}+0.183xRZ_{EZM}+0.160xRZ_{HCM}$, where F is the quantification of FMS-like phenotypes observed in a population**.** "Z" and "RZ" represent standardized and reversed z-scores from each domain. The index was validated in reserpine-treated Sprague Dawley (SD) rats, a well-characterized FMS model, then applied to Dahl salt-sensitive (SS) rats, a strain exhibiting inherited FMS-like traits. To assess predictive validity, we tested drugs with known or proposed clinical relevance on SS rats: Pregabalin and Milnacipran (FDA-approved for FMS), Indomethacin (NSAID), DAMGO (opioid agonist), and Metformin (a repurposing candidate). Dosing schedules reflected their pharmacologic profiles, with daily treatments for agents with cumulative effect and acute testing for fast-acting drugs. Behavioral assays, conducted post-treatments, provided data to calculate F-scores, computed relative to control SS and reserpine-treated SD rats. Pregabalin and Metformin significantly reduced SS F-scores ($p<0.0001$), indicating superior efficacy in relieving FMS-like behaviors, lowering scores below reserpine values. Milnacipran had moderate effect, and Indomethacin transiently produced analgesia ($p=0.0239$). DAMGO induced dose-dependent hyperalgesia, consistent with its clinical limitations.Our results establish the index as a translationally relevant tool to evaluate FMS preclinical models and treatments. The SS rat exhibited predictive pharmacological patterns reflective of clinical data. The findings position the FAM index as a powerful platform for advancing FMS research and identify Metformin as a promising therapeutic candidate.

Disclosures: L.F. Ferrari: None. **A. Wilkinson:** None. **N. Taylor:** None.

Poster

PSTR117: Preclinical Pain Models and Measurements

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Program #/Poster #: PSTR117.06/G8

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Contract 75N95024D00038

Title: Pharmacological characterization of reference analgesics in the rat paclitaxel and oxaliplatin models of chemotherapy-induced peripheral neuropathy

Authors: *M. URBAN[1], Y. ZHANG[1], M. CIKLIC[1], K. KROZSER[1], K. BUBAN[1], E. DUGAN[1], C. CONRAD[2], V. BRINGS[2], S. A. WOLLER[2], S. IYENGAR[2], T. HANANIA[1];
[1]PsychoGenics, Inc., Paramus, NJ; [2]NINDS/NIH, Rockville, MD

Abstract: In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), we evaluated a variety of reference analgesic compounds in the rat paclitaxel and oxaliplatin models of chemotherapy-induced peripheral neuropathy (CIPN) to characterize the pharmacology associated with these models. Adult male and female Sprague Dawley rats (n=10, each sex) were used in these studies. For the paclitaxel model studies, paclitaxel (4 mg/kg, IP) was injected on alternate days (Day 1, 3, 5, 7) and effects of reference analgesics on hind paw cold and mechanical allodynia were evaluated during Weeks 5 and 6, respectively. For the

oxaliplatin model studies, oxaliplatin (3 mg/kg, IV) was injected 2 days per week for a period of 4 weeks and effects of reference analgesics on hind paw cold and mechanical allodynia were evaluated during Weeks 6 and 7, respectively. Hind paw mechanical allodynia was determined with von Frey filaments using the "up-down" testing method, and hind paw cold allodynia was determined using the acetone test. In the paclitaxel model, hind paw cold and mechanical allodynia were maximal by Weeks 5-6, whereas hind paw cold and mechanical allodynia were maximal in the oxaliplatin model by Weeks 6-7. In the paclitaxel and oxaliplatin models, cold and mechanical allodynia were dose-dependently inhibited following administration of morphine sulfate (0.3 - 3 mg/kg, SC), gabapentin (10 - 100 mg/kg, PO), and pregabalin (10 - 60 mg/kg, PO). In the oxaliplatin model, administration of duloxetine (60 mg/kg, PO) inhibited cold, but not mechanical, allodynia, whereas duloxetine had no effect on cold or mechanical allodynia in the paclitaxel model. Administration of celecoxib (3 - 30 mg/kg, PO) or diazepam (1 - 10 mg/kg, PO) had no effect on cold or mechanical allodynia in the paclitaxel or oxaliplatin model. Pharmacological characterization of the paclitaxel and oxaliplatin CIPN models further highlights efforts within the NIH HEAL Initiative's PSPP program to validate clinically relevant models to be incorporated into evaluating novel assets towards accelerating the development of novel non-opioid, non-addictive analgesics.

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Poster

PSTR117: Preclinical Pain Models and Measurements

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Program #/Poster #: PSTR117.07/G9

Topic: E.01. Somatosensation – Pain and Itch

Support: This project has been funded in whole or in part with Federal funds from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Services, under Contract No. 75N95024D00038

Title: Profiling Pain Therapeutics Within the NIH Preclinical Screening Platform for Pain Program

Authors: S. A. WOLLER[1], C. CONRAD[2], S. SHARMA[2], *S. IYENGAR[3];
[1]DTR, NIH/NINDS, Rockville, MD; [2]DTR, [3]NINDS/NIH, Rockville, MD

Abstract: The Preclinical Screening Platform for Pain (PSPP) program, within the NIH HEAL Initiative, was developed to accelerate the discovery and development of potential non-opioid, non-addictive pain therapies. Evaluation within the PSPP workflow includes in vitro assessment of safety, abuse liability, and protein binding, and in vivo assessment of PK, side effect profile,

efficacy in pain-related models, and/or abuse liability. To understand profiles of novel candidate therapeutics, 4 classes of clinically used drugs were evaluated in the workflow: opioids (morphine 0.3, 1, 3, 6, 10 mg/kg SC), gabapentinoids (gabapentin 10, 30, 60, 100, 300 mg/kg PO), SNRIs (duloxetine 3, 10, 30, 60, 100 mg/kg PO), and NSAIDs (celecoxib 3, 10, 30, 100 mg/kg PO). All in vivo studies were conducted in a blinded manner using male and female Sprague Dawley rats (Envigo), in fully powered groups, and included vehicle and positive control groups. Pre-determined inclusion criteria were applied for each endpoint assessed. To create a profile, efficacy data were transformed into a percent efficacy and plotted on a radar chart so efficacy in 5 models (plantar incision, L5/L6 SNL, MIA, paclitaxel CIPN, and oxaliplatin CIPN) and 2 endpoints per model (mechanical allodynia behavior, cold allodynia behavior, guarding behavior, or dynamic weight bearing) could be visualized together. Transformed data of the most effective dose at the most effective time, in both sexes, indicated that morphine produced 60-100% efficacy in all models and endpoints. Gabapentin produced 4-83% efficacy, with greatest efficacy observed in mechanical allodynia behavior across models. Celecoxib produced 0-58% efficacy with the greatest efficacy observed in the MIA model of osteoarthritis. Finally, duloxetine produced 0-78% efficacy with the greatest efficacy in the dynamic weight bearing endpoint in the MIA model, the mechanical allodynia behavior endpoint in the plantar incision model, and the cold allodynia behavior endpoint in the L5/L6 SNL model. Together these data indicate that each class of clinically-used drug has a unique profile when evaluated in preclinical models. Profiling clinically-used drugs will aid in the interpretation of data for candidate therapeutics evaluated in the PSPP program.

Disclosures: S.A. Woller: None. **C. Conrad:** None. **S. Sharma:** None. **S. Iyengar:** A. Employment/Salary (full or part-time): NINDS/NIH. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Retiree, Eli Lilly and Company.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.08/G10

Topic: E.01. Somatosensation – Pain and Itch

Title: Neuron-as-a-sensor : a detailed method to map CIPN

Authors: *B. MAISONNEUVE;
NETRI, Lyon, France

Abstract: Chemotherapy-Induced Peripheral Neuropathy (CIPN) remains a prevalent and debilitating side effect of cancer treatment, with limited preventive or therapeutic options. The FDA’s recent draft guidance, Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy: Developing Drug and Biological Products in Oncology, highlights a pressing need for more predictive and translatable preclinical models to address this clinical gap. In response,

NETRI has applied it's Neuron-as-a-Sensor (NaaS) approach - an integrated, multimodal platform designed to recapitulate the peripheral nervous system (PNS) environment - to the assessment of CIPN mechanisms.
The NaaS platform combines NETRI's compartmentalized microelectrode array (MEA) devices, human iPSC-derived neuronal cells, and an experimental methodology leveraging electrophysiological recordings (via Axion's Maestro platform) and a data analysis pipeline using proprietary software (UpLink and DataLink). This system has been used with a panel of reference compounds selected to span key mechanistic pathways implicated in CIPN, with the aim to describe their effect with a n-dimensional metrics matrices.
We first characterized a sensory neuron/astrocyte co-culture as a PNS sensing unit and explored the added value of incorporating a central nervous system (CNS) component via connected dorsal horn neurons. Microfluidic compartmentalization is employed to replicate physiological neuronal architecture and maintain functional segregation.
Next, we describe a standardized multistep experimental protocol designed to elicit and measure system responses to time and CIPN-targeted stimuli - thermal (hot and cold), inflammatory,...) - in order to capture key phenotypic features of CIPN. Finally, we detail our n-dimensional data analysis framework that integrates compartmentalization metrics to distinguish discreet CIPN states.
Together, these innovations position Neuron-as-a-Sensor as a next-generation preclinical assay for early-stage evaluation of chemotherapy agents, offering enhanced predictive power and mechanistic insight into CIPN pathophysiology.
Neuron-as-a-Sensor for CIPN represents a carefully streamlined method for assessing novel chemotherapy drugs with early, enhanced predictivity. NaaS positions as an innovative way to phase out the notoriously poor predictors for pain that are animal models. Moreover, the development of this method acts as a blueprint for deploying NaaS into other indications like Vaccine Pain, Dermatology or Food & Safety Neurotoxicity.

Disclosures: B. Maisonneuve: None.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.09/G11

Topic: E.01. Somatosensation – Pain and Itch

Title: Digital Signature Library: using neurons as universal bio-digital sensors

Authors: *A. TOMA;
NETRI, Lyon, France

Abstract: Neurons are processing their inputs through firing or not firing, which can be equated to producing zeros and ones. Since every single organ in the body is innervated, the nervous system can essentially by seen as distributed network of bio-digital sensors. By connecting (and

fluidically isolating) neurons to a target organ, be it other neurons in CNS applications or any organs in PNS applications, we can encode organ states (healthy, diseased, altered⋯) into digital signatures that in turn populate a Digital Library, creating a framework for fingerprinting and ranking effects of screened drug compounds based on the desired functional outcome. In this effort running across multiple studies and indications, using NETRI's DuaLink MEA, DuaLink Shift MEA and Trialink MEA compartmentalized chips in conjunction with Axion's Biosystems electrophysiology platform Maestro, we innervated various targets organs "at a distance" (skin, peripheral nervous system, gut) and recorded their activity in healthy and altered states. Using dedicated NETRI's UpLink software and purpose-made database DataLink, we were able to extract, process and analyze with statistical relevance the sensory neuron digital signatures for each state. By defining digital signatures as a n-dimensional MEA-metric matrix of proportional ratios between a reference state (healthy) and a target state (altered) of multiple replicates, we were able to drastically diminish the impact of individual culture's variability and show the quantification of drug candidate effects on a scale defined by reference compounds. More profoundly, this was done non-destructively on acute or chronic timescales, without the use of imagery or chemical assays. The central notion emerging from this effort is the standardized digitization power that well calibrated fluidically-isolated neuronal cultures bring to organ functional analysis. From assessing the effects of compounds on a disease, a cream on a skin, a nutrient in the gut, or orienting the repositioning of a drug, using neurons-as-biodigital-sensors offer an impactful and agnostic platform solution in a wide variety of applications that extend far beyond neuroscience.

Disclosures: A. Toma: None.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.10/G12

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant DE022129

Title: Spontaneous pain behavior in an undisturbed rodent: analysis of 3D movement

Authors: *M. UMORIN[1], L. NGUYEN[2], P. KRAMER[3];
[1]Biomed. Sci., Texas A&M Univ. Col. of Dent., Dallas, TX; [2]Texas A&M Univ. Col. of Dent., Plano, TX; [3]Texas A&M Univ. Sch. of Dent., Dallas, TX

Abstract: Measuring spontaneous behavior in rodents with orofacial pain has focused primarily on the grimace scale. We hypothesized that other spontaneous behaviors would significantly change in orofacial pain models. Determining spontaneous pain behaviors in undisturbed rodents is a powerful method in pain research and would increase the viability of preclinical studies for drug development. This study is the first to apply 3D modeling to orofacial pain models.Two

kinds of nociception were tested: bilateral Vericella zoster virus (VZV) injection into whisker pad and bilateral ligation of the anterior tendon of masseter (LIG). Animals were recorded for 1-hour-long sessions with 6 cameras. Recordings were made prior to treatment and 7 days after the treatment. Using DeepLabCut and Anipose software, 3D coordinates were obtained for nose, lower jaw, eyes, ears, front and hind paws, base of tail, and the tip of the tail for every frame of the recordings. Calculating the absolute coordinates of the body parts permitted identifying animal posture like rearing and sitting. Activities like face wiping and stretching could be determined based on the distances between the body parts. Our results show that animals treated with VZV wiped their face significantly less but reared significantly more than naïve animals. Rats treated with LIG showed no difference in rearing and face wiping compared to the naïve animals. However, LIG treatment showed increased frequency of shorter distance between head and tip of the tail compared to naïve animals. Also, both LIG and VZV treatments increased asymmetric twisting of the body to the left as manifested by higher frequency of decreased nose-to-left hind paw distance and increased nose-to-right hind paw distance. Thus, quantification of behavior based on the 3D positions of the body parts can serve as a sensitive tool for assessing different kinds of spontaneous nociception in undisturbed rodents.

Disclosures: M. Umorin: None. **L. Nguyen:** None. **P. Kramer:** None.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.11/G13

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH (F31NS134275)
NIH (5T32DA055569-03)
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HHMI

Title: Separating between analgesia and sedation in evoked pain behavior using the automated reproducible mechano-stimulator (ARM).

Authors: *J. BURDGE[1], J. K. THACKRAY[2], I. ABDUS-SABOOR[3], V. E. ABRAIRA[4]; [1]Rutgers Univ., New York, NY; [2]Rutgers Univ., Piscataway, NJ; [3]Biol., Columbia Univ., NEW YORK, NY; [4]Cell Biol. and Neurosci., Rutgers, The State Univ. of New Jersey, warren, NJ

Abstract: To meet the burden posed by chronic pain, researchers have worked to identify potential analgesics using rodent and other animal models, but these have failed to translate into new analgesics for patients. A potential cause of this translational dearth is the outdated

techniques used to measure pain in rodents, which often have limited analysis outputs that confound the effects of analgesia with sedation. This problem is especially prevalent in the common variety of pain assays, high-throughput evoked assays. We have developed the ARM (automated reproducible mechano-stimulator) system, and shown that it eliminates error, bias, and confounds due to the researcher's presence in evoked pain assays. Further development of the device has allowed for the measurement of a range of behavioral features (Burdge, 2025), including both automated measures of mechanical sensitivity (withdrawal latency, mechanical threshold) and more complex measures of the behavioral response (paw max height, velocity, distance traveled, shaking, and guarding). We then validated the device across inflammatory (CFA, carrageenan) and neuropathic pain models (SNI). To separate between analgesia and sedation we will use the ARM system to collect this diverse range of behavioral readouts efficiently, and then use them to fingerprint the effects of various compounds. C57BL/6J mice will have neuropathic pain induced via a spared nerve injury (SNI) surgery. Pain behavior will then be measured using 0.5 g and 1 g stimuli, with baseline SNI pain behavior compared against that shown with a selection of compounds that have previously been shown to decrease SNI mechano-sensitivity and cause varying levels of sedation, including morphine, gabapentin, prgabalin, mexiletine, and a robust Nav 1.8 inhibitor **(**A-803467). Open-field Moseq data will also be collected to compare against readouts of spontaneous pain and locomotion. The effects of each compound on the collected behavioral readouts will then be analyzed to distinguish between compounds with greater or lesser analgesic or sedative effects. This would expand the ARM system's functionality to be the first evoked pain assay capable of making this distinction.

Disclosures: J. Burdge: A. Employment/Salary (full or part-time): Rutgers University, Tactorum Inc (No Salary). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tactorum Inc (stock). **J.K. Thackray:** None. **I. Abdus-Saboor:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tactorum Inc (Stock). **V.E. Abraira:** None.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.12/G14

Topic: E.01. Somatosensation – Pain and Itch

Support: P30DA048742
T32DA007234

Title: Chronic Alcohol Consumption Increases Mechanical and Cold Sensitivity

Authors: *R. SCHORN[1], M. S. RIEDL[4], L. S. STONE[2], A. M. LEE[3], L. VULCHANOVA[1]; [2]Anesthesiol., [3]Pharmacol., [1]Univ. of Minnesota, Minneapolis, MN; [4]Dept Neurosci., Univ. Minnesota, Minneapolis, MN

Abstract: Over one third of people with alcohol use disorder (AUD) report persistent pain, and individuals with chronic pain often drink alcohol to self-medicate symptoms. Despite the high prevalence of chronic pain and alcohol use disorder, little is known about the neural mechanisms underlying this comorbidity. The purpose of this study was to investigate alcohol-induced hypersensitivity (AIH) and explore how chronic alcohol affects pain recovery. We tested the hypothesis that chronic alcohol exposure induces mechanical and cold hypersensitivity and delays resolution of nerve injury-induced hypersensitivity. We previously reported that chronic alcohol exposure, performed using the two-bottle choice chronic intermittent access (CIA) paradigm, produced mechanical AIH after 4-6 weeks of drinking in adult mice. In female mice, cold AIH developed after 4 weeks of drinking, with ongoing analysis of males suggesting no emergence of cold AIH by that time point. In a model of acute inflammatory pain, we have reported that male and female mice undergoing CIA have delayed recovery from capsaicin-induced mechanical hypersensitivity. Looking only at females, we found CIA did not worsen cold hypersensitivity in capsaicin-injected mice. In a model of recovering neuropathic pain via sciatic nerve crush, alcohol-consuming mice exhibited minimal recovery of mechanical thresholds over 3-4 weeks, whereas water-consuming counterparts recovered within this time frame. Ongoing analysis suggests CIA appears to slightly heighten cold sensitivity in both sexes after nerve crush. These findings reveal that chronic voluntary alcohol consumption induces mechanical and cold hypersensitivity and subsequently prolongs the duration of recovery in different pain models. This work was supported by NIH grants P30DA048742 and T32DA007234.

Disclosures: R. Schorn: None. **M.S. Riedl:** None. **L.S. Stone:** None. **A.M. Lee:** None. **L. Vulchanova:** None.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.13/G15

Topic: E.01. Somatosensation – Pain and Itch

Support: NSF NRT Award #2152260

Title: Etiology-specific molecular changes in rodent chronic pain models: a systematic review and analysis

Authors: *Z. D. REYNOLDS;
Neurosci. Grad. Group, UC Davis, Davis, CA

Abstract: Pain is an important biological signal to protect from bodily injury, but chronic pain is a maladaptive disease that extends the experience of pain beyond the initial event. Chronic pain involves sensory, affective, and cognitive symptoms that significantly reduce quality of life and require multimodal treatment. Current therapies include physical and emotional therapy,

analgesics, surgery, and neuromodulation, but these treatments are often applied broadly across chronic pain conditions despite variable efficacy and frequent side effects. Tailoring treatments to different pain etiologies requires a clearer understanding of the structures involved and the molecular changes occurring. To create a cohesive picture of contemporary understandings of pain-related molecular changes, we conducted a systematic review of studies examining genomic, proteomic, and transcriptomic changes in rodent models of chronic pain. Studies were labelled neuropathic or inflammatory according to the type of chronic pain modeled, with individual models separated within these groups. The most predominant chronic pain models were nerve transections, chronic constriction injuries, and inflammation. Inflammatory chronic pain models consistently show modulation of circulating cytokines, with changes being region-specific. Neuropathic chronic pain models suggest a disruption in various receptors and ion channels, leading to changes in excitability that are distinct in both region and neuronal subtype. Changes underlying cognitive deficits like short-term memory are seen across etiologies, with evidence suggesting that changes in plasticity-related components are underlying the deficits. An overall key component across etiologies is a shift in the excitatory/inhibitory balance in sensory regions through changes in ion channels and receptors. Altogether, this systematic review provides evidence that different etiologies of chronic pain induce distinct molecular changes throughout the neuraxis. Future studies of molecular changes involved in chronic pain would benefit from comparing their results across etiologies. Further investigation into the molecular changes involved in the chronification of pain are needed to move therapy towards a proactive rather than reactive stance.

Disclosures: Z.D. Reynolds: None.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.14/G16

Topic: E.01. Somatosensation – Pain and Itch

Title: Generation and characterization of a sensory neuron TrkA knock-out mouse model

Authors: *E. O'NEIL[1], X. CHI[3], W. GUO[1], J. WANG[4], B. L. ADAMS[5], B. LI[2];
[2]Neurosci., [1]Eli Lilly and Co., Indianapolis, IN; [3]Eli Lilly Co., Noblesville, IN, ; [4]Eli-Lilly and company, indianapolis, IN; [5]Global Pain Res. and Develop., Lilly Res. Labs, Indianapolis, IN

Abstract: Generation and characterization of a sensory neuron TrkA knock-out mouse model Estefania O’Neil*, Xian Xuan (Grace) Chi*, Wenhong Guo*, Jun Wang, Benjamin Adams, Baolin Li Pain and Neuronal Health, Neuroscience Discovery, Eli Lilly and Company *: Equal contribution It is known that NGF and it’s high affinity receptor, TrkA, are associated with modulation of nociception in adult humans and animals (Mantyh et al.)(Chang DS, et al.).TrkA is expressed in various tissues, such as peripheral/central nervous tissues, immune tissues, and skin tissue. Global constitutive TrkA knock-out (KO) mice don’t survive beyond 1 month

(Smeyne et al), likely due to severe sensory and sympathetic toxicity. A previously generated tamoxifen induced transgenic mouse model (O'Sullivan et al) suggested sensory neuron-specific deletion of TrkA could be achieved but did not occur at 100% of sensory neurons. In order to achieve TrkA KO in 100% of DRG sensory neurons, we generated a CRISPR/Cas9 mediated loxP flanked TrkA mouse, then crossed it with a Pirt-Cre mouse in which the Cre was expressed specifically in the sensory neurons. The sensory neuron TrkA knock-out mouse line was confirmed by 100% loss of TrkA mRNA and protein in sensory neurons in the DRG. Different from the constitutive TrkA KO mice, our Pirt-cre/TrkA KO mice are viable into adulthood with normal fertility. IHC and histological analysis suggest that sensory neuron, sciatic nerve, skin, and knee joint developed normally in our sensory neuron TrkA KO mice. The sensory neuron TrkA KO reduced sensitivity of mechanical stimulation and abolished NGF induced thermos sensitivity significantly in our Pirt-Cre/TrkA KO mice. This model affords the potential to further explore the NGF/TrkA axis. **References:** Mantyh PW *et al*. *Anesthesiology*. 2011;**115**(1):189-204. Chang DS et *al. J Pain Res*. 2016;**9**:373-383. Richard J Smeyne et al., Nature, 1994; 368:246-249. InSug O-Sullivan et al., Int. J. Mol. Sci. 2022, 23, 12076 This study was supported 100% by Lilly. None of the authors has a conflict of interest.

Disclosures: E. O'Neil: None. **W. Guo:** None. **J. Wang:** None. **B.L. Adams:** None. **B. Li:** None.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.15/H1

Topic: E.01. Somatosensation – Pain and Itch

Title: Establishment, characterization, and validation of an in vitro sensory neuroimmune model for pain drug discovery

Authors: *A. DOMANSKYI, I. PARKKINEN, R. LUND, E. POLLARI, C. STENFORS, M. MORALES;
Orion Pharma, Orion Corp., Turku, Finland

Abstract: Modeling chronic pain *in vitro* is pivotal for understanding pain mechanisms and advancing analgesic drug discovery. There is a high need for physiologically relevant pain models to identify safe and effective analgesics. To address this, we aimed to model chronic inflammatory pain *in vitro*. We have established and characterized *ex vivo* cultures of rat dorsal root ganglion (DRG) sensory neurons and their co-culture with rat bone marrow-derived macrophages. These models were utilized to study the effects of selected cytokines on the spontaneous activity of sensory neurons, assessed by using chronic calcium imaging and electrophysiology on a multielectrode array system (MEA). Our findings indicate that a single dose of IL-1β induces a long-lasting effect, up to 96 hours, by increasing spontaneous activity in rat sensory neurons, as measured by calcium imaging and MEA. This effect was validated

pharmacologically by blocking IL-1β signaling, testing multiple other compounds activating or inhibiting neuronal activity such as capsaicin, prostaglandin/bradykinin, lidocaine and tetrodotoxin, and further characterized in rat DRG cultures using RNAscope and transcriptomics. In the sensory neuron/macrophage co-culture model we have demonstrated that IL-1β, similar to lipopolysaccharide, induces a long-lasting increase in the spontaneous activity of sensory neurons. Furthermore, we have validated the results obtained in rats through a combination of studies employing human primary and iPSC-derived sensory neurons. Our results demonstrate the utility of this model to characterize novel targets and analgesic drug candidates and improve understanding of the role of neuro-immune interactions in chronic pain.

Disclosures: **A. Domanskyi:** A. Employment/Salary (full or part-time): Orion Corporation. **I. Parkkinen:** A. Employment/Salary (full or part-time): Orion Corporation. **R. Lund:** A. Employment/Salary (full or part-time): Orion Corporation. **E. Pollari:** A. Employment/Salary (full or part-time): Orion Corporation. **C. Stenfors:** A. Employment/Salary (full or part-time): Orion Corporation. **M. Morales:** A. Employment/Salary (full or part-time): Orion Corporation.

Poster

PSTR117: Preclinical Pain Models and Measurements

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.16/H2

Topic: E.01. Somatosensation – Pain and Itch

Title: Functional MRI Following Sensory Stimulation in Rat Monosodium Iodoacetate Model of Osteoarthritis Pain as a Tool for Drug Therapy Discovery

Authors: *P. LEHTINEN[1], P. STENROOS[2], R. SALO[2], H. KOIVISTO[2], S. VIRTANEN[3], H. LAAKSO[2], H. TANILA[2], A. DOMANSKYI[3], O. GRÖHN[2], C. STENFORS[3];
[1]Inst. of Biomedicine, Univ. of Turku, Turku, Finland; [2]A.I. Virtanen Inst. for Mol. Sci., Univ. of Eastern Finland, Kuopio, Finland; [3]Orion Pharma, Orion Corp., Turku, Finland

Abstract: Managing chronic pain in osteoarthritis (OA) is a significant challenge, with existing treatments often providing insufficient relief. A key issue in developing new therapies is the translational gap between preclinical animal models and clinical outcomes. This study explores the use of functional magnetic resonance imaging (fMRI) to evaluate pain processing in the brain of a monosodium iodoacetate (MIA) -induced rat model of OA, alongside the pharmacological intervention of pregabalin (PGL). Thirty-two male Wistar rats were divided into sham and MIA groups, with the latter receiving intra-articular MIA injections to induce OA. Mechanical sensitivity was assessed using the von Frey test, and fMRI was conducted at baseline, on day 21, and after PGL treatment on day 22. By day 21, the MIA group exhibited significant hypersensitivity, with fMRI showing thalamic and retrosplenial cortex activation in response to mechanical stimuli. PGL treatment on day 22 significantly reduced mechanical hypersensitivity and decreased brain activity in pain-related regions, including the thalamus, frontal cortex, insula, and cingulate cortex. These results indicate that fMRI can provide objective measures of

pain processing and the effectiveness of analgesic treatments in preclinical models, potentially bridging the gap between animal studies and clinical trials. The study underscores the potential of fMRI as a tool for drug discovery in chronic pain management, highlighting the need for further research with various analgesics to fully understand its utility.

Disclosures: P. Lehtinen: None. **P. Stenroos:** None. **R. Salo:** None. **H. Koivisto:** None. **S. Virtanen:** A. Employment/Salary (full or part-time): Orion Pharma, Orion Corporation. **H. Laakso:** None. **H. Tanila:** None. **A. Domanskyi:** A. Employment/Salary (full or part-time): Orion Pharma, Orion Corporation. **O. Gröhn:** None. **C. Stenfors:** A. Employment/Salary (full or part-time): Orion Pharma, Orion Corporation.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.01/H3

Topic: E.01. Somatosensation – Pain and Itch

Support: NS038261

Title: Il-23r signaling in the right central amygdala modulates pain and anxiety-like behaviors in a rat model of chronic neuropathic pain

Authors: *M. I. ALEMAN[1], N. ANTENUCCI[2], V. NEUGEBAUER[2];
[1]Translational Neurosci. and Pharmacol., [2]Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Chronic pain is a prevalent and debilitating condition that significantly diminishes quality of life. The multidimensional nature of pain highlights the significant role of brain processes. Neuroimmune signaling has been implicated as a contributor to chronic pain, but is less well understood in the brain, and the specific molecular pathways contributing to its persistence remain incompletely characterized. The amygdala, specifically, the central nucleus (CeA), is a key limbic structure that integrates nociceptive inputs with emotional and affective processing and is increasingly recognized for its role in modulating pain perception. Recent evidence points to the involvement of neuroinflammatory signaling in pain-related amygdala neuroplasticity. The IL-23 receptor (IL-23R) is expressed on neurons and activated upon binding of its ligand IL-23. Preliminary transcriptomic data suggest an upregulation of IL-23 and IL-23R in the right CeA in rats with spinal nerve ligation (SNL) compared to sham controls, suggesting a localized neuroimmune mechanism in chronic pain processing. To assess the behavioral consequences of IL-23R signaling, we utilized microdialysis to deliver a competitive antagonist of IL-23R into the right CeA of SNL and control Sprague-Dawley rats, four weeks post-surgery. Male and female rats were tested. Behavioral assessments included mechanical sensitivity (von Frey), vocalizations in response to nociceptive stimuli, and anxiety-like behaviors (elevated plus maze and light-dark box). IL-23R blockade decreased mechanical hypersensitivity in both sexes,

with a trend for decreased in emotional-affective responses in females. These findings implicate IL-23R activation in the right CeA as a potential contributor to pain hypersensitivity and anxiety in neuropathic conditions, potentially via neuroimmune communication between glial cells and neurons.

Disclosures: M.I. Aleman: None. **N. Antenucci:** None. **V. Neugebauer:** None.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.02/H4

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grants NS038261
NS106902
NS109255

Title: Interleukin-17a and neuroimmune signaling in the central amygdala in a chronic neuropathic pain model

Authors: *G. JI, V. NEUGEBAUER;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Neuroimmune signaling has been implicated in peripheral and spinal pain mechanisms whereas little is known about the role of neuroimmune signaling in brain regions associated with different aspects of pain. The complex interactions of glia cells with neurons contribute to synaptic modulation and neuroplasticity. Our previous studies demonstrated that the amygdala with its central nucleus (CeA) is an important brain center at the intersection of nociception and emotion involved in pain modulation. Amygdala neuroimmune signaling has been implicated in various CNS functions and disorders. Recent evidence suggests that the proinflammatory cytokine interleukin-17 (IL-17), acting on its specific receptor (IL-17R) expressed by immune, glial, and neuronal cells, is implicated in pain mechanisms, but its potential effects on synaptic function and pain modulation in the brain are largely unexplored. In this study, we addressed the question if IL-17a and its receptor IL-17Ra are involved in pain regulation in the CeA in the spinal nerve ligation (SNL) mouse model of chronic neuropathic pain. We found that the IL-17a receptor (IL-17Ra) is expressed by CRF neurons, non-CRF neurons, and astrocytes, but not microglia cells in the CeA. The up-regulation of IL-17Ra expression was detected in both neurons and astrocytes in the CeA in SNL mice. IL-17a application to brain slices from SNL mice increased neuronal excitability and had facilitatory effects on spontaneous excitatory postsynaptic currents (EPSCs) of CeA neurons. Blocking IL-17Ra deceased neuronal excitability and had inhibitory effects on spontaneous EPSCs in CeA neurons. Expression patterns of IL-17RA in different cell types and the synaptic effects of IL-17a activation and blockade suggest a role of the IL-17 system in the neuro-immune cross-talk

occurring in the CeA and its potential involvement in synaptic changes in chronic neuropathic pain.

Disclosures: G. Ji: None. **V. Neugebauer:** None.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.03/H5

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant R01NS038261
NIH grant R01NS118731

Title: Effects of chemokine CXCL10/CXCR3 signaling on central amygdala neurons under normal and neuropathic pain conditions

Authors: *T. KIRITOSHI, P. D. PRESTO, O. PONOMAREVA, J. D. CARDENAS TORO, G. JI, I. PONOMAREV, V. NEUGEBAUER;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Neuroplasticity in the central nucleus of the amygdala (CeA) plays a key role in pain modulation and emotional-affective aspects of pain. Our recent studies suggest the potential involvement of non-neuronal mechanisms such as neuroimmune signaling in pain-related neuroplastic changes in the CeA and behaviors. In line with these findings, our transcriptomic analysis revealed the upregulation of C-X-C motif chemokine ligand 10 (CXCL10), a key chemokine involved in immune responses, in the CeA under chronic neuropathic pain conditions. However, cellular and synaptic effects of CXCL10 on CeA neurons remain to be determined. Here we examined the effects of exogenous CXCL10 and pharmacological blockade of its receptor CXCR3 on neuronal excitability and synaptic transmissions in CeA neurons under baseline and chronic neuropathic pain conditions. Whole-cell patch-clamp recordings were obtained from neurons in the latero-capsular division of the CeA (CeLC) in brain slices from sham control and neuropathic mice (4 weeks after L5 spinal nerve ligation, SNL model). In current-clamp mode, neuronal excitability was measured by injecting depolarizing currents steps. In voltage-clamp mode, excitatory postsynaptic currents (EPSCs) were evoked by electrical stimulation of presumed nociceptive input from the parabrachial nucleus (PB). Application of recombinant CXCL10 increased excitability of CeLC neurons in sham controls. A selective CXCR3 antagonist (NBI 74330) showed a trend to decrease excitability in a subpopulation of CeLC neurons in the SNL model. Neither recombinant CXCL10 nor NBI 74330 had significant effects on synaptic transmission. These results suggest that CXCL10 can enhance excitability of CeA neurons while there is little endogenous CXCL10 activity in the CeA, at least at 4-week time point after SNL.

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Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.04/H6

Topic: E.01. Somatosensation – Pain and Itch

Support: NS129552

Title: Cgrp signaling modulates central amygdala crf neuron activity in a mouse model of migraine

Authors: *N. ANTENUCCI[1], F. PORRECA[3], E. NAVRATILOVA[4], V. NEUGEBAUER[2]; [2]Pharmacol. and Neurosci., [1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [3]Dept Pharmacol., [4]Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: Migraine is a debilitating neurological disorder with a higher prevalence in females than males, often associated with heightened emotional and sensory pain processing. The central amygdala (CeA), particularly corticotropin-releasing factor-positive (CRF) neurons, plays a pivotal role in integrating nociceptive and affective signals. Calcitonin gene-related peptide (CGRP) has been implicated in migraine pathophysiology, yet its influence on CeA CRF neurons remain unclear. We investigated the effects of CGRP receptor blockade on CeA CRF neuronal excitability in a nitroglycerin (NTG)-induced mouse model of migraine. Adult male and female mice received intraperitoneal NTG injections to induce a migraine-like condition. Whole-cell recordings were obtained from visually identified CeA CRF neurons in brain slices. Afferent fibers from the parabrachial nucleus (PBN) were stimulated electrically to assess synaptic transmission. Electrophysiological parameters, including action potential firing rates, voltage sag (V-SAG), input-output (I-V) relationships, excitatory postsynaptic currents (EPSCs), inhibitory postsynaptic currents (IPSCs), and paired-pulse ratios (PPRs), were measured before and after application of a CGRP receptor antagonist (CGRP 8-37). CGRP receptor blockade decrease firing rates in both sexes, with a more pronounced effect at higher current injections. Females displayed greater V-SAG amplitudes, suggestive of enhanced hyperpolarization-activated cyclic nucleotide-gated (HCN) channel activity, which was decreased by CGRP receptor blockade. The I-V curve slope was steeper in males, indicating higher input resistance; CGRP receptor blockade decreased the slope in both sexes. EPSC peak amplitudes and areas under the curve were greater in males and were decreased by CGRP receptor antagonism in both sexes. Conversely, IPSC peak amplitudes were greater in males and increased further by CGRP receptor blockade in both sexes. PPRs remained unchanged across conditions, arguing against presynaptic changes. These findings reveal sex-specific differences in CeA CRF neuronal excitability and synaptic transmission in a migraine model and demonstrate that CGRP receptor

antagonism mitigates changes in neuronal hyperexcitability and synaptic plasticity. The data add evidence for the therapeutic potential of CGRP-targeted interventions in migraine.

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Poster

PSTR118: Brain Mechanisms of Persistent Pain

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Program #/Poster #: PSTR118.05/H7

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant NS038261

Title: Activation of amygdala CRF neurons drives neuroimmune signaling

Authors: *M. MAZZITELLI[1], N. ANTENUCCI[2], V. NEUGEBAUER[2];
[2]Pharmacol. and Neurosci., [1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Pain is a multidimensional experience with a significant averse-affective component. The amygdala is a limbic brain structure critically involved in the emotional-affective aspects of behaviors and in pain modulation. The central nucleus of the amygdala (CeA) serves major output functions and contains the highest density of extra-hypothalamic corticotropin releasing factor (CRF), which is implicated in several neuropsychiatric disorders. Recent work in our lab showed enhanced excitability of CeA-CRF neurons at the acute pain stage and pain-like behaviors evoked by the acute optogenetic activation of CRF neurons under normal conditions. Neuroimmune signaling is now recognized as an important pain mechanism but remains largely unexplored in the brain, and mechanisms of activation are not well understood. Microglia are the primary immune cells of the central nervous system and serve important neuroprotection functions. Accumulating evidence points to a sexually dimorphic role of microglia signaling in pain processing Here, we tested the hypothesis that the chemogenetic activation of CeA-CRF neurons under normal conditions drives pain-like behaviors through a mechanism that involves microglia activation, and there may be sex differences.For the chemogenetic activation of CRF neurons, a Cre-inducible viral vector encoding Gq-DREADD (AAV5-hSyn-DIO-hM3D(Gq)-mCherry) was injected stereotaxically into the CeA of male and female transgenic Crh-Cre rats. After 3 weeks, DREADD activators (deschloroclozapine, DCZ or clozapine N-oxide, CNO) were administered intraperitoneally for 7 days. A selective colony stimulating factor 1 receptor (CSF1R) inhibitor (PLX3397) was injected into the CeA the day before the behavioral experiments to inhibit local microglia. Nocifensive mechanical thresholds, emotional responses (evoked vocalizations), and anxiety-like and spontaneous (grimace test) behaviors were measured to determine the effects of the chemogenetic activation of CeA-CRF neurons with and without intra-CeA PLX3397 injection. Chemogenetic activation of CRF neurons in the CeA resulted in decreased mechanical thresholds and increased evoked vocalizations in both sexes

and promoted anxiety-like behaviors in females only. Intra-CeA PLX3397 injection blocked the facilitatory effects of the chemogenetic activation CeA-CRF neurons in male, but not in female, rats, suggesting a sex-specific contribution of amygdala microglia to pain behaviors generated by the activation of CRF neurons.These data suggest that hyperactivity of amygdala CRF neurons induces pain like-behaviors that depend on neuroimmune signaling in male but not female rats.

Disclosures: M. Mazzitelli: None. **N. Antenucci:** None. **V. Neugebauer:** None.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

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Program #/Poster #: PSTR118.06/H8

Topic: E.01. Somatosensation – Pain and Itch

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Title: Inhibition of amygdala CRF neurons at the induction stage of chronic neuropathic pain has long-lasting inhibitory effects on pain behaviors

Authors: *V. NEUGEBAUER, N. ANTENUCCI, T. KIRITOSHI, O. PONOMAREVA; Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Chronic pain often arises from the abnormal processing of pain signals in the brain. Corticotropin-releasing factor (CRF) neurons within the amygdala are key mediators of the emotional and sensory components of pain and have been shown to increase their activity during the acute phase of neuropathic injury. However, their causal role in the transition from acute to chronic pain remains poorly defined. In this study, we investigated whether early inhibition of CRF neurons in the central nucleus of the amygdala (CeA) could prevent or mitigate the establishment of chronic pain behaviors. Using a chemogenetic approach, male CRF-Cre+ rats received injections of a Cre-dependent inhibitory DREADD vector (pAAV-hSyn-DIO-hM4D(Gi)-mCherry) or control vector (pAAV-hSyn-DIO-mCherry) into the right CeA. Following spinal nerve ligation (SNL), clozapine-N-oxide (CNO) (1 mg/kg, i.p.) was administered twice daily for 7 days, targeting the acute post-injury phase. Pain-related behaviors were assessed for four weeks, using von Frey testing, vocalizations, grimace scale, and anxiety-like behavioral assays (light-dark box, elevated plus maze). Chemogenetic inhibition of CRF neurons during the acute phase significantly decreased both evoked and non-evoked pain behaviors (von Frey and vocalizations) in the chronic phase (4 weeks postinduction of SNL) compared to controls. To test for the involvement of neuroimmune signaling as an underlying

mechanism, immunohistochemical analysis of microglial activation in the CeA was conducted at four weeks postinduction of SNL. Preliminary findings suggest altered microglial reactivity in animals with early CRF neuron inhibition, indicating a possible interaction between neuronal and immune components in chronic pain development, suggesting that early CRF neuron activity can modulate long-term neuroimmune signaling. These findings identify a critical temporal window, in which CRF neuronal activity drives chronic pain development by engaging neuroimmune processes, suggesting that targeting amygdala CRF neurons may offer a preventive strategy against neuropathic pain chronification.

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Poster

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Program #/Poster #: PSTR118.07/H9

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant R01NS038261
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Title: Impaired prolactin regulation of kappa-opioid neurons in hypothalamus promotes functional pain. A sex-difference perspective

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Abstract: Elevated prolactin (PRL) levels have been linked to several hormone-dependent pain disorders that are more prevalent in females, referred to as functional pain syndromes (FPS). Stress, as well as systemic dynorphin, an endogenous kappa opioid receptor (KOR) agonist, can elevate PRL blood levels, predominantly in females. Tuberoinfundibular dopamine (TIDA) neurons in the hypothalamic arcuate nucleus (Arc) provide tonic inhibition of PRL release from pituitary lactotrophs. Arc KOR-TIDA neurons are modulated by serum PRL, which acts as a feedback mechanism to reduce PRL secretion. In this project, we test the hypothesis that stress disrupts the PRL-mediated feedback mechanism, leading to enhanced PRL release and contributing to an FPS-like condition. To investigate this, we induced the FPS model in KOR-Cre male and female mice using a repeated restraint stress (RRS) paradigm. RRS is an established model known to induce PRL-dependent FPS in female mice. Following assessments of periorbital mechanosensitivity using von Frey filaments and anxiety-like behaviors in the light-dark test, brain slice physiology experiments were conducted in two groups: a stressed

group (3 days post-stress) and a stress-resolved group (14 days post-stress). Whole-cell patch-clamp recordings were performed on KOR-positive Arc-TIDA neurons in brain slices. KOR-positive cells were labeled with inhibitory DREADD three weeks before slice preparation, while TIDA neurons were labeled via intravenous injection of fluorogold one week before recordings. Estrous cycle stages in female mice were monitored for 3-4 days prior to experimentation. Results showed an increased number of silent neurons in the stressed female group compared to the stressed male group and the stress-resolved male and female groups. Superfusion of PRL enhanced spontaneous discharge in the stressed male group but had no effect in the stressed female group. However, in stress-resolved female mice, PRL increased neuronal firing in some neurons.These findings suggest that PRL modulation of hypothalamic Arc-TIDA neuron activity is impaired under acute stress conditions in females, potentially contributing to FPS. This impaired sensitivity to PRL may play a role in sustaining FPS, but it appears to recover in the stress-resolved state.

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Poster

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Title: Cortical mechanisms of comorbidity between ADHD and pain sensitization in a mouse model

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a complex and multifactorial neurodevelopmental disorder, with a prevalence of 8% in children worldwide. Core symptoms include attentional deficits, hyperactivity, and impulsivity. Clinical studies suggest that pain sensitization develops in subjects with ADHD. However, the mechanisms and neural circuits involved remain poorly understood. Our team has previously validated an ADHD-like mouse model obtained by neonatal intracerebroventricular injection of 6-hydroxydopamine (6-OHDA). We showed that 6-OHDA mice exhibited a marked sensitization to thermal and mechanical stimuli, suggesting that ADHD conditions increase nociception. Moreover, by combining different approaches, we also demonstrated that the anterior cingulate cortex (ACC) hyperactivity alters the 'ACC - posterior insula (PI)' circuit, and triggers changes in spinal networks that underlie pain hypersensitivity. We hypothesize that neuroinflammation triggers ACC hyperactivity and the comorbidity between ADHD and pain sensitization. Using immunofluorescence staining, we demonstrated changes in the morphology of microglia and astrocytes, indicative of cellular reactivity. With RT-qPCR, we have identified upregulated transcript levels of inflammatory and oxidative stress mediators, pointing to a pro-inflammatory milieu in the cingulate and insular cortices. Using mass spectrometry and high-throughput phosphoproteomic assays, we characterized impaired protein expression, dysregulated kinase activity, and altered signaling pathways in ADHD-like conditions. All of these changes lead to impairments in specific inflammatory pathways and cellular processes, which may underlie ADHD and comorbid pain hypersensitivity. The identification of shared mechanisms, engaging overlapping neuronal circuits and inflammation, and underpinning both disorders, is key to better treatments.

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Poster

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Topic: E.01. Somatosensation – Pain and Itch

Support: SERB-Department of Science & Technology, Govt of India

Title: Connexin 43 gap junction channels increase in the spinal cord of rats after nerve ligation

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Abstract: Peripheral nerve damage is clinically associated with both spontaneous pain and tingling as well as hypersensitivity to peripheral stimuli like touch. In comparison to acute inflammatory pain, neuropathic pain arises from maladaptive functioning of the nervous system. Changes at the spinal cord level are important as this is the first site where the sensory stimuli are

subjected to altered processing. Mechanisms like changes in excitability and neurotransmitter profile of primary sensory neurons in the DRG, phenotypic switching of Aβ fibers which start transmitting pain and sprouting of nerve fibers from deeper dorsal laminae have been proposed to give rise to neuropathic pain. Facilitation by glial cells could also be involved as shown by activation of p38 MAPK in microglia after L5 spinal nerve ligation. However, the role of gap junctions or electrical synapses has not been fully delineated in this condition. Gap junctions predominantly connect glial cells. These channels act as low pass filters which synchronize synaptic activity and thus were hypothesized to produce hyperexcitability in neuropathic pain. The aim of the present study was to characterize connexin 43 gap junction channels in the dorsal horn of spinal cord of rodents. To address this issue, we performed partial sciatic nerve ligation and observed hypersensitivity to von Frey filaments over a 4 week period. Thereafter, both light and electron microscopic evaluation of the nerve showed demyelination and axoplasmic damage. Maximum nociception measured as 50% withdrawal threshold (g) was on day 14 after nerve ligation. Administration of morphine (10 mg/kg) on day 14 post-PSNL reversed nociception at 3 h though not ketoprofen (5 mg/kg). Rats administered morphine as above for consecutively 10 days, once daily, did not develop tolerance. Rats with PSNL was sacrificed on day 14 and their lumbar spinal cord were subjected to immunohistochemistry and Western Blot studies. Both microglia and astrocytes were increased in number on the affected side of the spinal cord compared to sham group. Counting of the glia was done by artificial intelligence using automated cell detection and quantitation. Connexin 43 was found to be increased on the ipsilateral side. Currently, co-localization is being done for the gap junction channels. Together, the current study suggest that gap junctions are increased in neuropathic condition at the spinal level and that opioids like morphine can be effective in its treatment.

Disclosures: D. Ray: None.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

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Program #/Poster #: PSTR118.10/H12

Topic: E.01. Somatosensation – Pain and Itch

Support: R61 NS131188

Title: Lysophosphatidic acid receptor 5 in insular cortex as a potential analgesic target in neuropathic pain

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Abstract: Neuropathic pain remains a significant clinical challenge and existing treatments have limited efficacy and often over rely on opioids. Pharmacological inhibition and genetic knockout

of lysophosphatidic acid receptor 5 (LPA5) lead to an analgesic effect on nerve injury-induced nociceptive hypersensitivity in rodents. However, the specific pain-associated regions where LPA5 is required for neuropathic pain remain unidentified. Here, we demonstrate a site-specific increase in the levels of *Lpa5* mRNA and LPA5 protein in the contralateral insular cortex and hippocampus 3-14 days after chronic constriction injury (CCI) of the unilateral sciatic nerve in mice. Blocking this time-dependent increase through microinjection of adeno-associated virus 5 (AAV5) expressing *Lpa5* shRNA (AAV5-LPA5 shRNA) into insular cortex mitigated CCI-induced development of nociceptive hypersensitivities. This effect was not seen after microinjection of AAV5-LPA5 shRNA into the hippocampus. Mimicking this increase through microinjection of AAV5 expressing full-length *Lpa5* mRNA into the insular cortex augmented responses to mechanical, heat and cold stimuli and induced ongoing pain in naïve mice. Moreover, systemic administration of selective LPA5 antagonist RLPA-76 alleviated CCI-induced mechanical allodynia and heat hyperalgesia. All treated mice displayed normal locomotor activities. Altogether, these findings suggest that LPA5 in the insular cortex plays a critical role in neuropathic pain genesis and support LPA5 as a potential target for neuropathic pain treatment.

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Poster

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Program #/Poster #: PSTR118.11/H13

Topic: E.01. Somatosensation – Pain and Itch

Support: NRF Grant RS-2025-00562132
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Title: Analgesic effects of transcutaneous auricular vagus nerve stimulation on partial sciatic nerve ligation-induced neuropathic pain in mice via serotonergic pathways

Authors: *H. SHIN[1], S. KIM[2];
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Abstract: The Partial Sciatic Nerve Ligation (PSNL) model is widely used as a representative animal model for studying chronic neuropathic pain. This study was conducted to investigate the analgesic effects of transcutaneous auricular vagus nerve stimulation (taVNS) and its underlying mechanisms in the PSNL model. Behavioral experiments demonstrated that taVNS significantly alleviated mechanical allodynia, with the most pronounced effects observed under multiple bilateral stimulation conditions. This analgesic effect persisted for up to 48 hours, suggesting the potential of taVNS as a non-pharmacological therapeutic approach for chronic pain management. To elucidate the analgesic mechanisms of taVNS, changes in neural activity in key brain regions

were analyzed using c-Fos expression. Immunohistochemical analysis revealed that taVNS induced differential neural activation by increasing c-Fos expression in the dorsal raphe nucleus (DRN) while decreasing it in the central amygdala (CeA). The DRN is a major nucleus associated with serotonin synthesis, whereas the CeA plays a critical role in pain signal integration and descending pain modulation, indicating that taVNS may regulate pain through serotonin-related pathways.
Further experiments using the serotonin synthesis inhibitor p-chlorophenylalanine (PCPA) demonstrated that the analgesic effects of taVNS were abolished, confirming the integral role of serotonin in the underlying mechanisms.
In conclusion, taVNS alleviates mechanical allodynia through differential regulation of DRN and CeA activity, mediated by serotonin pathways. These findings support the potential of taVNS as a therapeutic option for chronic pain and highlight the need for further research to better understand its mechanisms.

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Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

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Program #/Poster #: PSTR118.12/H14

Topic: E.01. Somatosensation – Pain and Itch

Title: Delineation of the neural circuit(s) and molecular changes that allow Calca^{PBN} neuron activation to drive nociplastic pain

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Abstract: Optogenetic or chemogenetic activation of *Calca* neurons in the parabrachial nucleus (*Calca*^{PBN}) promotes pain phenotypes including tactile hypersensitivity (allodynia) that can outlast the stimulus by weeks in the absence of any nerve injury - a model of nociplastic pain. This effect is blocked by inhibiting serotonergic neurons (*Slc6a4*) in the rostral ventral medulla that project to the medial dorsal horn. We aim to delineate the neural circuit from *Calca*^{PBN} → *Slc6a4*^{RVM} → spinal cord and postulate that the central nucleus of the amygdala (CeA) is an important intermediate in this circuit because it is a major target of *Calca*^{PBN} neurons and is strongly implicated in pain. To gain insight into the molecular changes that contribute to nociplasticity, we initiated a multi-phase, single-cell RNA sequencing of PBN and CeA neurons at baseline, onset, peak and recovery phases using a fixed-tissue protocol to avoid post-mortem artifacts. Our data revealed a significant up-regulation of many immediate-early genes (IEG) in the PBN and CeA at the onset and peak phases. Of the upregulated IEGs, inactivation of the *Bdnf* gene was our first choice to assess its functional role in nociplastic pain.

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Poster

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Topic: E.01. Somatosensation – Pain and Itch

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Title: Tiam1-mediated synaptic plasticity in NAc D2-MSNs as a brain memory mechanism for neuropathic pain

Authors: *F. QIN, Q. WANG, C. YAO, L. LI;
The Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Pain memory, also known as sensitization or central sensitization, refers to the phenomenon where the nervous system "remembers" painful experiences and continues to send pain signals even after the original injury has healed. Understanding pain memory is crucial for developing new treatments for chronic pain, potentially including strategies to "erase" or dampen these memory traces. Synaptic plasticity, the neuron's ability to modify and strengthen connections, plays a crucial role in both pain memory and general memory. Tiam1 (TIAM Rac1 Associated GEF 1) is a Rac1 guanine nucleotide exchange factor (GEF) that promotes dendritic and synaptic growth during hippocampal development by inducing actin cytoskeletal remodeling. Our recent study identified Tiam1-mediated synaptic plasticity in spinal dorsal horn excitatory neurons as a spinal memory mechanism for peripheral neuropathy. However, whether and how brain pain memory contributes to neuropathic pain has not been explored. Here, using multiple neuropathic pain animal models, we demonstrate that in D2-MSNs (D2 receptor-expressing medium spiny neurons) in the nucleus accumbens (NAc) shell, Tiam1-mediated synaptic structural via actin cytoskeleton reorganization contributes to the persistent nature of neuropathic pain, and functional plasticity via synaptic NMDAR stabilization underlies the central sensitization, and that these actions together are essential for the development and maintenance of neuropathic pain. Furthermore, pharmacological blockade of Tiam1 signaling in the NAc shell by small-molecular inhibitor or antisense oligonucleotides (ASOs) persistently alleviates neuropathic pain sensitivity. Our findings suggest that Tiam1-coordinated synaptic structural and functional plasticity in NAc D2-MSNs serves as a brain memory for neuropathic

pain and that erasing this memory storage has long-lasting consequences in neuropathic pain management.

Disclosures: **F. Qin:** A. Employment/Salary (full or part-time): The University of Alabama at Birmingham. **Q. Wang:** A. Employment/Salary (full or part-time): The University of Alabama at Birmingham. **C. yao:** A. Employment/Salary (full or part-time): The University of Alabama at Birmingham. **L. Li:** A. Employment/Salary (full or part-time): The University of Alabama at Birmingham.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

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Topic: E.01. Somatosensation – Pain and Itch

Support: Center on compulsive behaviors, NIH

Title: Sexually dimorphic functions of central amygdala neurons expressing CGRP receptor and PKCδ in pain modulation

Authors: ***S. SINGH**[1], T. WILSON[2], A. DANKO[3], B. NEUGEBAUER[3], S. CHAUDHRY[3], J. LIN[3], L. LEWTER[4], W. FORTUN[3], S. VALDIVIA[3], B. J. KOLBER[5], Y. CARRASQUILLO[2]; [2]Natl. Ctr. for Complementary and Integrative Hlth., [1]NIH, Bethesda, MD; [3]Natl. Ctr. for Complementary and Integrative Hlth., Natl. Inst. of Hlth., Bethesda, MD; [4]The Univ. of Texas at Dallas, Richardson, TX; [5]Neurosci., Univ. of Texas at Dallas, Dept. of Neurosci., Richardson, TX

Abstract: The central amygdala (CeA) plays a critical role in pain processing, with distinct neuronal subpopulations contributing uniquely to nociceptive modulation. In this study, we elucidated the functional differences between central amygdala-calcitonin gene related peptide receptor- expressing neurons (CeA-CGRPR) and central amygdala- protein kinase c delta-expressing neurons (CeA-PKCδ) neurons in pain processing. Quantitative analysis of phosphorylated ERK (pERK)-positive cells revealed both exclusive and co-expressed pERK expression within CeA-CGRPR and CeA-PKCδ neurons, highlighting their independent and convergent roles in ERK-mediated pain signaling. CeA-CGRPR neurons displayed heightened excitability in the posterior CeA during neuropathic pain, while CeA-PKCδ neurons exhibited increased late-firing activity across CeA regions, with regular spiking prevalent in female mice. Behaviorally, chemogenetic inhibition of CeA-CGRPR neurons reversed nerve injury-induced hypersensitivity across all pain modalities tested (i.e. tactile, cold, heat and pressure) in both sexes whereas chemogenetic activation of CeA-CGRPR neurons induced hypersensitivity regardless of modality and sex. Chemogenetic inhibition of CeA-PKCδ neurons also reduced injury-induced hypersensitivity in both sexes, but with sex-specific patterns: in female mice, inhibition alleviated hypersensitivity to tactile and pinch stimuli, while in male mice, it reduced

hypersensitivity across all tested modalities—cold, heat, and tactile. Conversely, chemogenetic activation of CeA-PKCδ neurons induced hypersensitivity in a sex-dependent manner; in females, activation increased sensitivity to tactile and pinch stimuli, whereas in males, it selectively enhanced hypersensitivity to tactile stimuli only. Persistent chemogenetic activation of CeA- CGRPR and -PKCδ neurons induces a prolonged hypersensitivity state that outlasts the period of neuronal stimulation. This suggest that sustained activation of these neurons may trigger lasting neuroplastic changes in pain processing. Notably, CeA-CGRPR neurons chemogenetic inhibition reduced formalin-induced nociceptive responses only in females, with no effect seen in either males or females after CeA-PKCδ neurons chemogenetic inhibition. In summary, these findings highlight distinct roles of CeA-CGRPR and CeA-PKCδ neurons in pain modulation. CeA-CGRPR neurons influence evoked pain broadly and spontaneous pain in a sex-specific manner, while CeA-PKCδ neurons have a more selective, sex-dependent effect on tactile and pressure sensitivity.

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Poster

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Title: Insular cortex mGluR5 modulates neuropathic pain in mice

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Abstract: Metabotropic glutamate receptor 5 (mGluR5) has been implicated in the modulation of chronic pain, but its role in the insular cortex remains unclear. In this study, we investigated the functional significance of mGluR5 in the insular cortex of neuropathic pain model mice. Through pharmacological experiments, we revealed that local administration of an mGluR5 antagonist (MTEP) into the insular cortex of naïve mice induced mechanical allodynia.

Conversely, administration of an mGluR5 agonist (CHPG) significantly alleviated pain behavior. To elucidate the underlying mechanism, we performed acute slice $Ca2^{+}$ imaging and found that MTEP treatment increased activity in pyramidal neurons of the insular cortex, observed under allodynia conditions. This activation was abolished by synaptic blockers, suggesting that MTEP does not act directly on pyramidal neurons. These results suggest that mGluR5 in non-pyramidal neurons contributes to the regulation of chronic pain, and mGluR5 in the insular cortex may serve as a promising therapeutic target.

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Poster

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Topic: E.01. Somatosensation – Pain and Itch

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Title: Cannabidiol Treatment Alters Glial Cell Activation in the Periaqueductal Gray in a Peripheral Neuropathy Model

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Abstract: Chronic pain affects 30% of the global population and poses a significant public health concern due to its functional, emotional, and socioeconomic consequences. Pain modulation is mediated by intricate neural circuits, including the periaqueductal gray matter (PAG), which is central in producing analgesia. Glial cells, particularly astrocytes and microglia, contribute to the persistence of pain by releasing pro-inflammatory substances that maintain nociceptive signaling. Cannabidiol (CBD), a non-psychoactive component of Cannabis sativa, has shown potential in reducing pain and anxiety, possibly through modulating both neural and glial mechanisms. To determine whether systemic administration of CBD or the presence of peripheral neuropathy influences glial cell recruitment within the PAG. Peripheral neuropathy was induced in male albino Wistar rats via chronic constriction injury (CCI) of the sciatic nerve, with sham-operated rats serving as controls. Nociceptive behavior was assessed on days 7, 14, and 21 post-injury. CBD or vehicle treatment began on day 21. The open field test was conducted on day 22, followed by reassessment of mechanical pain sensitivity on day 23. Rats were then euthanized, and brain tissue from the PAG was collected to measure the expression of GFAP and IBA, markers of astrocytes and microglia, respectively. All procedures adhered to the

ethical guidelines approved by the Animal Experimentation Ethics Committee of FFCLRP-USP (19.1.1111.59.0). CCI induced mechanical allodynia, shown by decreased paw withdrawal thresholds on the injured side. Three days of subchronic CBD treatment, starting on day 21, significantly alleviated allodynia. Despite the presence of neuropathic pain, no notable changes were observed in locomotion or anxiety-related behaviors in the open field test, suggesting that this pain model did not impair these aspects of behavior. At the cellular level, sciatic nerve injury reduced GFAP and IBA expression in the ventrolateral PAG (PAGvl), indicating altered glial activity. CBD treatment reversed these effects, particularly restoring glial marker expression. Nonetheless, further research is necessary to validate these results and better understand astrocyte involvement in neuropathic pain, especially within the PAGvl region. These findings suggest that CBD's analgesic effects may be partly attributed to its ability to restore glial homeostasis within pain-regulatory brain regions. Our data provide valuable insight into the therapeutic potential of CBD in modulating glial reactivity and support its further investigation as a potential treatment for chronic pain.

Disclosures: C.R. Leite-Panissi: None. **S. Antonelli:** None. **M.G. Gagliardi:** None. **A.A. Ferrarese-Tiballi:** None.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.17/I3

Topic: E.01. Somatosensation – Pain and Itch

Support: NSFC 82173999

Title: Locus coeruleus norepinephrinergic signaling triggers microglial pruning of insular-prefrontal circuits underlying pain-associated cognitive decline

Authors: *X. LIU;
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Abstract: Acute pain can enhance episodic memory, whereas chronic pain is commonly associated with cognitive decline. However, the neural mechanisms underlying the transition from pain-induced cognitive enhancement to impairment remain poorly understood. Using the spared nerve injury (SNI) mouse model, we observed that novel object recognition (NOR) memory was enhanced during the acute phase (1-3 days post-injury) but significantly impaired during the chronic phase (two weeks post-injury). Chemogenetic and optogenetic manipulation, combined with behavioral analysis, demonstrated that the anterior insular cortex (aIC)-to-prelimbic cortex (PrL) circuit enhanced NOR memory during the learning and consolidation phases in the acute phase. However, this circuit was suppressed in the chronic phase, leading to cognitive deficits. Meanwhile, we found that microglia density in the PrL increased and exhibited enhanced presynaptic engulfment activity during the chronic phase. Projection

terminals from acute phase pain-responsive aIC neurons in the PrL were engulfed by microglia in the chronic phase. Pharmacological depletion of microglia restored NOR memory deficits in chronic SNI mice. Further chemogenetic and pharmacological experiments suggested that chronic activation of the locus coeruleus (LC)-to-PrL norepinephrinergic neurons, was sufficient to activated PrL microglia via β2-adrenergic receptors, leading to memory impairment. This pathology was rescued by microglial depletion or β2-adrenergic receptor antagonism. Overexpression of CD55 (a complement regular) in the PrL to block complement C3b deposition suppressed aberrant microglial pruning and restored chronic-phase NOR memory. Meanwhile, we found that a Chinese medicine compound costunolide, screened from inhibition of micorglia phagocytosis activity, effectively rescued chronic SNI-induced memory deficits and excessive microglial phagocytic activity. Collectively, our findings demonstrate that acute pain enhances cognition via aIC-PrL circuit activation, whereas chronic pain drives hyperactivity in the LC (norepinephrine) -PrL (microglia β2) pathway, leading to pathological microglial engulfment of aIC-PrL projections and subsequent cognitive decline. This study provides novel insights into the dynamic interplay between pain and cognition.

Disclosures: X. Liu: None.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.18/I4

Topic: E.01. Somatosensation – Pain and Itch

Support: NCT05697159
NCT05112120
NCT05090124
NIHR Cambridge Biomedical Research Centre

Title: Jak inhibition links decreased pcc-insula connectivity to improved nociplastic pain in rheumatoid arthritis: a 7t mri study

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Abstract: Nociplastic pain, typified in fibromyalgia (FM), is prevalent in rheumatoid arthritis (RA) and remains a critical unmet clinical need. Janus kinase (JAK) inhibitors are a recent immunologic therapy class offering pain relief in RA, but their effect on nociplastic pain

mechanisms is poorly understood. We hypothesised that JAK inhibition will reduce both subjective FM pain scores and brain functional connectivity markers—specifically between the default mode network (DMN) and the insula—using resting-state functional magnetic resonance imaging (fMRI). We further explored whether these changes in brain connectivity were distinct from those following tumour necrosis factor (TNF)-alpha inhibition, another immunologic treatment, or placebo. RA patients who were newly prescribed JAK inhibitors (baricitinib or filgotinib) completed the ACR FM 2011 survey criteria, a validated subjective score of nociplastic pain. They also underwent a 7T MRI brain scan, including an 8-minute multiband resting-state fMRI scan, repeated 12 (±1) weeks later. The data were pre-processed using the default CONN functional connectivity toolbox pipeline and analysed with functional connectivity Multivariate Pattern Analysis (fc-MVPA) to identify regions whose pattern of connectivity with the rest of the brain significantly changed after treatment. The connectivity of these regions was then entered into a region-of-interest analysis with bilateral anterior, middle, and posterior insula regions and correlated with FM score change, controlling for age and gender. This association was then tested in RA patients who had TNF inhibition or placebo and the same MRI and questionnaire measures. Patients treated with JAK inhibitors showed significant reductions in FM scores (n=26, Paired Samples T-test, T=5.13, $p<0.001$), as did those receiving TNF inhibitors (n=22, T=2.38, p=0.03), but not those in the placebo group (n=11,T=0.66, p=0.51).The functional connectivity of the posterior cingulate cortex (PCC), a major hub of the DMN, significantly changed after JAK inhibition (F=7.23, $p<0.001$ FDR-corrected). Reduced connectivity between the PCC and the left anterior insula correlated with reduced FM scores (Pearson r=0.42, p=0.04), but not in TNF inhibition (r = 0.14, p=0.5) or placebo (r=0.09, p=0.8). These findings suggest that JAK inhibition reduces nociplastic pain in RA, potentially by attenuating aberrant DMN-insula connectivity—a mechanism not observed with TNF inhibitors or placebo. Although both drugs act peripherally, only JAK inhibition appears to impact brain functional connectivity, suggesting distinct downstream effects requiring further investigation.

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Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.19/I5

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH-NS126451

Title: Right Fronto-Parietal Role in Resilience to Chronic Low Back Pain: A Longitudinal Mobile Brain/Body Imaging (MoBI) Study of Response Inhibition

Authors: *M. JAMMOUL[1,2], D. EINSTEIN[3], O. CARACCIO[2], E. G. FREEDMAN[3], J. J. FOXE[3], P. Y. GEHA[2,3];
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Abstract: Chronic low back pain (CLBP) is the leading cause of disability worldwide, yet early predictors of pain chronification remain poorly defined. The right fronto-parietal network—particularly the right superior longitudinal fasciculus (SLF)—has been recently shown to predict resilience to CLBP. This network is known to be implicated in body awareness and cognitive control, processes thought to be altered in chronic pain. Here we set to explore the function of the right fronto-parietal network using response inhibition in sub-acute low-back pain (SLBP) patients (duration of pain less than 12 weeks). We hypothesize that patients who recover by 6 months (SLBPr) will show improved inhibitory control and distinct neural responses compared to healthy controls and patients whose pain persists (SLBPp). Previous studies in chronic pain conditions like fibromyalgia and migraine have shown altered N2 and P3 responses during No-Go tasks, with migraine patients exhibiting impaired behavioral inhibition, reflecting changes in inhibitory control mechanisms. We use Mobile Brain/Body Imaging (MoBI) to investigate response inhibition in individuals with SLBP and matched healthy controls (HC) over two visits separated by 6 months after which SLBP patients have either resolved pain (SLBPr) or persistent chronic pain (SLBPp/CLBP). Participants perform a Go/No-Go task during walking and sitting while high-density EEG and motion data are recorded. Event-related potentials (ERPs) with focus on N2 and P3 measures, behavioral performance (d-prime), and motion parameters are compared across groups and conditions. Preliminary analysis in 7 SLBP patients and 6 HC shows that SLBP participants exhibit significantly reduced N2 amplitudes during No-Go trials compared to controls at Cz (t-test, $p = 0.047$) and CPz ($p = 0.013$) during sitting, with less significant differences during walking. Behavioral d-prime scores were not significantly different between the groups. These early findings indicate that neurophysiological measures of response inhibition are different during subacute pain. Ongoing analyses will assess whether these markers will be more pronounced in the resilient patients to shed light on the behavioral and neural phenotype of resilience to chronic pain.

Disclosures: M. Jammoul: A. Employment/Salary (full or part-time): University of Rochester Medical Center. **D. Einstein:** A. Employment/Salary (full or part-time): University of Rochester Medical Center. **O. Caraccio:** A. Employment/Salary (full or part-time): University of Rochester Medical Center. **E.G. Freedman:** A. Employment/Salary (full or part-time): University of Rochester Medical Center. **J.J. Foxe:** A. Employment/Salary (full or part-time): University of Rochester Medical Center. **P.Y. Geha:** A. Employment/Salary (full or part-time): University of Rochester Medical Center.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.20/I6

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant DA060906

Title: Etiological basis for chronic pain genetic variation in multiple brain and dorsal root ganglia cell types

Authors: *S. TOIKUMO[1,3], M. PARISIEN[4], M. LEONE[5,6], C. SRINIVASAN[5], H. YU[2], A. ARENDT-TRANHOLM[7], T. J. PRICE[7], W. LUO[2], A. R. PFENNING[5], R. P. SEAL[6], L. DIATCHENKO[4], S. G. WAXMAN[8,9], R. KEMBER[1,3], H. KRANZLER[1,3];
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Abstract: Chronic pain is a major unmet clinical problem. Despite their diverse manifestations, pain conditions often share a similar genetic architecture. Although genome-wide association studies (GWAS) of pain traits have identified many risk loci, linking them to specific neurobiological substrates is challenging. Given genetic overlap across pain traits, we hypothesized that the shared genetics converge on human-specific brain and dorsal root ganglia (hDRG) neuronal sub-types. Using stratified LD score regression, we integrated chronic pain meta-GWAS data (N = 1,235,695) with single-cell RNA-seq data from human brain (461 neuronal clusters) and hDRG (16 clusters), and single-cell ATAC-seq data from human brain (27 neuronal/glial clusters) and mouse dorsal horn (14 clusters). Of 461 brain cell-types, we found enrichment in 15 GABAergic clusters (subcortical, striatal medium spiny neurons) and 76 glutamatergic clusters, mainly prefrontal intratelencephalic, hippocampal CA1-3, and amygdalar neurons. Of the 16 hDRG cell types, Aδ fibers (Aδ.LTMR and hPEP.PIEZOh), and C-fiber peptidergic (hPEP.TRPV1.A1.2) and non-peptidergic (hNP1 and hTRPM8) neurons were enriched were significantly enriched. In mouse dorsal horn, we observed broadly enriched chromatin accessibility in midventral neurons, oligodendrocytes and OPCs. We also identified putative cis-regulatory elements in brain excitatory (hippocampal, isocortical), inhibitory (striatal, isocortical) neurons, and astrocytes across the isocortex, hippocampus, striatum, and substantia nigra. In the brain, gene-level heritability mapped to key processes including kinase activity (PTPRO, PTPRT), GABAergic synapse (BSN, CDH13, CTBP2, DAG1, PTPRO), axon guidance (DCC, SLIT2), and neuron projection development (DCC, PTPRO, RHOA, SEMA6D, SLIT2). In hDRG, enriched genes implicated both GABAergic and glutamatergic signaling (e.g., BSN, MDGA2, NPTN, NRXN1, PTPRD). Finally, single-cell RNA-seq from cervical DRG of patients with acute vs chronic pain (N = 12) showed enrichment of GWAS loci among differentially expressed genes (e.g., EFNB2, GABBR1, GRK4, LSAMP, NCAM1, NRXN1) in both neuronal (N = 9) and non-neuronal (N = 7) cells. Our findings define a cell-type-specific genetic landscape for chronic pain, implicating inhibitory and excitatory neurons in CNS and PNS, and offering a basis for translational studies.

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None. **H. Kranzler:** 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.; Dr Kranzler is a consultant to Sobrera Pharmaceuticals, Altimmune, and Lilly. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr Kranzler is an inventor on U.S. provisional patent "Multi-ancestry Genome-wide Association Meta-analysis of Buprenorphine Treatment Response.". F. Consulting Fees (e.g., advisory boards); Dr. Kranzler is a member of advisory boards for Altimmune and Clearmind Medicine.

Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.21/I7

Topic: E.01. Somatosensation – Pain and Itch

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Title: Deconstruction of a spino-brain-spinal cord circuit drives chronic pain

Authors: Q. WANG[1], ***J. LEE**[1], Y. YUAN[2], L. YUAN[1], J. XIONG[1], X. CHEN[2];
[2]Biol., [1]Stanford Univ., Stanford, CA

Abstract: Inflammation or nerve injury at periphery can cause chronic pain. The spinal cord-projecting neurons in the rostral ventromedial medulla (RVM^{SC} neurons) facilitate pain chronification. However, the neuronal pathway that transmitting information about peripheral injury to these descending RVM^{SC} neurons is unknown. Here we report a closed-loop circuit extending from spinal cord to ventral posterolateral thalamus and posterior complex of the thalamus, proceeding to primary somatosensory cortex; then returning to the spinal cord via lateral superior colliculus, ultimately connecting to μ-opioid receptor expressing RVM^{SC} neurons. Silencing any node along this multisynaptic circuit has minimal effect on nociception in healthy mice, but can eliminate mechanical hypersensitization and restore normal nociceptive response thresholds in mouse models of inflammatory and neuropathic pain. Repetitive, but not acute, activation each node within this circuit in healthy mice is sufficient to cause robust chronic mechanical hypersensitization. Our findings elucidate a spino-brain-spinal circuit loop linking ascending and descending pathways that specifically drives chronic mechanical pain, and identify novel cellular targets for treating chronic pain.

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Poster

PSTR118: Brain Mechanisms of Persistent Pain

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Topic: E.01. Somatosensation – Pain and Itch

Support: Brain and Behavior Research Foundation (NARSAD Young Investigator grant 27197 to M.C.C.)
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Rita Allen Scholar Award in Pain (to M.C.C.)
Foundation for Anesthesia Education and Research Mentored Research Training Grant (to J.M.T.)

Title: Neuropathic pain-related hypoexcitability of mesolimbic dopamine neurons

Authors: *J. M. THOMPSON[1], R. D. GRAHAM[3], J. GOFF[2], M. CREED[4];
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Abstract: Chronic pain (CP) is characterized by increased prevalence of mood disorders including depression that complicate treatment, however the underlying mechanisms for this association are not well understood. Development of a hypodopaminergic state due to decreased activity of dopamine neurons in the ventral tegmental area (VTA) is thought to be causally related to development of negative affective states, however direct evidence for this is lacking. In particular, the projection to the nucleus accumbens core (VTA->NAc) is involved in computing positive reward prediction error, but it is unknown if pain-related decreases in the activity of this synapse are responsible for a hypomotivational state. We hypothesized that VTA->NAc neuron activity is decreased following spared nerve injury (SNI)-induced neuropathic pain, corresponding to development of a hypomotivational phenotype. Using ex vivo patch clamp electrophysiology, we found that action potential firing of VTA->NAc neurons was significantly decreased at 5 weeks but not 1 week following SNI due to earlier entry into depolarization block. We then assessed for a depression-like amotivational phenotype using a reward and motivation-based resetting progressive ratio task and found that mice had reduced motivation for reward at 5 weeks but not 1 week following SNI. These results suggest that decreased activity of VTA->NAc neurons is related to development of a pain-related hypomotivational state and supports

the development of therapeutic strategies to mitigate these changes for treatment of CP-related mood disorders.

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Poster

PSTR118: Brain Mechanisms of Persistent Pain

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.23/I9

Topic: E.01. Somatosensation – Pain and Itch

Title: Shared Genetic Architecture Between Pain and Subcortical Brain Volumes

Authors: L. YUAN[1], H. ZHAI[1], ***K. WANG**[2];
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Abstract: Pain is one of the most prevalent health conditions globally, characterized by a complex biological basis and substantial genetic influence. Accumulating evidence has highlighted a robust association between pain and structural abnormalities in the brain, particularly within subcortical regions. However, the shared genetic mechanisms linking pain and subcortical brain volumes remain largely unexplored. The present study aimed to elucidate the extent of polygenic overlap and identify functionally relevant shared genomic loci between these traits. GWAS summary statistics for a composite pain phenotype—including limb, back, neck, head, and abdominal pain—were obtained from the FinnGen R12 release (N = 500,348), representing common forms of chronic somatic pain. GWAS data on subcortical brain volumes were derived from a cohort of 74,898 individuals, focusing on eight subcortical structures: the caudate, putamen, hippocampus, pallidum, thalamus, nucleus accumbens, amygdala, and ventral diencephalon. The bivariate causal mixture model (MiXeR) was applied to quantify polygenic overlap, and the conditional/conjunctional false discovery rate (cond/conjFDR) framework was used to identify shared genomic loci. To further investigate the biological relevance of the shared loci, summary-data-based Mendelian randomization (SMR) analysis was performed, integrating expression quantitative trait locus (eQTL) data with GWAS results for 15 specific diseases or symptom phenotypes characterized by pain. MiXeR analysis revealed that pain and subcortical brain volumes share a substantial proportion of genetic variation. A total of 86 significant loci were identified through conjFDR analysis, corresponding to 77 independent shared genomic regions. Among these, 23 represented novel pain-associated loci, 30 were novel for subcortical volumes, and 14 were novel for both traits. These loci were mapped to 610 protein-coding genes, of which 29 were found to be associated with the expression of both pain and subcortical volume traits. Notably, SMR analysis identified 12 overlapping genes showing significant associations with pain phenotypes specifically related to musculoskeletal and connective tissue disorders. These findings reveal substantial genetic overlap between pain and subcortical brain volume

phenotypes. The identified loci may provide novel insights into the neurobiological mechanisms underlying pain.

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Poster

PSTR118: Brain Mechanisms of Persistent Pain

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Program #/Poster #: PSTR118.24/I10

Topic: E.01. Somatosensation – Pain and Itch

Support: NSERC Grant RGPIN-2023-05350
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CIHR PDF 193919

Title: From Brain to Behaviour - Whole Brain Mapping of Neural Activity Underlying Individual Differences in Chronic Pain Vulnerability

Authors: *D. C. BOORMAN, L. J. MARTIN;
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Abstract: Chronic pain persists in some individuals long after tissue healing, while others recover fully from similar injuries—a disparity that remains poorly understood. To uncover the brain mechanisms that drive this variability, we combined whole-brain activity mapping with individual-level behavioural phenotyping in a mouse model of neuropathic pain. This approach allows us to identify region-specific neural activation patterns associated with pain vulnerability, moving beyond descriptive biomarkers toward functional insight into the circuits that shape chronic pain susceptibility. Outbred CD1 mice (n=30; 20F, 10M) received a chronic constriction injury (CCI) of the sciatic nerve and were tested twice daily for 5 days on a 0°C cold plate. Females showed significantly longer and more variable hind paw withdrawal (HPW) durations ($p < 0.01$). Whole-brain c-Fos expression was quantified in a subset (n=15) using ABBA and QuPath across 1,277 regions. Linear regressions revealed strong correlations between HPW behaviour and activity in many canonical pain-processing regions, including periaqueductal gray ($R^2 = 0.418$), basomedial amygdala ($R^2 = 0.49$), orbital cortex ($R^2 = 0.55$) and ACC ($R^2 = 0.35$). Several lesser-studied regions also correlated with pain behaviour, including the nucleus of Darkschewitsch ($R^2 = 0.49$), and the supramammillary nucleus ($R^2 = 0.34$), suggesting potential novel contributors to individual vulnerability. In a parallel experiment, FosTRAP::Ai14 mice (n=5 control, n=5 CCI) were tested on the cold plate pre-injury and injected with tamoxifen to TRAP active neurons. Following injury and re-testing, brains were collected to identify persistent and newly recruited cell populations. Group comparisons revealed elevated activation in pain-related regions, including insular cortex ($d = 2.35$, $p = 0.006$), anterior olfactory nucleus ($d = 1.65$), and prelimbic cortex ($d = 0.81$). Together, these experiments identify whole-brain substrates of chronic pain susceptibility. This mechanistic insight provides a roadmap for future

studies targeting key nodes and pathways to modulate persistent pain. Ongoing experiments will further extend this framework to include peripheral (nerve, DRG, spinal) and affective dimensions of chronic pain, integrating multimodal behavioural assays to build a systems-level model of pain vulnerability.

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Poster

PSTR118: Brain Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.25/I11

Topic: E.01. Somatosensation – Pain and Itch

Support: YWW was supported by the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) under grant K01NS124911.

Title: Socioeconomic and Lifestyle Determinants of Chronic Musculoskeletal Disorders in Brazil: A Network Analysis of a Population-Based Study Involving 87,648 Brazilian Adults

Authors: *Y. WOLDEAMANUEL[1], A. OLIVEIRA[2];
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Abstract: Background: Musculoskeletal disorders (MSKDs) are the primary cause of disability worldwide. While the links between socioeconomic and lifestyle factors and MSKDs have been extensively researched in Europe and North America, there is limited data about this relationship in Latin America. Objectives: This study aims to estimate the prevalence of chronic musculoskeletal disorders (MSKDs) in Brazil and explore their associations with socioeconomic and lifestyle factors. Design: This research is a cross-sectional study based on a subanalysis of the open-access database from the 2019 Brazilian National Health Survey. Conducted between 2019 and 2020, this survey was a nationwide, cross-sectional study involving 87,648 adults. Methods: Prevalence estimates were calculated using weighted sample strata, while the relationship between MSKDs and socioeconomic and lifestyle factors was analyzed through network analysis and weighted Poisson regression models with robust variance. Results: The estimated weighted prevalence of chronic MSKDs was 26.1% (95% CI, 25.5-26.8%). The network analysis demonstrated a significant correlation between MSKDs prevalence and factors such as higher BMI, alcohol consumption, smoking, and low income. Further, the regression models indicated that MSKD prevalence was positively associated with obesity, sleep disorders, smoking, alcohol use, and depression, while showing an inverse relationship with physical activity, even after adjusting for sociodemographic differences. Conclusions: This research identifies specific socioeconomic and lifestyle factors that correlate with MSKDs and

underscores the urgent need for national health initiatives aimed at MSKD prevention through targeted lifestyle changes, particularly for lower-income populations in Brazil.

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Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

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Program #/Poster #: PSTR119.01/I12

Topic: E.02. Somatosensation – Touch

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the Institute for AI and Beyond of the University of Tokyo, JSPS Grants-in-Aid for Scientific Research 18H05525, 20K15926, 22K21353

Title: Toward Artificial Induction of Texture Perception Through Patterned Optogenetic Stimulation in Mouse Somatosensory Cortex

Authors: *R. YOSHIDA[1], K. YAMASHIRO[1,2], N. MATSUMOTO[1,3], Y. IKEGAYA[1,3];
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Abstract: Texture perception represents one of the most complex aspects of somatosensation, involving multidimensional neural representations that encode surface roughness, friction, and compliance. In the primary somatosensory cortex (S1), texture information is processed through coordinated activity of diverse neural populations, creating precise spatiotemporal patterns that distinguish between different tactile qualities. While previous attempts to artificially induce tactile sensations have focused on simple pressure detection using electrical stimulation, these approaches fundamentally lack the spatial precision required for complex texture perception. Rather than engaging specific neural ensembles, they indiscriminately activate neurons around electrode sites without the fine temporal control necessary for texture representation. In addition, it has been difficult to identify optimal stimulation patterns necessary to replicate natural texture-encoding neural activity.To overcome these limitations, we developed an optogenetic approach to artificially induce texture perception in mice by precisely controlling neural activity patterns in S1. We first established a texture discrimination Go/No-Go behavioral paradigm where mice learned to distinguish between different surface textures presented to their whiskers, achieving >80% accuracy. Moreover, during this behavioral training, local field potentials (LFPs) were simultaneously recorded from S1 to capture neural signatures associated with specific texture presentations. In parallel, channelrhodopsin-2 was expressed in S1 neurons via in utero electroporation, enabling light-mediated neural activation. A digital micromirror device then provided precise spatiotemporal light stimulation with single-cell resolution across a 2 mm²

cortical area, allowing targeted activation of specific neural populations with millisecond temporal precision. Our current work focuses on characterizing texture-specific LFP patterns during natural whisker stimulation to identify distinct neural signatures for different surface textures. Building on these findings, we are developing optogenetic stimulation protocols based on these neural patterns to selectively activate corresponding ensembles in the absence of peripheral input. Ultimately, our approach aims to establish the foundation for future integration with machine learning algorithms to optimize stimulation patterns and achieve robust artificial texture perception.

Disclosures: R. Yoshida: None. **K. Yamashiro:** None. **N. Matsumoto:** None. **Y. Ikegaya:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.02/J1

Topic: E.02. Somatosensation – Touch

Support: DFG WI 5636/2-1

Title: Intrinsic physiology and synaptic connectivity of genetically specified VIP-expressing GABAergic neurons in L2/3 of mouse barrel cortex.

Authors: *H. NAM, M. MOCK, M. WITTE, J. F. STAIGER;
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Abstract: Neocortical GABAergic interneurons (INs) can be categorized into three main subpopulations based on their molecular identity: Parvalbumin (PV)-expressing INs, somatostatin (SST)-expressing INs, and vasoactive intestinal polypeptide (VIP)-expressing INs, with the latter accounting for app. 12% of the total population. These VIP INs play a crucial role in information processing in the barrel cortex (a specific region of rodent primary somatosensory cortex), mainly by forming disinhibitory circuits with SST and PV INs. This makes them one of the major players in maintaining the neocortex's balance between excitation and inhibition. Our recent studies indicate that VIP cells can be divided into at least three main molecular subgroups: those expressing calretinin (CR), cholecystokinin (CCK), and choline acetyltransferase (ChAT). In these studies, however, their precise differences in electrophysiology, morphology, and especially in their connectivity pattern to SST-IN, PV-IN, or excitatory cells remained only incompletely understood. In our study, we now focused on VIP+/ChAT+, VIP+/CR+, VIP+/CCK+ cells while performing intralaminar L2/3 paired patch-clamp recordings and optogenetics to detect their postsynaptic target cells, along with post-hoc morphological characterization. Additionally, we analysed the electrophysiological properties of each VIP subtype. We show that VIP-ChAT INs preferentially target SST cells, whereas VIP-CR INs target both PV and SST cells, and VIP-CCK INs preferentially target excitatory cells. Each of

the three VIP subtypes exhibits a wide-ranging electrophysiological and morphological profile, which shows over the subgroups no statistically significant differences, except for the distribution of action potential firing patterns. Overall, this makes the entire VIP cell population diverse in molecular identity, electrophysiological properties, morphology, and connectivity. Our findings draw attention to the significant importance of this varied population of VIP INs in maintaining E/I balance and their contribution in somatosensory information processing. Notably, in light of evidence showing that their dysfunction is linked to various neurological and psychiatric disorders, affecting cognitive functions like schizophrenia and epilepsy, highlighting its crucial role in maintaining normal brain dynamics.

Disclosures: H. Nam: None. **M. Mock:** None. **M. Witte:** None. **J.F. Staiger:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.03/J2

Topic: E.02. Somatosensation – Touch

Support: R01NS107599

Title: Lateral spread in sensory cortex as a novel gain mechanism in selective detection

Authors: *A. LAM[1,2], E. ZAGHA[3];
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Abstract: Neocortex is a context-dependent connectivity machine. And yet, the mechanisms underlying dynamic functional connectivity within the neocortex are poorly understood. One likely contributing factor is gain modulation of the upstream region. Here, we investigate the contribution of lateral spread as a potential gain mechanism in the context of a selective detection task in mice. In this task, mice learn to selectively respond to a single paddle deflection in the whisker field of one side of the face (target) and ignore identical deflections of the opposite side (distractor). Target and distractor stimuli evoke similar responses within their primary somatosensory cortex (S1) center response fields. And yet, target stimuli effectively propagate beyond S1 to multiple cortical and subcortical regions while distractor stimuli do not. Using widefield Ca^{2+} imaging, we determined the extent of target vs. distractor lateral spread within sensory cortex. For expert performing mice, we found that target stimuli evoke significantly larger volumes of activation compared to distractor stimuli. Moreover, we found a stronger relationship between peak (center response field) activation and lateral spread for target compared to distractor stimuli, which emerges with learning. Using a simplified neural circuit model, we demonstrate that modulations of lateral inhibition can account for the differences in target vs. distractor evoked spatial activations. From these findings, we propose that modulation

of lateral spread in sensory cortex could be a potent mechanism of stimulus gain underlying dynamic functional connectivity.

Disclosures: A. Lam: None. **E. Zagha:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

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Topic: E.02. Somatosensation – Touch

Support: NRTS 2199 from the American Academy of Neurology to William Zeiger
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24POST1193716 Postdoctoral fellowship from the American Heart Association to Baruc Campos

Title: Parvalbumin and somatostatin interneurons regulate circuit plasticity in the healthy and injured somatosensory cortex

Authors: *B. CAMPOS[1], W. ZEIGER[2];
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Abstract: Adaptive circuit plasticity plays crucial roles in the healthy and injured brain. The primary somatosensory barrel cortex (S1BF) of mice exhibits plasticity throughout development and into adulthood and is thus an ideal brain region to study circuit mechanisms that underlie plasticity. Precise regulation of the balance between excitation and inhibition is thought to be important for sensory processing. Shifts in the excitation:inhibition (E:I) balance have been proposed to both mediate adaptive plasticity in the healthy brain and also to underlie impairments after injury. The cortical E:I balance is governed by complex and dynamic interactions between excitatory pyramidal cells (Pyr) and inhibitory GABAergic cells, including parvalbumin (PV) and somatostatin (SST) interneurons. PV and SST interneurons provide direct inhibition onto Pyr cells, synapsing onto peri-somatic regions and apical dendrites, respectively. Little is known about how the activity of these cells change during experience-dependent plasticity or after injury. To test this, we used longitudinal in vivo two-photon calcium imaging and chemogenetic manipulations of PV and SST interneurons in the S1BF. In the healthy cortex, using a well-established chronic whisker trimming protocol to induce sensory experience-dependent plasticity. We found that in deprived, but not spared, barrels there was a substantial recruitment of PV cells responding to the spared whisker, mirroring changes in selectivity previously reported for Pyr cells. We then used chemogenetics to acutely manipulate the activity of PV cells and found that increasing PV cell activity strongly reduces sensory evoked responses in Pyr and SST cells. We also found that chronic inhibition of PV cells potentiates whisker trimming induced recruitment of Pyr cells to the spared whisker. In the injured cortex, we

targeted photothrombotic strokes to a single barrel (C1) and recorded the activity of PV and SST interneurons in an adjacent barrel (D2) over time during recovery. We found that sensory evoked PV cell activity is selectively reduced from the whisker corresponding to the lesioned barrel (C1), mirroring results we have previously found for Pyr cells. We also found that acute chemogenetic inhibition of PV cells leads to an increase in the number of whisker responsive SST cells. We hypothesize that post-stroke reductions in PV activity may lead to increased SST activity that constrains cortical plasticity and we are currently analyzing our SST imaging data to test this. Together, our results will contribute significantly to our understanding of the mechanisms regulating circuit plasticity in both the healthy and injured cortex.

Disclosures: B. Campos: None. **W. Zeiger:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

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Program #/Poster #: PSTR119.07/J5

Topic: E.02. Somatosensation – Touch

Support: NIH Grant 2 R01 NS092367
NIH Grant 5 K99 NS129753-02

Title: Dissociable effects of selective attention and global arousal in whisker somatosensory cortex

Authors: C. CEN[1], S. LI[2], L. RODRIGUEZ[3], D. E. FELDMAN[2], ***D. L. RAMAMURTHY**[4,2]; [2]Neurosci., [1]UC Berkeley, Berkeley, CA; [3]Univ. of California Berkeley, Berkeley, CA; [4]Psychology, UC Riverside, Riverside, CA

Abstract: Selective attention is a neurobiological process that enables preferential processing of behaviorally relevant stimuli. In contrast to the stimulus-specific effects of selective attention, global arousal refers to a state of increased alertness associated with active behaviors, generally leading to broad, non-selective increases in neural activity across cortical areas. We recently showed that mice can flexibly shift attention between specific whiskers based on recent reward history, locally boosting neural activity in the corresponding whisker columns in primary somatosensory cortex (S1), with cortical layer-specific differences. Here, we investigated the relationship between arousal and attention effects across cortical layers in mice trained on a whisker touch detection task. Using DeepLabCut, we tracked indicators of arousal (pupil size, whisker motion, and body motion) in mice during touch detection behavior in two-photon calcium imaging and Neuropixels recording experiments. We examined how arousal influences neural activity in S1 across cortical layers and under conditions where mice are attending toward or away from whisker touch stimuli to understand how arousal interacts with whisker-specific attentional effects on neural activity. L2/3 PYR cells are strongly boosted by selective attention, but different subsets of the population are differentially modulated by arousal and attention. As a

population, L2/3 VIP cells are strongly and non-selectively recruited by arousal, with only ~15% selectively boosted by attention to specific whiskers, which may correspond to molecularly distinct subtypes. Like selective attention, arousal primarily boosts neural activity in L2/3 and L5, but not in L4. However, selective attention effects in L2/3 and L5 are present during both high and low arousal trials, indicating that while attention and arousal engage similar cortical layers, attention operates independently of global arousal state. Together, these findings illustrate dissociable effects of arousal and selective attention on sensory processing, potentially mediated by distinct local circuits.

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Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.08/J6

Topic: E.02. Somatosensation – Touch

Support: RCSA Scialog, Shurl and Kay Curci Foundation

Title: Critical window post-stroke is influenced by biological sex

Authors: *R. FAKHREDDINE[1], M. MONAHAN[2], K. HONG[2];
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Abstract: Sex differences in stroke outcomes are well documented, but it is unknown how males and females differ in their timing and duration of the critical window- a limited period of heightened plasticity when the brain is most responsive to rehabilitative interventions. While this window is typically defined by motor recovery, the timeline for tactile feedback remains poorly understood and may follow a distinct trajectory. To explore critical windows of tactile recovery, we developed an isolated tactile model of photothrombotic stroke in mice, which allowed us to investigate the effect of various rehabilitation timing on recovery. Mice were trained to perform a whisker-mediated tactile detection task to establish baseline levels of perception. Focal ischemia was induced using photothrombosis, and were given varying periods of rest(1, 7, or 14 days) before resuming training. While animals did not completely recover to pre-lesion levels, earlier retraining led to better recovery.Separating the groups by sex revealed significant differences in timing of the t critical window post stroke. Male mice improved in tactile sensation with immediate (1d) training post-stroke, while female mice benefited more from delayed (7d) training. Minimal recovery was observed in the 14d rest group suggesting the tactile critical window occurs within the first week post-stroke for both sexes, but offset in timing. Our work reveals significant differences in the neuroplastic timeline between sexes. These results shed light on an understudied aspect of stroke rehabilitation and motivate future studies that incorporate sex-specific timing strategies for rehabilitation paradigms.

Disclosures: R. Fakhreddine: None. **M. Monahan:** None. **K. Hong:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

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Topic: E.02. Somatosensation – Touch

Support: IRP Grant
SNSF Grant #310030_204562

Title: Pathway-specific modulation of membrane potential dynamics in layer 2/3 pyramidal neurons of the mouse somatosensory cortex in vivo

Authors: *I.-W. CHEN, A. HOLTMAAT;
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Abstract: Layer 2/3 (L2/3) pyramidal neurons in the primary somatosensory cortex (S1) receive long-range inputs from various brain areas, which influence their processing of sensory signals. We investigated how these long-range pathways modulate whisker-evoked responses by combining optogenetic activation of axons from the first-order ventral posterior medial thalamic nucleus (VPM), the higher-order posterior medial thalamic nucleus (POm), primary motor cortex (M1), and contralateral S1 (contraS1) with whole-cell recordings from L2/3 pyramidal neurons in anesthetized mice. Whisker deflections or optogenetic activation of these pathways typically evoked subthreshold depolarizations. Photostimulation (100 ms) of VPM and POm axons induced rapid and sustained depolarization lasting up to ~1 s. Activation of M1 axons elicited similarly sustained responses but these included an intermediate inhibitory phase (~0.1-0.2 s after stimulation onset). In contrast, activation of contraS1 axons produced a transient depolarization that did not persist into intermediate or late (~0.2-0.5 s after stimulation onset) phases. Upon simultaneous whisker and optogenetic stimulation, the activation of VPM or POm axons enhanced both the early (~0-0.1 s after stimulation onset) and late phases of whisker-evoked responses. Simultaneous activation of M1 axons selectively increased late phase responses, while activation of contraS1 axons suppressed them. These findings suggest that thalamocortical inputs generally enhance whisker-evoked responses in L2/3 pyramidal neurons of S1, whereas corticocortical inputs differentially engage inhibitory mechanisms to shape sensory responses over time. Ongoing experiments aim to elucidate the underlying mechanisms and functional relevance of this pathway-specific modulation.

Disclosures: I. Chen: None. **A. Holtmaat:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.10/J8

Topic: E.02. Somatosensation – Touch

Support: FamilieSCN2A Action Potential Award
R01MH125978

Title: Examining SCN2A loss-of-function in sensory perception

Authors: *K. A. SALVATI[1], R. P. ALEXANDER[2], E. PARKHILL[1], E. HAMADA[1], D. E. FELDMAN[3], K. J. BENDER[1];
[1]Neurol., UCSF, SAN FRANCISCO, CA; [2]Neurol., UCSF, San Francisco, CA; [3]Neurosci., UC Berkeley, Berkeley, CA

Abstract: 90% of people with autism spectrum disorder (ASD) exhibit atypical sensory processing. Changes in tactile sensitivity, altered tactile detection, and attention to specific sensory stimuli are well documented, but the cellular and circuit mechanisms that underlie these alterations are not well understood. One hypothesis for a central locus that modulates tactile processing is the primary somatosensory cortex (S1). In S1, layer 5 (L5) pyramidal neurons (PYR) act as coincidence detectors: integrating "bottom-up" subcortical sensory information and top-down "higher-order," contextual input at the basal and apical dendrites, respectively. This integration is critical for conscious perception, and studies have suggested that loss of L5 PYR coincidence detection corresponds to loss of consciousness with anesthesia. Thus, L5 PYR functional deficits may cause a breakdown in sensory perception, a hypothesis associated with atypical tactile sensitivity in ASD. Our lab has shown that L5 PYR function depends on *Scn2a*, and that *Scn2a* haploinsufficiency diminishes dendritic excitability. Herein, we investigate whether *Scn2a* haploinsufficiency affects sensory perception. We trained wild type (WT) and *Scn2a*$^{+/-}$ mice to perform a Go/No-Go whisker detection task. In varying whisker deflection amplitude, psychophysical response curves were generated for WT and *Scn2a*$^{+/-}$ mice. In parallel, we performed two-photon calcium imaging to capture S1 L5 PYR apical dendrite calcium responses to whisker deflections during the behavior task. Preliminary psychometric functions demonstrate that stimulus strength likely increases response probability in both WT and *Scn2a*$^{+/-}$ mice. However, *Scn2a*$^{+/-}$ mice show weaker responses at moderate-to-high whisker deflections and lower response probability at 50% and 100% max whisker deflection amplitude relative to WT mice. All suggest *Scn2a*$^{+/-}$ mice require more intense stimuli for detection, which reflects a considerable shift in their perceptual threshold. We anticipate this trend to persist, with *Scn2a*$^{+/-}$ mice showing reduced sensitivity to whisker deflection and a greater reliance on stronger stimuli to guide behavior. We also anticipate that calcium signals in apical dendrites will reflect this difference, with *Scn2a*$^{+/-}$ mice showing smaller and less frequent calcium responses to the same stimuli compared to WT mice. Future directions will examine how *Scn2a*$^{+/-}$ knockdown in S1 L5 PYR, specifically, impairs dendritic integration of sensory stimuli. These results will help determine if *Scn2a*$^{+/-}$ and L5 dendritic integration is *necessary* to encode the perception of tactile stimuli.

Disclosures: K.A. Salvati: None. **R.P. Alexander:** None. **E. Parkhill:** None. **E. Hamada:** None. **D.E. Feldman:** None. **K.J. Bender:** 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.; Regal Therapeutics.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.11/J9

Topic: E.02. Somatosensation – Touch

Support: NINDS Grant U01NS103558

Title: Imaging Acetylcholine Dynamics across Cortical Layers during Behaviors

Authors: *C. WANG[1], S. A. HIRES[2];
[1]USC, LOS ANGELES, CA; [2]Biol. Sci., USC, Los Angeles, CA

Abstract: Traditionally, acetylcholine is thought to be globally released in the cortex, acting as a broadcast signal to modulate the brain state and cortical neuronal activity. Recent anatomical studies revealed specific input-output relationships for distinct motifs within Basal Forebrain cholinergic neurons (BFCNs; Gielow & Zaborsky, 2017) and layer-specific innervation of BFCNs in the primary Somatosensory Cortex (S1; Allaway et al., 2020). These suggest the possibility that BFCNs projecting to different layers of S1 receive inputs from distinct sets of brain regions. However, direct evidence for distinct, layer-specific spatiotemporal dynamics of cortical acetylcholine is missing. Hence, we imaged the acetylcholine dynamics across S1 layers using an aluminum-coated microprism and a novel acetylcholine sensor GRAB-ACh4m during spontaneous behavior. To assist layer segmentation for prism imaging, we retrogradely traced from L2/3 and L5A of vibrissal Motor Cortex (vM1) to label L2/3 and L5 of S1. We tracked facial movements and pupil fluctuations during imaging and regressed the contributions of different movement predictors to acetylcholine dynamics across layers. To further test potential functional divergence of cortical acetylcholine, we delivered odors, air puffs, and social interactions in separate imaging sessions. Together, these results delineate the contributions of stimulus and stimulus-evoked movements to acetylcholine dynamics across cortical layers during a diverse set of behaviors.

Disclosures: C. Wang: None. **S.A. Hires:** None.

Poster

PSTR119: Barrel Cortex

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Program #/Poster #: PSTR119.12/J10

Topic: E.02. Somatosensation – Touch

Support: R21MH137452
R01NS133751
P01NS074972

Title: Layer 1 dependent mechanisms of associative learning in mouse primary somatosensory cortex

Authors: *H. ZURITA[1], E. GERON[1], S. S. DELLAL[1], R. TREMBLAY[1], J. SHIN[2], R. MACHOLD[1], B. RUDY[1];
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Abstract: Acetylcholine (ACh) is important for plasticity and learning, but the cellular and circuit-level mechanisms by which ACh regulates these processes in neocortex remain unclear. We implemented a cortical microstimulation task in adult male and female mice, pairing microstimulation of the infragranular cortex in the whisker representation of the primary somatosensory cortex (wS1) with a water reward. Learning in this task was previously shown to depend on perirhinal inputs targeting layer 1 (L1) of wS1 (Doron, Shin, et al., 2020). To monitor ACh dynamics, we used two-photon imaging of GACh, a genetically encoded fluorescent ACh sensor expressed in wS1. GACh signals during early training differed from those observed once the stimulus-reward association was established. Genetic ablation of choline acetyltransferase (ChAT) in basal forebrain neurons projecting to wS1 abolished ACh release and impaired both acquisition and consolidation of the microstimulus-reward association, while the contralateral hemisphere in the same mouse learned normally. We also mapped perirhinal inputs to distinct L1 cell-types and performed two-photon imaging to determine their roles during learning. These experiments revealed that perirhinal activity and cholinergic release converge on L1 to drive cell-type-specific responses critical for acquiring the association. Together, our results demonstrate that ACh release in wS1 is necessary for this cortical-dependent microstimulation-reward association and that perirhinal input synergizes with cholinergic signaling in L1 to gate associative learning.

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Poster

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Program #/Poster #: PSTR119.13/J11

Topic: E.02. Somatosensation – Touch

Title: Neural correlates of probabilistic perceptual decision-making in the somatosensory cortex during virtual reality navigation

Authors: *A. G. ARMSTRONG[1], Y. VLASOV[2];
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Abstract: Harnessing behavior that neural systems have evolved to achieve is critical when determining how perceptual decisions arise in the brain. Traditionally, it is thought such decisions are produced by gradual accumulation of sensory evidence through a hierarchically organized feed-forward cascade of neuronal activities that transform early stimulus representations in the primary somatosensory cortex (S1) through the secondary somatosensory cortex (S2) to a perceptual decision processed in pre-motor areas. Recently, this prevailing view has been challenged by observation of choice-correlated neural activity as early in the hierarchy as the barrel cortex (wS1). On the contrary, the exact role of wS1 in this process is debated based on controversial results of loss-of-function behavioral experiments that often require prolonged training and unnatural behavioral reports, which showed wS1 can be dispensable for some sensory-guided decisions. Here, to elucidate the role of wS1 in decision-making, we developed an ethological whisker-guided virtual reality (VR) paradigm that closely mimics natural navigation in underground burrows. Untrained mice navigate left and right turns at high speeds by sensing VR walls with just a pair of C2 whiskers. Inactivating fewer than 200 neurons in layer 4 of the C2 barrel column resulted in loss of ability to produce turns contralateral to the lesion[1]. Using a probabilistic model of collision avoidance in the presence of noise and uncertainties, we hypothesize that wS1 is involved in a feedback control loop that requires continuous updates and predictions to infer the optimal path for collision avoidance when making the decision to turn in the virtual environment. We show that neural activity during the decision exhibits dramatic collapse of the high-dimensional spiking activity to just a single latent variable accounting for 90% of the variance. This collapse is subsequently followed by a slower and almost synchronous ramping up of neural activity across the whole cortical column. We show that this latent variable is consistent with models of gradual accumulation of noisy sensory evidence to a decision bound. Analysis of multiple variance signatures during the decision supports these models[2]. These observations indicate that wS1 may directly participate in a categorical coding of all-or-none decision variable via cortico-cortical feedback loops involving S2 through which sensory information reverberates to be transformed into perception and action. [1] Armstrong, A.G. & Vlasov, Y. (2025a) *BioRxiv*, 2025.02.17.638764 [2] Armstrong, A.G. & Vlasov, Y. (2025b) *BioRxiv*, 2025.03.29.646003

Disclosures: A.G. Armstrong: None. **Y. Vlasov:** None.

Poster

PSTR119: Barrel Cortex

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Program #/Poster #: PSTR119.14/J12

Topic: E.02. Somatosensation – Touch

Title: Psychometric characteristics of decision-making during natural whisker-guided navigation in a tactile virtual reality

Authors: *S. ZHANG[1], Y. VLASOV[2];
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Abstract: Perceptual decision-making paradigms typically require weeks of training and rely on goal-directed behaviors influenced by rewards. To investigate the behavioral psychometric characteristics in ethologically relevant perceptual decision-making task, we utilized active whisker-guided navigation in tactile virtual reality (VR).
Here, mice are head-fixed on a suspended ball and navigate left and right turns at fast locomotion speeds. A pair of walls are placed on both sides of the mouse's snout and controlled by a real-time VR system to guide straight or turning movements. The main session is unrewarded, not goal-directed, unfamiliar to the mice, and designed to simulate natural behavior of navigating left and right turns directed by sensing the approaching walls by their whiskers. We quantify turning success based on angular change and calculate reaction times from the first peak angular velocity following wall movement. From this, we get three psychometric characteristics: (1) turning accuracy as a function of wall distance, (2) reaction time as a function of wall distance, and (3) turning accuracy as a function of reaction time. The curve of accuracy and wall distance approximately presents a classical 'S' shape indicating that the shorter the distance, the higher the success rate. Wall distance of 5 mm can generate approximately 50% of the accuracy of correct execution of right and left turns. The second curve shows that decision time is positively correlated with the wall distances, indicating that stronger stimuli (i.e., closer walls) leads to faster decisions. And the last curve shows that in this untrained and unrewarded natural task, the decision accuracy and the reaction time are negatively correlated, suggesting that more accurate decisions are made more quickly. Our results are in line with most decision-making models, demonstrating that in our natural, unrewarded, and untrained decision-making VR paradigm, similar data analysis pipelines can be effectively applied. Notably, the 5 mm wall distance—where turning accuracy is 50%—is a critical threshold for study on perceptual uncertainty and will be a critical point in our future investigations of the neural mechanisms underlying decision-making. By linking stimulus strength, behavioral performance, and reaction time, this study establishes a behavioral paradigm for studying perceptual decision-making. These findings provides a behavioral basis for subsequent electrophysiological recordings.

Disclosures: S. Zhang: None. **Y. Vlasov:** None.

Poster

PSTR119: Barrel Cortex

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Program #/Poster #: PSTR119.15/J13

Topic: E.02. Somatosensation – Touch

Support: R01NS107599

Title: Activities of sensory and frontal cortices in sequence learning in wild type and FMR1 KO mice

Authors: *R. CARDONA[1], S. PURI[1], K. PARK[1], D. GARCIA[1], E. ZAGHA[2];
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Abstract: Learning to recognize and predict temporal sequences is a key component of sensory processing and is disrupted in several neurodevelopmental disorders such as Fragile X Syndrome (FXS). Sequence learning is marked by the ability to anticipate outcomes by forming preparatory responses before a sequence ends. However, the neural mechanisms that support this form of learning remain poorly understood. This study investigates how subjects learn and respond to repeated sensory sequences, focusing on the activities of the frontal cortex (FC) and the sensory cortex (S1). Furthermore, we investigate how behavioral and neural dynamics differ in wild type (WT) and FMR1 knockout (KO) mice, a mouse model of FXS. We trained WT and FMR1 KO mice on a whisker-based, operant pattern sequence task. For trained WT mice, evidence of sequence learning is supported by differential behavioral responding to stimulus sequences and stimulus elements. In contrast, FMR1 KO mice responded similarly to different stimulus sequences, suggesting impaired sequence learning. Throughout training, we recorded dorsal cortex activity using widefield calcium imaging. Analyses of the neural imaging data are directed at characterizing sensory cortex stimulus encoding and frontal cortex activation as potential contributors to WT and FMR1 KO task performance. Understanding these cortical dynamics will provide insights into the neural basis of sequence learning deficits in FXS and other autism spectrum disorders.

Disclosures: R. Cardona: None. **S. Puri:** None. **K. Park:** None. **D. Garcia:** None. **E. Zagha:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.16/J14

Topic: E.02. Somatosensation – Touch

Support: 1SC3GM122657

Title: Exploring molecular and genetic interactions in the murine barrel cortex after sensory deprivation during development

Authors: *K. A. RIVERA GOMEZ[1], J. C. BRUMBERG[2];
[1]City Univ. of New York Queens Col., Flushing, NY; [2]Dept Psychology, Queens College, CUNY, Flushing, NY

Abstract: Sensory deprivation (SD) during the critical period of neural development induces microglial-regulated pruning of perineuronal nets (PNs), a neuron-specific form of the extracellular matrix (ECM) that preferentially surrounds Parvalbumin (PV+) interneurons that are important for information processing in cortical networks. This research elucidates molecular interactions in the barrel cortex after SD. We targeted macrophage/microglia response markers in extracellular matrix remodeling using RNAScope and Immunohistochemistry. Following SD, tissue plasminogen activator (tPA), a serine protease expressed in neurons and microglia leading to neuronal death following excitotoxicity, displayed an increased expression in SD animals compared to wildtype. Microglial GABA receptors (Gabbr1 and Gabbr2) expressed during development, specifically involved in the maturation of inhibitory circuits by targeting the PV bouton, showed a decrease in regional expression of both markers after SD. Legumain (Lgmn), an asparaginyl endopeptidase, upregulated in microglia after spinal cord injury and in extracellular matrix remodeling, has also been shown to be related to metalloproteinases directly, such as MMP9, which is secreted by microglia that act on various substrates including aggrecan, the main component of PNs. Lgmn was significantly upregulated in the somatosensory cortex of animals after SD. The expression of Aquaporin 4 (Aqp4), an astrocytic membrane protein with implications in astrocyte-microglia communication, is upregulated during inflammatory lesions in SD animals, suggesting a role in astrocytic involvement during ECM remodeling. SD also caused an increase in the protein expression of Microglia-associated anti-inflammatory triggering receptor expressed on myeloid cells (TREM2), indispensable for activating, mediating transformation, and microglial instruction of astrocytic synaptic engulfment during neurodevelopment. These results show microglial signatures involved in the degradation of PNs and the potential involvement of microglial-astrocytic collaboration for increased plasticity in the barrel cortex after sensory deprivation.

Disclosures: K.A. Rivera Gomez: None. **J.C. Brumberg:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.17/J15

Topic: E.02. Somatosensation – Touch

Support: Neuroscience Network NRW Grant iBehave

Title: An in silico framework for multi-scale modeling and analysis of in vivo neuron-network mechanisms

Authors: *B. MEULEMEESTER;
Max Planck Inst. for Neurobio. of Behavior, Bonn, Germany

Abstract: The electrophysiological response of a neuron to synaptic input is the result of a complex interplay between neurobiological mechanisms that originate from both the neuron and the network scale, such as ion channel dynamics, synapse activation dynamics, network connectivity, and morphological features. Currently, there is no general framework available that can model and systematically investigate the impact of these individual but codependent multi-scale mechanisms on each other, or the neuronal output. For this reason, we here present the In Silico Framework (ISF): a multi-scale simulation environment for the generation and investigation of empirically constrained multi-scale models that can account for the response of a single neuron under in vivo conditions. Because ISF implements explicit mechanistic detail and captures biological heterogeneity across scales, it enables precise and testable *in silico* predictions of *in vivo* responses. It supports the investigation of targeted manipulations at both the neuronal and network levels, and facilitates the identification of minimally sufficient mechanisms by reducing heterogeneous multi-scale models to generalizable, analytically tractable representations.

Disclosures: B. Meulemeester: A. Employment/Salary (full or part-time): Max Planck Institute for Neurobiology of Behavior.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.18/J16

Topic: E.02. Somatosensation – Touch

Support: ERC 633428
ERC 101069192
DFG SFB 1089
DFG SPP 2041
German Federal Ministry of Education

Title: Broad receptive fields in cortex facilitate efficient and robust population encoding of sensory information

Authors: *M. ROYO CANO[1], A. BAST[2], R. FRUENGEL[1], C. P. DE KOCK[3], M. OBERLAENDER[3];
[1]In Silico Brain Sciences, Max Planck Inst. for Neurobio. of Behavior, Bonn, Germany; [2]Janelia Res. Campus, Ashburn, VA; [3]Integrative Neurophysiol., Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: In conventional views of the cortical circuitry, sensory processing begins in layer 4 (L4), where inputs from primary thalamus evoke responses that are selective to specific stimulus

features. However, it has become increasingly clear that in parallel to this canonical circuit, the same thalamic input also drives responses in layer 5 pyramidal tract (L5PT) neurons, the main output cells of the cortex. In contrast to the selective responses and hence narrow receptive fields (RFs) in L4, L5PTs respond unselectively to a variety stimulus, having broad RFs. We recently reported the mechanism underlying these broad RFs: layer 6 cortico-cortical (L6CC) cells, with long horizontal axons, receive direct sensory input from thalamus and project to L5PTs in multiple columns driving their responses. However, it remains unclear what information about the sensory stimulus L5PTs could broadcast to their downstream targets despite their unspecific responses. To address this question, we combine anatomically and functionally realistic multi-scale models of the barrel cortex with electrophysiological measurements in vivo. We find that the broad RFs of L5PTs form the basis for a population code that robustly broadcasts every sensory input that arrives in the barrel cortex simultaneously to any of its downstream subcortical target areas. In fact, any small population of L5PTs — no matter whether they are located within the same or across different cortical barrel columns— encodes the identity of the sensory input. The reliability and efficiency of this population code are determined by both the width of the RFs as well as their variability from cell to cell. In essence, the broader the RFs and the greater their variability across L5PTs, the smaller is the population required to convey the same sensory information to downstream areas. Our findings indicate that sensory input is encoded in parallel by two complementary population codes: one that is based on highly selective responses of the neurons in L4—i.e., narrow RFs— and a second one that is based on unselective and highly variable responses of the L5PTs—i.e., broad RFs.

Disclosures: M. Royo Cano: None. **A. Bast:** None. **R. Fruengel:** None. **C.P. De Kock:** None. **M. Oberlaender:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.19/K1

Topic: E.02. Somatosensation – Touch

Support: NIH U01MH10907
NIH R01NS140230

Title: Local and Global Neural Dynamics Underlying Stimulus and Choice Across Sensorimotor Cortex

Authors: *A. S. BLAESER, M. A. CLOUGH, A. M. AHRENS, J. L. CHEN;
Biol., Boston Univ., Boston, MA

Abstract: Animals are often repeatedly exposed to the same environmental stimulus but may choose to respond differently depending on behavioral goals. How the brain switches between goal- and non-goal-directed behavior on a moment-to-moment basis is unclear but likely

involves complex multiscale interactions between sensory and motor areas. To investigate how sensorimotor interactions support flexible behavior, mice were trained to perform a whisker-based discrimination task that required them to repeatedly switch their response to the same tactile stimuli in a goal- and non-goal-directed manner. During the task, local optogenetic inactivation of either somatosensory or motor cortex altered behavior independently of goal-related context. Using a Quadroscope, we performed simultaneous two-photon calcium imaging of four regions of sensorimotor cortex. To disentangle local and global activity patterns, we compared population activity subspaces encoding task information versus inter-areal communication. We found that stimulus, choice, and stimulus-choice associations were equally represented locally within primary somatosensory (S1), secondary somatosensory (S2), and primary motor (M1) cortex. In S1 and S2, subspaces encoding task information were distinct from communication subspaces shared with other areas. In M1, subspaces encoding choice and stimulus-choice associations became more aligned with communication channels with S1 and S2 during goal-directed phases of the trial. This information flowed in a top-down manner from motor to sensory areas and was necessary for correct choice behavior. Our results demonstrate that while task information may be locally distributed across sensorimotor cortex, flexible communication between sensory and motor areas is critical for adaptive stimulus-driven behavior.

Disclosures: A.S. Blaeser: None. **M.A. Clough:** None. **A.M. Ahrens:** None. **J.L. Chen:** None.

Poster

PSTR119: Barrel Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.20/K2

Topic: E.02. Somatosensation – Touch

Support: NIH Grant F99NS141346
NIH Grant U01MH10907
NIH Grant R01NS140230

Title: Cell-type-specific genetic variation associated with individual differences in goal-directed learning.

Authors: *A. CAREY[1], H. DANTE[1], D. LEE[1], N. TAN[1], D. POWERS[1], K. ROBERTS[2], J. L. CHEN[1];
[1]Boston Univ., Boston, MA; [2]Wellcome Sanger Inst., London, United Kingdom

Abstract: Individuals exhibit variability in their ability to learn complex tasks. This variation could reflect intrinsic or environmental factors. We investigated whether genetic variation associated with learning could manifest as gene expression differences in specific neuronal or non-neuronal cell types. To test this, we assayed mice on sensory-guided learning using an a large-scale automated homecage training system. Mice were given 6 weeks to perform a 2-

alternative forced choice tactile working memory task. Over 350 mice of different genetic background were tested including Diversity Outbred (DO) mice and their eight founder inbred lines (129S1, NZO, CAST, A/J, WSB, C57, NOD, PWK). By comparing inbred strains, we observed heritable differences in task learning. Individuals from inbred strain (NZO) were consistently able to achieve expert task performance while all individuals from two other strains (PWK, NOD) failed to do so. To identify genes associated with learning, Quantitative Trait Loci, expression QTL, and differential gene expression analysis were performed on DO mice. Through this, 531 learning associated genes were identified across neocortex, hippocampus, and striatum. To determine if these candidate genes converged onto specific cell types, we performed spatial transcriptomics on naïve and trained NZO, PWK, and NOD animals. Latent factor analysis identified cell-type-specific gene expression patterns that were unique to background strains. We found differentially expressed candidate genes between learner and non-learner strains in 36 out of 202 subclasses and supertypes including in oligodendrocyte and striatal interneuron subtypes. By comparing naïve and trained animals, additional cell types, including glutamatergic cortical neurons, were identified that showed training-induced gene expression changes irrespective of task learning. Interesting, cell types that showed training-induced expression changes were more likely to be similar across background strains and vice versa. These findings show individual differences in task learning is associated with cell-type-specific gene expression patterns that is both inherited and experience dependent.

Disclosures: A. Carey: None. **H. Dante:** None. **D. Lee:** None. **N. Tan:** None. **D. Powers:** None. **K. Roberts:** None. **J.L. Chen:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.01/K3

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC016066

Title: Assessment of Lateral Line Efferent Innervation, Hair Cell Function, and Rheotaxis Behavior in Chrna9 Mutant Zebrafish

Authors: S. COHEN-BODENES[1], K. NGUYEN[1], J. RUDIN-LURIA[1], R. A. VOSS[1], *L. SHEETS[2];
[1]Otolaryngology, Washington Univ. in St. Louis, St. Louis, MO; [2]Washington Univ. Sch. of Med. In St. Lo, Saint Louis, MO

Abstract: Background: Cholinergic efferent innervation modulates hair cell response to stimuli through activation of acetylcholine receptors (Chrna9), which hyperpolarizes hair cells and suppresses their activity. While Chrna9 and its role in lateral line response to reafferent stimuli have been defined in zebrafish, the effects of its loss-of-function on efferent innervation, hair cell

function, and lateral line mediated behavior have not been evaluated. Here we assessed these properties in mutants lacking Chrna9.
Methods: Mutants and siblings at 5-7 days post-fertilization were used in all experiments. To assess efferent presynaptic contacts, dopaminergic innervation, and hair cell density in lateral line neuromasts, larvae were immunolabeled with antibodies to Synaptophysin, Tyrosine Hydroxylase, and Otoferlin. Loss of chrna9 expression was validated with HCR RNA-FISH. To assess hair cell mechanotransduction (MET), we incubated larvae in FM1-43 and measured the difference of fluorescence intensity in live images of neuromasts. To evaluate hair cell responses to stimuli, we measured evoked Ca2+ responses using a transgenic line expressing plasma-membrane-targeted GCaMP6s. To assess rheotaxis behavior, we delivered a flow stimulus in a parametrized 3D printed micro flume, collected videos of the larvae swimming with a high-speed camera, and tracked and categorized rheotaxis behavior using Deep Lab Cut and SimBA.
Results: Synaptophysin label had no change in average intensity or average number of presynaptic puncta in *chrna9-/-*. The average number of hair cells per neuromast was also comparable. Dopaminergic innervation was detected in all larvae and may present some variance in *chrna9-/-*.
We observed no significant difference in FM1-43 uptake in *chrna9-/-*, suggesting that hair cell MET is not strongly impacted. Experiments evaluating evoked Ca2+ responses in lateral line hair cells are ongoing.
chrna9-/- larvae performed rheotaxis, but their swimming behavior and ability to swim against the incoming flow was affected. Spatial heatmaps showed, during the first 10 sec, *chrna9-/-* were pushed toward the back of the arena. Time series analysis showed they accelerated and that their swimming behavior was amplified to perform efficient rheotaxis after 20 sec flow stimulation.
Conclusions: *chrna9-/-* lateral line organs show comparable synaptophysin labeling, dopaminergic innervation, and hair cell counts per neuromast. Chrna9 loss-of-function has some impact on rheotaxis behavior. Additional studies aim to analyze the swimming kinematics of *chrna9-/-* larvae during rheotaxis behavior and to probe for other variances in efferent synaptic contacts.

Disclosures: S. Cohen-Bodenes: None. **K. Nguyen:** None. **J. Rudin-Luria:** None. **R.A. Voss:** None. **L. Sheets:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.02/K4

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01DC016066
NIH R25DC020706

Title: Ampa-mediated excitotoxic injury evokes a calcium surge in zebrafish lateral line afferent nerves

Authors: P. ROYCHOWDHURY[1], *M. E. WARCHOL[2], L. SHEETS[3];
[1]Washington Univ. Sch. of Med., St. Louis, MO; [2]Otolaryngology, Washington Univ., St. Louis, MO; [3]Otolaryngology, Washington Univ. Sch. of Med. In St. Lo, Saint Louis, MO

Abstract: Background: Glutamate excitotoxicity via excessive activation of Ca^{2+}-permeable AMPARs (CP-AMPARs) is a primary driver of cochlear synaptopathy, which can lead to the progressive degeneration of auditory nerves and exacerbate age-related hearing loss. Understanding the effects of postsynaptic Ca^{2+} influx on afferent nerves during excitotoxic injury is crucial for developing therapeutic strategies to prevent synaptopathy and progressive hearing loss. However, real-time visualization of excitotoxic injury in the mammalian cochlea is challenging. The zebrafish lateral line offers a transparent, genetically tractable model for in vivo, time-lapse imaging of hair cells, synapses, and afferent neurons. Here, we employed live imaging to visualize Ca^{2+} dynamics in the afferent neurons of the zebrafish lateral line.**Methods:** 6-7-day old transgenic zebrafish expressing a Ca^{2+} indicator in their afferent neurons *(tg(hsp70:GCaMP6s:Sill1))* and an RFP in their macrophages (*tg(mpeg1:tdtom)*) were imaged. Fish were paralyzed with α-bungarotoxin and mounted in an imaging chamber before visualizing the post-synaptic elements of each neuromast with a spinning disc confocal microscope. After baseline images, fish were exposed to 200 μM AMPA for 15-30 minutes—conditions previously shown to simulate excitotoxic injury—prior to rinsing with embryo media. Time-lapse imaging followed for 2-3 hours, and results were compared to control fish (no AMPA exposure) as well as fish that were co-treated with 40 μM CNQX (competitive AMPA receptor antagonist). **Results:** Following AMPA exposure, nearly half of GCaMP6s-expressing afferent nerves (~47%) showed a robust surge of post-synaptic Ca^{2+} activity ~10-25 minutes after drug removal. Co-administration of 40 μM CNQX with 200 μM AMPA reduced the incidence of the Ca^{2+} surge (20%). There was no evidence of a Ca^{2+} surge when 40 μM CNQX was co-administered with 100 μM AMPA or in the control condition (no AMPA or CNQX). In addition, 18% of neuromasts showed localized postsynaptic flashes following AMPA exposure. These flashes corresponded with subsequent macrophage recruitment to the terminal, suggesting that they are a signal of localized injury.**Conclusions:** Live imaging of the lateral line following AMPA-mediated excitotoxic injury revealed a dose-dependent postsynaptic Ca^{2+} surge that could be competitively inhibited with the use of an AMPA receptor antagonist. Future studies will include NMDA receptor antagonists, pharmacological manipulation of calcium induced calcium release, and light-sheet imaging to resolve Ca^{2+} activity throughout the entire lateral line after excitotoxic injury.

Disclosures: P. Roychowdhury: None. **M.E. Warchol:** None. **L. Sheets:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.03/K5

Topic: E.05. Auditory and Vestibular Systems

Support: Military Operational Medicine Research Program at U.S. Army Medical Research and Development Command

Title: Topical administration of P13 peptide as ear drops for protection against repeated low-level blast-induced auditory dysfunction

Authors: M. Y. GOVINDARAJULU[1], G. PHUYAL[1], J. K. KRISHNAN[3], J. B. LONG[1], ***P. ARUN**[2];
[1]Blast-Induced Neurotrauma Br., [2]Walter Reed Army Inst. of Res., Silver Spring, MD; [3]APG, Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Military personnel in certain occupational specialties that are routinely exposed to repeated low-level blasts often report hearing dysfunction. We found that repeated low-level (4psi) blasts increased the expression of multiple toll-like receptors (TLRs) in the rat inner ear, indicating that those blast conditions adversely affect the auditory system. 13Therapeutics developed the P13 peptide, an inhibitor of multiple TLRs that readily penetrates the tympanic membrane. We have tested the efficacy of P13 applied as ear drops against repeated low-level blast-induced auditory dysfunction in rats. Under isoflurane anesthesia, rats were exposed to one 4psi blast per day for three days. For pre-exposure protection testing, P13 was administered as ear drops under isoflurane anesthesia at 24 hr and 1 hr before the first blast and then continued once per day until euthanasia. For post-exposure recovery testing, P13 was administered 1 hr after the third blast and continued once per day until euthanasia. Efficacy was evaluated using Auditory Brainstem Response (ABR) & Distortion Product Otoacoustic Emission (DPOAE) measurements on days 1, 7, 14 and 28 after the third blast, and pathological evaluation were conducted on days 1 and 30 post-blast. DPOAE signals for different sound stimuli revealed that the repeated blasts at 4psi caused a significant decrease in DPOAE signals on days 1, 7, 14 and 28 and that the pre- or post-exposure treatment with P13 failed to improve outcomes at any of those time points. In contrast, ABR testing revealed that a significant decrease in ABR amplitude for 80dB sound (4kHz) occurred at days 1 and 7 after blasts and that P13 treatments elicited significant improvements when initiated as either a pre- or post-blast intervention. P13 pre/post-treatment protected against the outer hair cell loss occurred at 24 hr after blast exposure. P13 pre/post-treatment also protected against the decreased mRNA levels of prestin and myo7a in the inner ear suggesting that blast exposure damages cochlear hair cells and P13 treatments protected against this damage. P13 pre/post-treatment decreased the mRNA levels of pro-inflammatory cytokines and increased the mRNA levels of anti-inflammatory cytokines in the inner ear after blast exposure. Pre-treatment with P13 was more efficacious compared to post-exposure treatment in protecting the inner ear from repeated low-level blast exposure. These data suggest that topical administration of P13 as ear drops may be effective for the prevention and treatment of repeated low-level blast-induced auditory dysfunction observed in personnel participating in military training.

Disclosures: M.Y. Govindarajulu: None. **G. Phuyal:** None. **J.K. Krishnan:** None. **J.B. Long:** None. **P. Arun:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.04/K6

Topic: E.05. Auditory and Vestibular Systems

Support: Shanghai ChemPartner
ChemPartner Corporation

Title: Investigating Multidimensional Mechanisms of Cochlear Damage Induced by Non-Gaussian Noise Exposure

Authors: H. SHEN[1], Y. XU[1], C. YUAN[1], J. J ZHOU[1], L. YANG[1], M. KLAPCZYNSKI[2], ***R. FENG**[2];
[1]Shanghai ChemPartner, Shanghai, China; [2]ChemPartner Corp., South San Francisco, CA

Abstract: Noise-induced hearing loss (NIHL) represents a critical health concern in military and industrial environments, where non-Gaussian noise can cause profound auditory damage. Hearing loss research is often limited to cellular and molecular level analysis, overlooking the link between systemic oxidative stress, inflammation, and cochlear injury. Our study pioneers a multidimensional framework to elucidate the cascade by which systemic oxidative stress leads to localized cochlear damage, hair cell apoptosis, and synaptopathy. In our model, we exposed mice to 110 dB non-Gaussian noise for two hours and evaluated the hearing impairment by using the auditory brainstem response (ABR) and distortion product otoacoustic emission (DPOAE). To assess the cochlear damage, we evaluated hair cell viability and apoptosis by myosin VIIa immunofluorescent (IF) staining and TUNEL assay. To evaluate synaptopathy, we used CtBP2 IF labeling to quantify synaptic density. To determine cochlear oxidative damage, we utilized 4-HNE and 8-OHdG IF staining to assess lipid peroxidation and DNA oxidation. For the spiral ganglion injury, we used NF200 IF staining and TUNEL assay to evaluate neuronal integrity and apoptosis. We analyzed stria vascularis atrophy using phalloidin IF staining. We also investigated the model on the systemic level by measuring oxidative stress and inflammation via serum levels of MDA, SOD, T-AOC, and TNF-α. Our study showed that animals exposed to non-Gaussian noise displayed significant ABR threshold shifts and DPOAE reductions. Our preliminary results of cochlear pathological changes indicate decreased viability and activated apoptotic pathways in hair cells and decreased synaptic density. Initial results also show increased cochlear oxidative damage, with strong signals for 4-HNE and 8-OHdG. We are currently quantifying spiral ganglion injury and stria vascularis atrophy, which initially appear to confirm the expected pathological changes. The increased systemic inflammation and oxidative stress substantiate our assumption of the synergistic character of these changes with cochlear hair cell apoptosis and synaptic loss, suggesting shared pathways underlying cochlear damage and synaptopathy. Based on our preliminary results, we propose that non-Gaussian noise induces auditory dysfunction by intricate interactions between systemic oxidative stress and local cochlear injury, leading to hair cell apoptosis, synaptopathy, and stria vascularis atrophy. We ultimately aim to establish the first multidimensional non-Gaussian NIHL model for early diagnosis, intervention strategies, and future drug discovery and development.

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Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.05/K7

Topic: E.05. Auditory and Vestibular Systems

Title: Pravastatin and Metformin enhances early recovery in a preclinical model of noise-induced hidden hearing loss

Authors: *R. AMANIPOUR[1], B. SHUSTER[2], B. MILON[1], R. HERTZANO[1];
[1]NIH, NIDCD, Bethesda, MD; [2]Sch. of Med., Univ. of Maryland, Baltimore, MD

Abstract: Background:
NIHHL involves permanent synaptic loss between inner hair cells (IHCs) and afferent auditory nerve fibers despite normal hearing thresholds (synaptopathy). No FDA-approved treatments exist for NIHHL. Our lab previously identified pravastatin and metformin as candidate therapeutics using a cochlear cell type-specific noise-response molecular atlas and the DrugCentral database. Both drugs inhibit HMG-CoA reductase, upregulated in auditory cochlear cells after noise exposure and linked to increased cochlear damage. This study evaluates whether these drugs, alone or in combination, can mitigate NIHHL.
Methods:
Seven-week-old B6CBAF1/J mice received pravastatin (25 mg/kg/day) and metformin (200 mg/kg/day), alone or in combination, via drinking water. Baseline auditory brainstem response (ABR) and distortion product otoacoustic emissions (DPOAE) were measured at 9 weeks. ABR assesses neural response strength and synaptic integrity; DPOAE evaluates outer hair cell function. At 10 weeks, mice were exposed to 97 dB SPL (8-16 kHz, 2 hours) noise to induce NIHHL. ABR wave-I amplitude was analyzed to assess hidden hearing loss, as reduced amplitudes indicate synaptic damage even with normal thresholds. Post-exposure assessments were conducted at 24 hours, 1 week, and 6 weeks. Cochlear tissues were collected at each time point for histological analysis of IHC synapses using CtBP2 and GluR2 antibodies.
Results:
In males, only combination treatment significantly reduced ABR threshold shifts at 16, 24, and 32 kHz 24 hours post-noise. In females, both combination treatment and pravastatin alone significantly reduced shifts at the same frequencies at 24 hours, indicating a sex-dependent drug response. DPOAE analysis showed reduced threshold shifts at 8, 24, and 32 kHz in males with combination treatment; no significant effects were observed in females.
ABR wave-I amplitude analysis revealed significantly higher amplitudes at 8, 24, and 32 kHz in males treated with combination therapy at 1 week post-noise, suggesting improved synaptic integrity. However, this effect was not sustained at 6 weeks. Histological analysis is ongoing to assess synapse preservation.

Conclusion:
Pravastatin and metformin, particularly in combination, may offer early protection against NIHHL in males, with pravastatin alone showing benefits in females. Enhanced ABR wave-I amplitudes with combination treatment suggest potential for accelerating neural recovery. Ongoing synaptic analysis at 1 and 6 weeks post-noise will help determine whether these treatments offer lasting protection against synaptopathy—a key step in evaluating their therapeutic potential.

Disclosures: R. Amanipour: None. **B. Shuster:** None. **B. Milon:** None. **R. Hertzano:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

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Program #/Poster #: PSTR120.06/K8

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC017147
NIH Grant DC018785

Title: Autophagy proteins are essential for aminoglycoside-induced hearing loss

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Abstract: Aminoglycosides (AGs) are highly potent, broad-spectrum antibiotics frequently used as first-line treatments for multiple life-threatening infections. Despite their severe ototoxicity, causing irreversible hearing loss in millions of people annually, no preventive therapy has been approved. We previously reported that GABARAP and several other central autophagy proteins are essential for AG-induced hearing loss. This finding opens avenues for the rational design and development of inhibitors that selectively target proteins in this pathway, thereby mitigating AG ototoxicity. Recently, we generated a mouse model with a targeted deletion of GABARAPL1, a homolog of GABARAP, and another model deficient in both GABARAP and GABARAPL1. We found that normal hearing is unaffected by the depletion of these proteins. Remarkably, both proteins are essential for AG-induced hearing loss, with GABARAP playing a more significant role. To further explore the therapeutic potential, we designed and validated short hairpin RNAs targeting the mouse and human *GABARAP* gene. By inhibiting GABARAP expression in inner ear hair cells using adeno-associated virus-mediated RNA interference, we successfully prevented AG-induced hair cell death and subsequent hearing loss. Our findings underscore the critical role of GABARAP in AG ototoxicity and highlight its potential as a therapeutic target for preventing AG-induced hearing loss.

Disclosures: J. Li: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); B.Z. and J.L. are named

inventors on a patent application related to this work. **B. Zhao:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); B.Z. and J.L. are named inventors on a patent application related to this work..

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.07/K9

Topic: E.05. Auditory and Vestibular Systems

Title: Reconstruction of place pitch perception by extra-cochlear laser stimulation:Behavioral and electrophysiological assessment of site-specific frequency responses in the cochlear

Authors: *K. FUKADA[1], K. HOSOKAWA[2], A. KAWASAKI[2], R. NAKAGAWA[2], K. SHIN'YA[2], T. FURUYAMA[3], Y. TAMAI[4], K. I. KOBAYASHI[2];
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Abstract: Cochlear implants are effective options for sensorineural hearing loss. However, they require invasive surgery (i.e., electrode implantation into the cochlear). Infrared laser stimulation has been investigated as a way to overcome this disadvantage because the laser can activate nerves without contacting tissues. This study aims to apply infrared laser stimulation to auditory prosthesis, and specifically evaluates the place pitch perception induced by extra-cochlear laser stimulation. Mongolian gerbils (*Meriones unguiculatus*), a standard model animal for auditory physiology, were used as subjects. Head-fixed classical conditioning was performed to investigate auditory perception elicited by laser stimulation of the cochlea. An optic fiber was inserted into the ear canal, and repetitive pulsed infrared laser irradiation (radiant energy 13.2 mJ/cm^2) to the apical-middle turn of the cochlea was presented as a conditioned stimulus for a reward (a drop of water). Licking behavior was recorded as a conditioned response. After the training was complied, gerbils showed conditioned licking responses to the pulsed laser without paired water. In test sessions, bandpass filtered clicking sounds (700-1400, 1400-2800, 2800-5600, 5600-11200, 11200-22400, and 22400-44800 Hz) were presented as stimuli. As a result, higher licking rates were observed with the presentation of low-frequency clicking sounds (700-1400 Hz and 1400-2800 Hz), which roughly correspond to the laser irradiation site in the cochlea, suggesting that laser-induced perception depended on the laser irradiation site. Subsequently, the electrophysiological cochlear response induced by the laser stimulation was recorded to evaluate how changing the laser irradiation site affects perceived pitch. The laser-irradiation site was adjusted to three different locations: the apical-middle, middle-basal, and basal turns of the cochlea. Tone masking on laser stimulation revealed that the amplitude of the compound action potential evoked by the laser was reduced by an acoustic masker, particularly around 1400 to 2800 Hz. The characteristic frequency of the masking tuning curve was shifted to a higher frequency following a change in laser irradiation site from apical to basal turn of the

cochlea. This result is consistent with the behavioral result and suggests that extra-cochlear laser stimulation causes frequency-specific activation of the cochlear nerve. These results indicate that altering the irradiation site could be used to modulate the place pitch perception.

Disclosures: K. Fukada: None. **K. hosokawa:** None. **A. Kawasaki:** None. **R. Nakagawa:** None. **K. Shin'ya:** None. **T. Furuyama:** None. **Y. Tamai:** None. **K.I. Kobayashi:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.08/K10

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC018304
R01DC012347
F31DC021883
CBC-AG-002
1R90DA060338

Title: Calcium Imaging of Mechanically Evoked Hair Cell and Afferent Population Activities in Mammalian Vestibular Inner Ear

Authors: *C. K. LUONG[1], M. KABIROVA[1], O. J. LUTZ[1], D. SILVIAN[1], K. ZHANG[1], R. EATOCK[2];
[2]Neurobio., [1]Univ. of Chicago, Chicago, IL

Abstract: We image Ca^{2+} signals in mouse utricular hair cells (HCs) and afferents to correlate moment-to-moment signaling across zones. The utricle encodes head tilt and linear acceleration to brainstem and cerebellum, enabling reflexes for vision, balance, and posture. Previous studies identified differences among HC types and showed that afferent response properties correlate with epithelial zone and spike regularity: irregular, adapting afferents innervate the striola, while regular, tonic afferents innervate the extrastriola. However, single-unit approaches lack simultaneous population-level spatial resolution.
To address this gap, we performed two-photon imaging of $Ca2^{+}$ signals in excised utricular epithelium and attached afferent nerve from mice (P3-P90). After removing overlying structures to expose mechanosensitive hair bundles, we applied a fluid-jet stimulus with step or sinusoidal waveforms (<20 Hz) and captured bundle motions with a custom tracking algorithm. HCs or afferents expressed the $Ca2^{+}$ indicator jGCaMP8m under cell-specific promoters. We quantified $\Delta F/F$ within regions of interest corresponding to HC subtypes, bundle polarities, and epithelial zones. We correlate both raw and deconvolved activity (inferred events) assessed synchrony within and across zones. We also developed an ROI-stitching method to map activity onto a canonical utricular epithelia.
Preliminary results indicate that within a given zone, Ca^{2+} activity correlations are insensitive to

bundle-orientation deviations under 20°, in line with the cosine tuning of hair cell sensitivity to stimulus angle. Additionally, afferent neuron gain shows expected zonal frequency tuning: striolar afferents have higher gain at higher frequencies compared to extrastriolar afferents. These data suggest that local mechanical coherence (i.e., shared fluid-jet drive) preserves synchronized signaling across hair cells despite small orientation differences, while zonal specializations in afferent tuning selectively amplify distinct frequency components as expected. These data will inform a population-level model of sensory coding in the mammalian vestibular epithelium, providing insight into how spatial organization and HC properties contribute to encoding head motion and orientation.

Disclosures: C.K. Luong: None. **M. Kabirova:** None. **O.J. Lutz:** None. **D. Silvian:** None. **K. Zhang:** None. **R. Eatock:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.09/K11

Topic: E.05. Auditory and Vestibular Systems

Support: Cystic Fibrosis Foundation
Rutgers Health Advance

Title: An AAV based gene therapy to prevent hearing loss and vestibular disorder after exposure to antibiotics in cystic fibrosis populations.

Authors: S. CHANDRASEKAR[1], ***T. MOWERY**[2];
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Abstract: Background: Cystic fibrosis is a genetic disorder that primarily affects the lungs of over 40,000 children and adults in the United States and over 100,000 people worldwide. The disorder is accompanied by severe life-threatening infections that must be treated with potent antibiotics. Aminoglycosides and glycopeptides are routinely used to treat infections in this population; however, at the high doses required they become ototoxic and vestibulotoxic leading to hearing loss and balance/vestibular disorders. The mechanism of action that leads to antibiotic-induced hair cell damage involves oxidative stress that induces synaptopathy (synapse removal) and neuropathy (auditory cell death. Thus, we have developed a targeted adeno-associated virus (AAV) gene therapy that expresses the transgenes for the antioxidative enzymes superoxide dismutase (SOD) in the hair cells of the cochlea and vestibule following intra-cisterna magna injection. Methods: Adult male and female Mongolian Gerbils (*meriones unguiculatus*) received baseline measures of hearing (auditory brainstem recordings) and vestibular (rotorod) function. Animals then received cisterna magna injections of SOD gene therapy. After three weeks of transgene expression animals received unilateral inner ear exposures to cochlear and vestibular hair cell damaging levels of antibiotics (gentamicin,

kanamycin, tobramycin, amikacin, or streptomycin) or glycopeptides (Anomycin, Teicoplanin, Ristocetin, Avoparcin). ABR and rotorod testing was carried out 1 week after exposure and then one month after exposure prior to perfusion and histological examination of the left (experimental) and right (control) ears. Results: We found that SOD gene therapy provided significant protection from auditory and vestibular impairments compared to control animals. Significance: This therapy could provide a co-treatment for cystic fibrosis patients at risk of antibiotic/glycopeptide induced auditory and vestibular damage that would greatly increase quality of life over time.

Disclosures: S. Chandrasekar: None. **T. Mowery:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.10/K12

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC012347 (CKL, MK, OJL, DS, DZ, RAE)
CBC-AG-002 (MK)
R01DC018304 (CKL)
F31DC021883 (OJL)
TPCN 1R90DA060338 (DS and KZ)

Title: Calcium imaging of vestibular epithelium: from single cells to populations

Authors: *M. KABIROVA[1], C. K. LUONG[1], O. LUTZ[2], D. SILVIAN[2], K. ZHANG[2], A. KURIAKOSE[3], A. GOVINDARAJU[3], R. RAPHAEL[3], R. EATOCK[1];
[1]Neurobio., [2]Univ. of Chicago, Chicago, IL; [3]Rice Univ., Houston, TX

Abstract: The utricle, one of the vestibular inner ear organs, detects linear acceleration and head tilt. The utricular sensory epithelium features two zones: the central striolar zone and the peripheral extrastriolar zone. These zones differ in hair cell and afferent structure, synaptic properties, and how they encode head motion information: striolar afferents rely on precise spike timing for high-frequency stimuli, while extrastriolar afferents use firing rate for encoding low-frequency motion. Afferents from these two distinct zones ultimately project to different brain regions and mediate separate functions. It is worth noting that these afferents integrate signals from populations of hair cells, not just single cells. Despite these well-documented differences, little is known about how populations of hair cells and afferents in two zones respond moment-by-moment to stimuli. To address this question, we are using calcium recordings from populations of hair cells or afferent terminals during fluid jet stimulation of hair bundles in a freshly isolated mouse utricle. However, because this approach is new to our field, here we investigate the relationship between voltage signals, which are the true drivers of cellular activity, and the calcium responses that provide insight into the activity of many cells at once.We

use two mouse lines that express the calcium indicator GCaMP8m in hair cells and afferents, allowing us to study presynaptic and postsynaptic calcium dynamics separately. Whole-cell recordings allow us to control voltage while measuring single-cell calcium-activated fluorescence (dF/F), linking hair cell receptor potentials or afferent spikes to calcium signals. Preliminary analyses reveal that calcium signals in hair cells are consistent with entry through $Ca_V1.3$ channels near ribbon synapses. Interestingly, whole-cell voltage stimulation of the patched hair cell can also evoke responses from neighboring hair cells, suggesting a previously undocumented form of coupling that is predicted by modeling of the utricular epithelium. In whole-cell recordings from calyceal afferent terminals on type I hair cells, depolarizing voltage steps evoke hotspots of calcium activity near the membrane, suggesting entry through clustered voltage-gated calcium channels. Additionally, we have developed a computational model that accurately simulates dependence of calcium traces on applied voltage. This model will help us to build a framework to infer voltage changes in cells from observed calcium signals. Altogether our study offers new insights into head motion encoding in vestibular epithelium.

Disclosures: M. Kabirova: None. **C.K. Luong:** None. **O. Lutz:** None. **D. Silvian:** None. **K. Zhang:** None. **A. Kuriakose:** None. **A. Govindaraju:** None. **R. Raphael:** None. **R. Eatock:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

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Program #/Poster #: PSTR120.11/K13

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC020052

Title: Genome-wide association study of vestibular traits in young and aged mice from the HMDP

Authors: *Y. NINOYU[1,2], R. FRIEDMAN[2];
[1]Kyoto Prefectural Univ. of Medicine: Kyoto Furitsu Ika Daigaku, Kyoto, Japan; [2]Univ. of California San Diego, San Diego, CA

Abstract: Age-related vestibular dysfunction is a major contributor to imbalance and falls in the elderly, yet its genetic basis remains poorly understood. To investigate genetic factors underlying vestibular function, we performed genome-wide association studies (GWAS) using the Hybrid Mouse Diversity Panel (HMDP), comprising 84 inbred mouse strains. In the young cohort, 5 to 7 female mice per strain were tested using vestibular sensory-evoked potentials (VsEPs). VsEP thresholds, P1-N1 amplitude, and P2 latency were used as quantitative traits for GWAS. In the aged cohort, both male and female mice were evaluated. Of the 84 strains, 44 included males and 62 included females (mean age: 21.7 ± 2.53 months). GWAS was conducted using FaST-LMM (factored spectrally transformed linear mixed model), incorporating 100 permutations and 1,000

bootstrap replicates. The genome-wide significance threshold was set at $p = 4.1 \times 10^{-6}$, corresponding to a family-wise error rate (FWER) of 0.05. Further analyses included linkage disequilibrium (LD) visualization with LocusZoom and gene annotation using the UCSC Genome Browser (GRCm38/mm10). In young mice, we identified suggestive loci on chromosomes 6 and 13. Genes within LD blocks were analyzed for pathway enrichment, and candidate genes were prioritized using a human bulk RNA-seq dataset. Genes preferentially expressed in the cochlea were further characterized using single-cell RNA sequencing to determine cell-type specificity. We identified genes enriched in vestibular hair cells and intermediate cells of the stria vascularis, supporting their involvement in vestibular function. VsEP testing in aged mice revealed broad phenotypic variability across strains. GWAS identified a genome-wide significant SNP on chromosome 7 in males, but not in females, suggesting sex-specific genetic influences on vestibular aging. These findings provide novel insights into the molecular architecture of vestibular function across age and sex and highlight candidate genes for future investigation of balance disorders.

Disclosures: Y. Ninoyu: None. **R. Friedman:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.12/K14

Topic: E.05. Auditory and Vestibular Systems

Title: Ancient Balance Organs: The Role of PIEZO channels in the Ctenophore Statocyst

Authors: *O. M. ARENAS SABOGAL[1], E. A. LUMPKIN[2];
[1]Univ. of California - Berkeley, Berkeley, CA; [2]Mol. & Cell Biol., UC Berkeley, Berkeley, CA

Abstract: Ctenophores are a powerful system for exploring the origins of sensory and neurobiological mechanisms, having diverged from all other extant animal lineages over 750 million years ago. Their statocyst represents one of the earliest systems for posture control and gravity detection. Although ctenophores display robust geotactic behaviors, the molecular mechanisms underlying gravity detection in this organism remain largely unknown. Here, we first characterize posture reorientation in freely swimming *Mnemiopsis leidyi* and then investigate the molecular basis of mechanosensation in the balancer cells of the ctenophore statocyst. We show that Yoda1, an agonist of mammalian PIEZO channels, inhibits activity in statocyst balancer cells. We identified and characterized the *M. leidyi* PIEZO ortholog (*MleiPIEZO*), demonstrating that it is intrinsically mechanosensitive and expressed in balancer cells. We also show that *MleiPIEZO* functions as a mechanosensor both in vitro and in vivo. Remarkably, *MleiPIEZO* can rescue crop distension defects in *Drosophila* PIEZO knockout flies, revealing a deep functional conservation of PIEZO channels. Our findings demonstrate that *MleiPIEZO* is a bona fide mechanically activated ion channel essential for statocyst function.

More broadly, we provide the first mechanistic insight into one of the earliest balance organs that appeared in animals.

Disclosures: O.M. Arenas Sabogal: None. **E.A. Lumpkin:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.13/K15

Topic: E.05. Auditory and Vestibular Systems

Support: VHA Grant I01RX003400

Title: Isolation, expansion, and differentiation of inner ear organoid progenitors

Authors: *R. K. DUNCAN;
Univ. of Mchigan, Ann Arbor, MI

Abstract: Inner ear organoids derived from pluripotent stem cells progress through major stages of inner ear development, generating otic progenitors at intermediate stages that are attractive donor material for regenerative medicine. However, there is currently no established methodology to isolate, cultivate, and expand this progenitor pool for downstream applications. In this study, we sought to isolate otic progenitors from stem cell-derived otic vesicles and identify the conditions for progenitor expansion while maintaining their ability to reassemble and differentiate into sensory epithelia. Mouse embryonic stem cells from a Pax2-EGFP reporter line were used to generate inner ear organoids and their intermediate otic vesicles. Aggregates at the otic vesicle stage were dissociated and subjected to fluorescence-activated cell sorting to isolate the Pax2-positive progenitors. Sorted cells were then introduced into two-dimensional and three-dimensional culture paradigms and cultured in base media with or without various growth factor and small molecule supplements (EGF, IGF1, FGF2, valproic acid, ascorbic acid, CHIR99021, and Repsox). After another 14 days in culture, the number of cells, the retention of GFP as proxy for progenitor status, and the development of epithelia were quantified. Some cultures were also examined by immunofluorescence for organoid production and differentiation of sensory hair cells using the hair cell marker MyoVIIa. Under two-dimensional culture conditions, we found no evidence of cellular expansion in base media though most cells remained GFP-positive. In contrast, when exposed to the supplement cocktail, strong evidence of cellular proliferation was tempered by the loss of the GFP reporter. Under three-dimensional culture conditions when progenitors were placed in Matrigel domes, the progenitor cells remained viable and GFP-positive but again only proliferated when exposed to supplement cocktails. Notably, many of these GFP-positive cells were able to reform vesicles and cysts similar to inner ear organoids. Additionally, many of these large cysts produced within the domes also generated MyoVIIA-positive hair cells. In this study, we found that isolated Pax2-positive progenitors from organoid cultures do not have the capacity to proliferate, reassemble into organoids, and differentiate into

sensory tissue, unless treated with a cocktail of growth factors and small molecules used elsewhere to expand cochlear stem cells. By refining this approach, we hope to identify the factors that enable expansion while maintaining progenitor status in order to produce plentiful donor material for regenerative medicine.

Disclosures: R.K. Duncan: None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.14/K16

Topic: E.05. Auditory and Vestibular Systems

Support: Mathers Foundation

Title: Psychedelics Induce the Formation of New Synapses in the Cochlea

Authors: *U. MANOR[1], B. MOHAR[2];
[1]UCSD, La Jolla, CA; [2]Janelia Res. Campus, Ashburn, VA

Abstract: Background:Sensorineural hearing loss (SNHL), a prevalent condition affecting millions worldwide, is primarily caused by the loss of synapses between sensory hair cells and spiral ganglion neurons (SGNs) in the cochlea. This synaptic loss, termed synaptopathy, leads to impaired auditory signal transmission to the brain. Recent research has revealed the potential of psychedelic drugs in promoting synaptogenesis (the formation of new synapses) in the brain. This led us to explore their potential impact on cochlear synapses, given the critical role of cochlear synaptopathy in its pathology.
Analysis of RNA-seq datasets revealed robust expression of 5-HT2A/B/C receptors in SGNs, all of which are known to be agonized by psychedelic compounds. Systemic IP administration of psychedelics and non-hallucinogenic analogs in healthy mice resulted in an increase in both cochlear and cortical synapses compared to vehicle controls. We also observed a significant increase in ABR Wave I amplitudes in some animals, consistent with enhanced synaptic transmission, and an increase in synaptic ribbons. We also observed increased neuritogenesis in treated SGN cultures, indicating a direct effect of these compounds on SGNs.
These findings demonstrate the ability of psychedelics to induce synaptogenesis in the cochlea, suggesting their potential for treating synaptopathy-associated hearing loss. The robust expression of 5-HT2 receptors in SGNs, increased neuritogenesis in treated SGN cultures, and the observed increase in synapses and synaptic transmission in vivo following psychedelic treatment support this hypothesis. Ongoing studies in mouse models of SNHL and other forms of synaptopathy (e.g. noise-induced, ototoxic drugs) will further elucidate the therapeutic potential of psychedelics for hearing restoration, offering hope for millions suffering from this debilitating condition. Just as importantly, these results demonstrate for the first time (to our knowledge) that

these compounds can directly act on peripheral neurons, greatly expanding their therapeutic potential beyond psychiatric disorders.

Disclosures: U. Manor: None. **B. Mohar:** None.

Poster

PSTR120: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.15/L1

Topic: E.05. Auditory and Vestibular Systems

Support: WashU Dept. Otolaryngology

Title: Sound encoding properties of inner hair cells in the living mouse cochlea

Authors: S. LIN[1], M. A. PRESKER, Jr.[1], G. MOLINA[2], K. K. OHLEMILLER[1], E. B. HAN[2], ***J. KIM**[3,1,2];
[1]Dept. of Otolaryngology, [2]Dept. of Neurosci., Washington Univ. Sch. of Med., St. Louis, MO; [3]Washington Univ., St. Louis, MO

Abstract: The cochlea is an exceptionally sensitive and precise sensory organ, capable of detecting sounds ranging from a ticking clock to a blasting siren. Inner hair cells (IHCs), the primary sensory cells for hearing, convert sound vibrations into electrical signals, transmitting auditory information to the brain. How IHCs, just ~3500 cells arranged in a single layer, encode such a vast range of sound intensities (0-10^{12}) is one of the most remarkable yet enigmatic features of the auditory system. While direct *in vivo* monitoring of the peripheral cellular dynamics has advanced our understanding of visual, olfactory, gustatory, and tactile sensory encoding, such high-resolution intravital interrogation of the auditory system has proven extremely challenging due to the cochlea's complex, fragile, and fluid-filled structure, while being deeply embedded in the temporal bone. Owing to these challenges, a knowledge gap in sound encoding exists between the mechanical vibrations at the organ level and the cellular activity at the single cell/nerve level. Here, to bridge this gap, we characterized the receptive properties of IHCs *in vivo* while preserving hearing function, by monitoring sound-evoked Ca^{2+} responses using two-photon cochlear imaging combined with hearing physiology. The number of activated IHCs, their activity levels, and response patterns were quantified across different sound frequencies and intensities. Individual IHCs exhibit frequency tuning curves shaped around their characteristic frequency (CF), the frequency at which they are most responsive. As sound intensity increases, more IHCs are recruited, each showing progressively larger Ca^{2+} responses. At high intensities, individual IHCs respond to a broader range of frequencies; however, their response amplitudes decrease as the stimulus frequency moves further from their CF along the tonotopic axis. The dynamic range of IHC Ca^{2+} responses is maximal at the CF and gradually diminishes with increasing tonotopic distance. Similarly, activity among neighboring IHCs is strongly correlated near the CF, with correlation strength declining exponentially over distance.

Our *in vivo* data reveal how individual IHCs contribute to encoding sound frequency and intensity, providing new insights for understanding peripheral auditory processing and advancing strategies to replicate the ear's remarkable sensitivity and selectivity in engineered devices.

Disclosures: S. Lin: None. **M.A. Presker:** None. **G. Molina:** None. **K.K. Ohlemiller:** None. **E.B. Han:** None. **J. Kim:** None.

Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.01/L2

Topic: E.05. Auditory and Vestibular Systems

Support: NIDCD F32DC022169
NIDCD R01DC018802-04
McKnight Foundation
New York Stem Cell Foundation

Title: Mouse motor cortex reflects movement, error and expectation of self-generated sounds

Authors: *A. M. KLINE[1], B. E. HOLEY[2], D. M. SCHNEIDER[1];
[1]Ctr. for Neural Sci., [2]Ctr. For Neural Sci., 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.E. Holey:** None. **D.M. Schneider:** None.

Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.02/L3

Topic: E.05. Auditory and Vestibular Systems

Support: Leon Levy Fellowship in Neuroscience, Leon Levy Foundation
NIH Grant 1R01-DC018802
New York Stem Cell Foundation

Title: Contextual modulation of motor-related predictions in mouse auditory cortex

Authors: *A. LA CHIOMA[1], D. M. SCHNEIDER[2];
[2]Ctr. for Neural Sci., [1]New York Univ., New York, NY

Abstract: Auditory perception relies on predicting the acoustic consequences of our actions. The auditory cortex (AC) responds differently to expected versus unexpected self-generated sounds. In the real world, the same motor action can produce different sounds depending on the environment in which the behavior is produced - e.g. footsteps sound different when walking on concrete compared to fallen leaves. Yet it remains untested whether AC dynamically updates predictions about self-generated sounds in a context-dependent manner. We developed a naturalistic audio-visual-motor virtual reality (VR) for head-fixed mice. Real-time locomotion tracking was performed to provide artificial footstep sounds that were yoked to a precise phase of the step cycle, creating an ethological and experimentally manipulable form of auditory reafference. While running on the treadmill, mice traversed two different contextual environments, each consisting of a distinct visual corridor accompanied by distinct footstep sounds. Using this system, we asked whether AC neural activity reflects predictions about the sound that footsteps are expected to produce in a given context, and to what extent contextual and motor signals integrate with auditory information. Following behavioral acclimation, we made high-density neuronal recordings from primary AC as mice traversed the two VR contexts and experienced expected or deviant footsteps. We observed overall suppression of neural responses to self-generated sounds compared to the same sounds heard passively. Subsets of neurons responded differently to the same sound heard in the expected versus the unexpected context. Population-level analysis indicates that context information is embedded in AC population activity. In addition to sound and context, neuronal responses were also largely affected by locomotion speed, with subsets of neurons tuned to a specific phase of stride cycle. To help isolate the contribution of auditory, context, and motor signals to the activity of individual neurons, we are using generalized linear models. Our results suggest that AC combines auditory and motor signals with visual cues for context-dependent processing of self-generated sounds.

Disclosures: A. La Chioma: None. **D.M. Schneider:** None.

Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.03/L4

Topic: E.05. Auditory and Vestibular Systems

Support: New York Stem Cell Foundation

Title: Non-vocal biophonics shape social coordination in behaving mice

Authors: *D. GARCIA[1], A. CORREDERA ASENSIO[2], R. E. PETERSON[3], P.-N. BARTH[3], S. CHANG[3], A. LA CHIOMA[2], D. M. SCHNEIDER[3];
[2]Neurosci., [3]Ctr. for Neural Sci., [1]New York Univ., New York, NY

Abstract: Rodents make sounds when they move over natural substrates like leaves and rocks, broadcasting their presence to potential predators and social partners alike. Although vocalizations are the most widely studied animal-produced sounds, for mice and other rodents, non-vocal biophonics likely dominate the acoustic milieu in the wild. Here, we combine high-resolution audio and video tracking as individual mice and pairs of mice behave on distinct substrata found in a mouse's natural habitat. We find that different natural surfaces (e.g. leaves, pebbles, sand) produce distinct acoustic signatures that vary in intensity, spectral bandwidth, and temporal features, and that distinct behaviors produce distinct acoustic profiles. These rich acoustic data are adequate to reliably decode the surface upon which a mouse is walking, the specific behavior a mouse is performing, and the sex of the mouse. We next asked whether non-vocal biophonics are used to guide social behaviors. In social assays, we find that pairs of mice synchronize their movements and display increased spatial coordination on noisy substrates even in the absence of vocalizations, visual cues, or somatosensory cues, suggesting that non-vocal sounds guide social behavior. Together, our results reveal that non-vocal self-generated sounds provide rich information that facilitates social coordination, highlighting a previously underappreciated capacity for sound in shaping naturalistic rodent behavior.

Disclosures: D. Garcia: None. **A. Corredera Asensio:** None. **R.E. Peterson:** None. **P. Barth:** None. **S. Chang:** None. **A. La Chioma:** None. **D.M. Schneider:** None.

Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant 5T32NS086750
NIH Grant 1F31DC021868
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McKnight Foundation
New York Stem Cell Foundation

Title: Cortical transformation of acoustic errors into skilled behavior

Authors: *G. W. ZEMPOLICH, D. M. SCHNEIDER;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Making mistakes is an important part of learning and performing skilled behaviors like speech or music. Equally important is knowing how to react to mistakes in order to improve with practice. However, the neural circuits that process mistake-related feedback and drive behavioral corrections in mammals remain poorly understood. Here, we identify how the mouse brain encodes error-related signals during skilled acoustic behavior, and how these signals drive adaptive motor cortical changes to improve performance. We developed a skilled, sound-guided behavior that requires mice to use real-time acoustic feedback to guide their ongoing forelimb movements and is auditory cortex dependent. Auditory cortex neurons encode error signals associated with distinct types of behavioral mistakes and the activity of error-sensitive neurons predicts both across-trial and within-trial changes in behavior. Skilled acoustic behavior also requires the secondary motor cortex (M2), a motor planning and execution region that receives acoustic input from auditory cortex. Following behavioral mistakes, persistent activity in M2 encodes specific acoustic errors, and these error signals modulate M2 dynamics within a low-dimensional space that governs motor planning. These data reveal a learned coordinate transformation that converts specific acoustic errors into adaptive adjustments in motor planning and behavior. Collectively, these results uncover a cortical circuit that detects errors and facilitates learning from mistakes during skilled behavior in mammals.

Disclosures: G.W. Zempolich: None. **D.M. Schneider:** None.

Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.05/L6

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant 1R01-DC018802
New York Stem Cell Foundation (no grant number)

Title: Auditory Processing of self and other in freely moving mice under perceived predatory risk

Authors: *A. CORREDERA ASENSIO, D. GARCIA, A. LA CHIOMA, D. M. SCHNEIDER;
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Abstract: In ethologically relevant contexts, distinguishing self-generated from externally generated sensory input is critical for survival. External cues can range from harmless (e.g., ambient noise, social partners) to threatening (e.g., predator sounds). We used wireless electrophysiology in freely moving mice to study auditory processing as they walked across surfaces that either naturally produced sound (e.g., leaves) or a silent surface paired with locomotion-triggered sounds in virtual reality. Using miniature microphones, we matched the intensity of playback sounds to real self-generated leaf sounds. Although auditory neurons are broadly tuned, responses were stronger to externally generated playback sounds, and we could accurately decode sound identity from single-neuron activity. When mice were placed with a cage-mate or non-cage-mate, neural responses varied with partner proximity and were slightly suppressed for self-generated sounds compared to those of a partner. Finally, visual predator cues led mice to alter behavior in ways that reduced sound production, with auditory cortical dynamics reflecting internal state changes.

Disclosures: A. Corredera Asensio: None. **D. Garcia:** None. **A. La Chioma:** None. **D.M. Schneider:** None.

Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.06/L7

Topic: E.05. Auditory and Vestibular Systems

Support: NIH 1R01-DC018802

Title: neural circuits for learned auditory expectations

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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

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR121.07/L8

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R00-DC015543
NIH Grant R01-DC021067

Title: Contributions and synaptic basis of diverse cortical neuron responses to flexible task performance

Authors: *G. YU[1], X. ZENG[4], B. F. ALBANNA[2], M. INSANALLY[3];
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Abstract: Flexible behaviors are critical for animals to adapt and survive in diverse and dynamic environments. However, the synaptic mechanisms that underlie flexible behaviors are largely unknown. To explore the synaptic origin and functional contribution of diverse response profiles to flexible task performance and dynamics we combined in vivo electrophysiological recordings from mice performing a go/no-go auditory reversal learning task with a novel, spiking recurrent neural network (RNN) model that incorporated excitatory and inhibitory spike-timing-dependent plasticity (STDP). Mice were trained to first respond to a target tone for water reward and withhold from responding to a non-target tone. Once animals reached expert levels of performance, we then implemented a rule switch and reversed which tone was rewarded requiring animals to remap stimulus-reward contingencies (d'=1.87±0.21, N=14 mice). We recorded single-unit responses from the auditory cortex of mice (n=1,327 cells) during all stages of reversal learning including pre-and-post reversal. We observed a wide range of single-unit response types from classically responsive cells that were highly modulated relative to pre-trial baseline to non-classically responsive cells with relatively unmodulated firing rates. To relate synaptic structure to spiking patterns over the response-type continuum, we developed a spiking RNN model incorporating both excitatory and inhibitory spike-timing-dependent plasticity trained to perform a similar go/no-go stimulus reversal learning task as behaving animals

(d′=3.72±0.31). While the network can be trained to perform the initial, pre-reversal task over a wide range of model parameters, we find that the network can only successfully learn the full reversal task when network parameters result in a balance of excitatory and inhibitory input to individual units. Interestingly, these balanced networks also demonstrate the greatest diversity of response types and the emergence of distinct functional roles for classically and non-classically responsive units as demonstrated by detailed network perturbations. We identify a specific parameter regime for these flexible, balanced networks where tonic inhibition lies between baseline and evoked excitation in a "see-saw" mechanism that facilitates stimulus-choice remapping. These results elucidate the relationship between synaptic dynamics, response type diversity, and behavioral flexibility.

Disclosures: G. Yu: None. **X. Zeng:** None. **B.F. Albanna:** None. **M. Insanally:** None.

Poster

PSTR121: Auditory Processing: Animal Models

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Program #/Poster #: PSTR121.08/L9

Topic: E.05. Auditory and Vestibular Systems

Support: R00-DC015543
R01-DC021067

Title: Frontal and sensory cortical dynamics during flexible auditory behavior

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Abstract: The mammalian auditory system is remarkably adaptable, allowing animals to flexibly respond to sensory information in dynamic environments. Flexible behaviors, such as perceptual learning, involve the engagement of 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, d'=1.8±0.3). Mice first 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. Both chemogenetic and optogenetic silencing experiments indicated that both regions are required for reversal learning (chemogenetics, d'=0.29±0.46, N=9 animals; optogenetics, d'= -0.08±0.10, N=7 animals). Single-unit responses in both regions were highly diverse, ranging from cells that are highly modulated to sensory stimuli (i.e., classically responsive) to those that appear to fire randomly (non-classically responsive). While classically responsive AC neurons exhibited delayed stimulus responses over

learning; in M2 we observed faster stimulus responses reflecting an unexpected switch in stimulus encoding dynamics from sensory to frontal areas as animals learned to remap stimulus-reward contingencies. Bilateral optogenetic inactivation of M2 inputs impaired reversal learning by preventing the recruitment of non-classically responsive neurons in AC. Population-level decoding revealed that while non-classically responsive cells were preferentially recruited in AC during periods of rapid learning, classically responsive neurons in M2 were recruited during expert performance. Using a dimensionality reduction approach, we found that population interactions were feedforward dominated during periods of early learning, and feedback dominated during periods of rapid learning. These results suggest a dissociable role for diverse neural response types where non-classically responsive cells in AC are critical for enabling flexibility while classically responsive neurons are important for task-execution once stimulus-reward contingencies have been remapped and the new task rule has been established.

Disclosures: T. Hou: None. **A. Eldo:** None. **B. Sidleck:** None. **D. Saeed:** None. **G. Yu:** None. **M. Insanally:** None.

Poster

PSTR121: Auditory Processing: Animal Models

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC021067
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Title: Dynamic gating of perceptual flexibility by non-classically responsive cortical neurons

Authors: *J. M. K. TOTH[1,2], B. SIDLECK[2], A. ELDO[2], O. LOMBARDI[2], T. HOU[3,2], M. KERLIN[2], X. ZENG[4,2], D. SAEED[2], P. AGARWAL[2], D. LEONARD[2], L. ANDRINO[5,2], T. INBAR[2,5], M. MALINA[5,2], M. INSANALLY[2];
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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 and encode flexible task rules. Additionally, both classically and non-classically responsive units 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 behavior. 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 heterogeneous, spanning the continuum from classically to non-classically responsive. We found that the proportion of non-classically responsive neurons significantly increased during late learning when the greatest gains in behavioral performance occur. Optogenetically silencing inputs from M2 selectively modulated non-classically responsive cells in ACtx and impaired reversal learning by preventing the remapping of a previously learned stimulus-reward association. Using advanced analyses of neural geometry, we found that non-classically responsive cells decreased network dimensionality during learning providing a task relevant manifold for implementing flexible behavior. This optimal manifold is under the control of top-down frontal inputs which constrain the overall dynamics in sensory cortex restricting its activity to a narrow subspace enabling the flexible remapping of stimulus-reward contingencies. Thus, non-classically responsive cells in sensory cortex are preferentially recruited by top-down inputs to enable neural and behavioral flexibility by providing a unique task-relevant subspace for learning.

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Poster

PSTR121: Auditory Processing: Animal Models

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Program #/Poster #: PSTR121.10/L11

Topic: E.05. Auditory and Vestibular Systems

Support: Institutional funds

Title: Internal state influences on auditory perceptual decision-making

Authors: *T. INBAR[1,2,3,4,5], N. H. ELSTE[2,3,5,1], M. N. INSANALLY[2,3,4,5,1];
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Abstract: Sensory-guided behaviors like auditory perceptual categorization are influenced by internal variables such as arousal, motivation, and expectation. Previous work has shown that the auditory cortex is a hub for perception integrating sensory, motor, and neuromodulatory signals.

Among these signals are sensorimotor inputs generated by spontaneous movements that are tightly coupled with neural population dynamics that reflect internal state conditions. However, the repertoire of movements expressed by animals is highly diverse and it remains unclear which movement motifs facilitate or disrupt decision-making, as well as the neural mechanisms by which these opposing effects emerge. To investigate how internal state conditions guide perceptual decision-making we combined high-density in vivo electrophysiological recordings from the auditory cortex of behaving animals with advanced computer-vision based algorithms for the precise tracking of movement motifs, and pupil-based arousal measurements. We recorded single-unit responses from the auditory cortex (n=711 neurons) while animals performed a 2-alternative forced choice auditory perceptual categorization task (N = 9 mice). Head-fixed mice were trained to lick in response to a cloud of pure tones composed of varying proportions of high and low frequency tones, requiring animals to categorize the sound stimulus according to its frequency content. We explored the structure of movement repertoires at two scales: (1) throughout entire sessions, and (2) the pre-stimulus time window immediately preceding behavioral decisions. To extract complex movement motifs, we first trained DeepLabCut to estimate frame-by-frame positions of multiple distinct key points on the face spanning the ears, nose, mouth, eyes, pupils, and tongue. These outputs were then used to train an unsupervised machine learning framework that discovers statistically recurring patterns in high-dimensional kinematic data (B-SOiD). This provided a dictionary of movement "syllables" that could be compared within and across animals. We found that some movement motifs were unique to individual animals and others were shared across animals. Evaluating a short time window preceding each behavioral decision revealed that animals expressed an even sparser subset of movement motifs, some of which reliably predicted correct or incorrect choices. These results suggest that animals exhibit specific anticipatory movements that reflect a 'primed' state that facilitates decision-making, while others predict perceptual errors.

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Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR121.11/L12

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01DC018650
NIH R00DC015014
Kavli Neuroscience Discovery Institute fellowships

Title: Revealing abrupt transitions from goal-directed to habitual behavior

Authors: *Z. WANG[1], S. Y. MOORE CORONA[2,3], Z. ZHU[4,2], R. SUN[5], A. LEE[2], A. CHARLES[5,3], K. KUCHIBHOTLA[2,4,5,3];
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Abstract: The speed of goal-directed to habit transitions has been debated since Clark Hull first asked in 1943: is habit formation slow or sudden? Using a 'volitional engagement' paradigm, we gave mice free access to citric-acid water that reduced—but did not eliminate—reward-seeking for plain water in an auditory go/no-go task. Animals learned to discriminate quickly but exhibited state-like fluctuations in engagement for thousands of trials. Strikingly, these fluctuations abruptly ceased ('transition') well after discrimination stabilized. Pre-transition behavior was sensitive to sensory-specific outcome devaluation, while post-transition behavior was not, indicating a transition from goal-directed to habitual behavior. HMM-GLM modeling pinpointed the transition to ~3 trials. Post-transition behavior showed orthogonal evidence for habitual control: increased motor stereotypy, reduced latencies, and altered phasic pupillary responses. Although the transition appears abrupt behaviorally, it could arise from gradual neural changes crossing a threshold, or a switch-like process that engages a readily available habit circuit. To adjudicate between these models, we focused on the dorsal striatum since bilateral lesions of the dorsolateral striatum (DLS) blocked the transition. Fiber photometry revealed a sharp drop in outcome-related and sharpening of stimulus-response activity in the DLS at the moment of a transition, supporting a switch-like mechanism. Thus, habits can emerge suddenly, mediated by an abrupt dorsal striatal shift from outcome- to stimulus-driven processing. Ongoing works uses optogenetic manipulation to examine the causal relation between dorsal striatal activity and transitions to habit. In addition, we are exploring cell-type (i.e., D1/D2 MSNs) and projection-specific pathways to define the precise circuit-level logic of decision control in the dorsal striatum.

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Poster

PSTR121: Auditory Processing: Animal Models

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Program #/Poster #: PSTR121.12/L13

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant F31DC022190
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Title: The auditory thalamus controls stimulus-driven choices

Authors: *S. KIM[1], K. V. KUCHIBHOTLA[1,2,3];
[1]Psychological and Brain Sci., [2]Dept. of Neurosci., [3]Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Recent work has shown that the auditory cortex (AC) is critical for initial learning of an auditory go/no-go task with simple pure tones, but becomes dispensable at expert stages. This raises two key questions: if cortical involvement fades, which auditory structures remain necessary for task execution? And, do these structures merely relay sensory information, or do they contribute to the decision process itself? The medial geniculate body (MGB) is a compelling candidate: it possesses strong links to action and decision circuits, has been implicated as a key sensory relay, and recent findings suggest it may encode higher-order choice and reward information. Here, we use temporally precise and probabilistic optogenetics to test the necessity and functional role of the MGB in expert auditory task performance. Mice were trained to lick in response to one pure tone (S+) and withhold licking to another (S−). After reaching expert performance (two consecutive days >85% accuracy), we initiated optogenetic manipulations. Full-trial silencing of the MGB (n=6, AAV1-CAMK2a-stGtACR2, bilateral) degraded performance to chance levels (d': 2.34+/-0.49 light-off vs. 0.20+/-0.55 light-on, $p<0.001$), with reduced hit rates, increased false alarms, slower reaction times, and diminished response vigor—demonstrating that the MGB is required for task execution even at expert levels. To dissociate sensory relay versus decision-related roles, we selectively silenced the MGB during either the stimulus period ('stimulus-only') or the choice window (closed-loop: light-on 100 ms post-tone, light-off upon first lick). Stimulus-only silencing had modest effects—performance degraded but remained above chance (d': 1.50+/-0.62 light-on), with unchanged hit rates and a mild increase in false alarms. In contrast, choice-window silencing replicated the full-trial deficits ($p=0.91$, two-way ANOVA), degrading performance to chance level and with animals exhibiting impaired hit rates, elevated false alarms, slower response times, and reduced response vigor. These results suggest that the MGB does not just act as a passive relay to downstream decision circuits but instead plays an active 'switchboard' role by linking learned auditory cues to appropriate actions during task execution.

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Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R00DC018600

Title: Noise-induced hearing loss disrupts behaviorally-modulated representations in auditory cortex

Authors: K. ZEMLIANOVA[1], T. MOWERY[2], S. G. KUJAWA[4], ***J. YAO**[3];
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Abstract: Noise-induced hearing loss (NIHL) is a leading cause of sensory impairment. It is caused by exposure to loud noise and accompanied by deficits in speech comprehension and cognitive function. Our recent work demonstrated the detrimental consequences of NIHL on auditory decision-making. Here, we examine the impact of NIHL on auditory cortex (AC) processing during auditory perceptual decision-making. We specifically examined how NIHL affects AC representations of sound features and perceptual categories in task-engaged and passive listening states. Adult gerbils were trained to distinguish slow (<6.25 Hz) vs. fast (>6.25 Hz) presentation rates of amplitude-modulated (AM) broadband noise by self-initiating trials and approaching one of two food trays. AC activity was recorded with chronically implanted multichannel arrays during task performance and passive listening sessions across pre- and post-NIHL conditions. Permanent NIHL was induced via a 2-hour, 120 dB SPL broadband noise exposure. Hearing thresholds were assessed with auditory brainstem response recordings before noise exposure (baseline) and 1-21 days after noise exposure. AM signals were presented at ~20-40 dB SPL above each animal's hearing threshold in both pre- and post-NIHL conditions to match sensation levels. During pre-NIHL recording sessions, AC decoding accuracy of perceptual categories (slow versus fast AM rates) was significantly enhanced during task engagement ($p<0.05$) and improved with longer temporal integration windows. These enhancements were accompanied by increased modulation index and reduced trial-to-trial variability among single-units and decorrelated population activity ($p<0.001$). After NIHL, AC decoding accuracy during task engagement was degraded relative to pre-NIHL ($p<0.005$) despite preserved firing rates and reduced variability. Surprisingly, AC decoding accuracy after NIHL was higher during passive listening than during active task engagement ($p<0.05$) and far exceeded behavioral performance ($p<0.005$). This enhancement coincided with increased synchrony and phase-locking to AM stimuli among single-units ($p<0.005$), suggesting compensatory plasticity that amplifies bottom-up encoding. Our results reveal a dissociation between sensory-driven and behaviorally-modulated AC representations after NIHL that likely reflects disrupted top-down input from higher-order areas (e.g., parietal or frontal cortex), leading to degraded perceptual decision accuracy.

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Poster

PSTR121: Auditory Processing: Animal Models

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Topic: E.05. Auditory and Vestibular Systems

Support: National Science Center, Poland, grant no. 2022/47/D/HS6/03323

Title: Inharmonicity and the perception of auditory outliers in high- and low-uncertainty conditions

Authors: *K. BASINSKI[1], T. DOMZALSKI[1], D. R. QUIROGA-MARTINEZ[2];
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Abstract: Predictive processing theories of perception posit that the brain forms top-down predictions about the incoming auditory stimuli and their causes. These predictions are formed using an internal, generative model that is constantly updated by statistical regularities in the incoming sensory data. A prediction error is generated when predictions do not fit the sensory data and is used to update the contents of the internal model. Error signals are thought to be moderated by the reliability (or precision) of the incoming stimuli, lending the most weight to stimuli that are most reliable. This precision-weighting scheme is important for perceptual learning, as it suggests that only high-precision prediction errors are being used to update the generative model and influence future predictions. In this work, we investigate the brain responses to high- and low-uncertainty contexts using a modified version of the RAND-REG paradigm used in previous studies (Barascud et al., 2016). Instead of tone pips, our approach uses complex tones that are either harmonic or inharmonic. Harmonic complex tones consist of frequencies that are integer multiples of one fundamental while inharmonic tones consist of unrelated frequencies and thus include more information. We hypothesize that inharmonicity should influence the encoding of regularity by downweighting sounds that are inharmonic. This effect should be present in the mismatch responses recorded with electroencephalography. In a previous study, Southwell and Chait (2018) established that outliers in a low-uncertainty context evoked a larger response than matched outliers in a high-uncertainty context. Preliminary behavioral results from our data suggest that while participants can consciously detect an outlier in both harmonic and inharmonic conditions, the reaction times do not differ between the conditions. This suggests that inharmonic sounds are not processed differently depending on context and goes against the precision-weighting hypothesies. It remains to be seen if these results are supported by electroencephalography data. The results of this study can inform current predictive theories of perception that rely on precision weighting to explain the generative model updating.

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Poster

PSTR121: Auditory Processing: Animal Models

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Program #/Poster #: PSTR121.15/M1

Topic: E.05. Auditory and Vestibular Systems

Title: Dynamics of task representation in mouse prefrontal cortex during serial reversal learning

Authors: *F. ZHU[1], X. LE[1], K. KUCHIBHOTLA[1,2,3];
[1]Psychological and Brain Sci., [2]Neurosci., [3]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Animals are capable of flexibly adapting their behaviors to changing features in the environment. When changes in the environment are predictable, animals can reuse existing representations to efficiently learn the appropriate behaviors. Here, we use a novel two-choice serial reversal task to investigate how representations of task variables develop as mice update their stimulus-action associations across multiple reversals. Mice (n = 8) rapidly learned to associate two auditory cues with left and right licks to obtain water reward and subsequently performed eight reversals of stimulus-action associations. To examine the dynamics of task representation, we performed longitudinal two-photon calcium imaging using a microprism in the prefrontal cortex throughout the entirety of the learning process. We imaged the same field-of-view over weeks to allow us to track neurons across reversals and identified cells that responded to single, multiple and conjoint task variables (i.e. stimuli, choice, and reward). Additionally, to test if the relationship between task representation of reversal learning is generalizable, we trained expert animals to perform a reversal with a new stimulus set. Our findings add to our growing understanding of how prefrontal cortex supports cognitive flexibility in a cognitively demanding two-choice reversal task.

Disclosures: F. Zhu: None. **X. Le:** None. **K. Kuchibhotla:** None.

Poster

PSTR121: Auditory Processing: Animal Models

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Topic: E.05. Auditory and Vestibular Systems

Support: R01DC018650
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Kavli NDI JHU

Title: The dynamics of auditory cortical astrocytes during sensorimotor learning

Authors: *S. MOORE CORONA[1], Z. YOU[2], Z. ZHU[3], K. KUCHIBHOTLA[4];
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Abstract: Astrocytes, the predominant glial cell type in the brain, have emerged as active participants in neural information processing and plasticity. However, their functional dynamics across learning remain poorly understood. Here, we used chronic fiber photometry and two-photon calcium imaging to longitudinally track populations or individual astrocyte Ca^{2+}

dynamics in the auditory cortex of awake mice (expressing Aldh1l1-dependent GCaMP6s in an inducible manner) across the acquisition of an auditory discrimination task. We trained mice to lick to a tone for water reward (S+) and withhold from licking to another tone (S−) to avoid a timeout. We added catch trials in which the reward contingency was changed in a block-based manner to understand how these signals change upon contextual cues. Over several days of training, astrocytes exhibited learning-related modulation of their Ca^{2+} dynamics, with cells showing enhancement of their evoked responses during rewarded trials. This increased activity arose within the first 100 trials of reward-based training and was not due to licking as the same astrocytes exhibited suppressed activity on errors of action (incorrect licking to the S-, false alarm). We observed two timescales of astrocyte activation, one 'early-in-trial' that aligned with the tone and initial lick. Another appeared later-in-trial, was broader and significantly larger, potentially associated with motor, reward and post-reward processing. Omitting reward on correct trials (hits, S+) led to biphasic responses where a transient increase in activity was followed by a profound suppression, suggesting that reward consumption may drive extended increases in astrocyte activity. Receiving extra reward amount (2x), led to a potentiation of these responses. Similar patterns of activity arose in correct trials with no licking (correct rejects to the S-) in the same reward-shift block. Finally, baseline activity in astrocytes efficiently tracked the reward-context. Together, these data suggest that astrocytes are tracking a more abstract context variable irrespective of movement. Interestingly, baseline reward-related signals extended beyond individual trials, potentially playing a role in maintaining a signature of reward and trial history for upcoming choices. Our data suggest that coordinated astrocyte ensembles may provide a scaffold for integrating reward signals with sensory processing to facilitate learning, potentially bridging trial-level and inter-trial computations. This study expands our understanding of astrocyte contributions to neural circuit dynamics underlying adaptive behavior.

Disclosures: S. Moore Corona: None. **Z. You:** None. **Z. Zhu:** None. **K. Kuchibhotla:** None.

Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.17/M3

Topic: E.05. Auditory and Vestibular Systems

Support: Mass General Seth Robbins Transformative Scholar in Tinnitus Award
R01 DC009836
Nancy Lurie Marks Family Foundation

Title: Fragmented non-REM sleep and increased sound-evoked awakening in a mouse model of noise-induced hearing loss

Authors: *A. R. CHAMBERS[1,2], C. TIMS[1], K. HANCOCK[1,2], E. LAWLER[1], D. B. POLLEY[2]; [1]Mass Eye & Ear, Boston, MA; [2]Otolaryngology, Harvard Med. Sch., Boston, MA

Abstract: During sleep, sounds retain their ability to potently and rapidly induce arousal. Sleep is thus vulnerable to disruption in cases of central auditory dysfunction. Poor sleep is a primary complaint of patients with hearing disorders such as tinnitus, and is common among people with sensorineural hearing loss. Uncovering a mechanistic link between hearing loss and sleep loss, e.g. via central hyperactivity and hyperarousal, could identify new ways to treat hearing disorders and insomnia, and help to explain the risk for dementia that is strongly associated with hearing loss. Here, we tested whether noise-induced hearing loss (NIHL) is associated with disrupted sleep in a mouse model. We used a noise exposure paradigm to produce a permanent threshold shift at high frequencies while leaving lower frequency hearing intact, and measured electrocorticography (ECoG) and electromyography (EMG) signals during wake and sleep. Mice were housed in custom-built, acoustically transparent enclosures while ECoG, EMG and video were recorded during either silence or in the presence of octave-band noise stimuli at varying intensities. We analyzed sleep architecture in silence by scoring periods of wakefulness, rapid-eye movement (REM) and non-REM sleep and defining sleep bout frequency and duration. Further, we analyzed sound-induced awakening thresholds to track the propensity of high and low frequency sounds to wake animals from sleep. We compared these metrics before and after NIHL or sham exposure. Mice exhibited fragmented sleep patterns after NIHL characterized by significantly shorter bouts of NREM sleep. Further, moderate intensity stimuli were more effective at waking mice after noise exposure. Meanwhile, no changes in sound-induced waking behavior were observed in control mice that underwent sham noise exposure. These results suggest that hyperarousal accompanies NIHL in mice, raising the possibility that excess central auditory pathway gain after NIHL extends to auditory arousal networks, disrupting sleep architecture and rousing the sleeping brain in response to inconsequential environmental sounds. As many aspects of sleep are readily quantifiable, the topic is well suited for parallel investigations in mice and humans.

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Poster

PSTR121: Auditory Processing: Animal Models

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Program #/Poster #: PSTR121.18/M4

Topic: E.05. Auditory and Vestibular Systems

Support: Howard Hughes Medical Institute
NIH Grant MH138935-01

Title: Decision history alters sensory adaptation behaviorally but not in auditory thalamus

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Abstract: Perception is shaped by recent stimuli and decisions, but the mechanisms linking these timescales of contextual modulation remain poorly understood. In one common type of auditory adaptation, a brief sound suppresses perception of and neural responses to subsequent stimuli for hundreds of milliseconds. In decision making tasks, whether the subject receives a reward on a given trial influences both the behavioral choice and neural activity on the subsequent trial. Whether, and if so, at what level of neural processing, these distinct timescales of contextual modulation interact remains unknown. We measured the time course and strength of sensory adaptation during an auditory decision-making task in which rats accumulated transient, pulsatile click stimuli ("Poisson Clicks task"). Adaptation profiles were inferred from both choice behavior and neural responses recorded in the auditory thalamus (MGB; medial geniculate body) and tail of the striatum (TS). In line with previous work, a click significantly reduced a subsequent click's influence on the behavioral choice and neural activity. The dynamic range of behavioral adaptation was significantly amplified by a previous reward, indicating an interaction between sensory adaptation and decision history. In contrast, reward history did not detectably alter neural adaptation in MGB and appeared to shrink the dynamic range of TS adaptation. This suggests sensory adaptation and reward history integrate to modulate behavior at other stages of processing. Consistent with downstream regions playing a role in sensory adaptation, thalamic and striatal adaptation recovered more quickly and had a smaller dynamic range than behavioral adaptation. These findings suggest that decision and stimulus history converge to shape auditory perception, but that this integration arises downstream of the auditory thalamus and striatum.

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Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.19/M5

Topic: E.05. Auditory and Vestibular Systems

Support: National Institute of Health Grant R01NS129874
Alzheimer's Association Research Grant 21-850571

Title: Auditory cortical mechanisms of self-generated sound-guided navigation under varying cue conditions

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Abstract: As we navigate our environment, we experience self-generated sounds such as the sound of our footsteps. In many situations, self-generated sounds can be predictable based on prior experience, and previous studies have shown that their corresponding neural representations are suppressed. However, in situations where we need to rely on sounds like navigating in the dark, self-generated sounds can provide crucial information to guide our behavior like the substrate being walked on and our location in our environment. While human studies do provide strong evidence for self-generated sounds actively influencing behavior, the neural mechanisms of encoding and utilizing these self-generated sounds are yet to be understood. To elucidate these mechanisms, we study the auditory cortex, a key candidate brain region that could encode behaviorally relevant self-generated sounds and facilitate sound-guided behavior. For this purpose, we designed a novel experimental setup for freely behaving rats, consisting of a track with different substrates underneath a uniform surface, such that running on different sections of the track generated different footstep sounds. First, rats were trained to navigate this track to find a fixed reward location. To test if well-trained rats use their own footstep sounds to guide their navigation, or if they use distal visual cues instead, we tested the rats' performance on the navigation task both with the lights on and in the dark. We found that when the lights were on, rats followed the distal visual cues to navigate, while in the dark they used their own footstep sounds to spatially orient and navigate. Next, we inactivated the auditory cortex of rats being tested in the dark which impaired their performance on this task. Finally, we recorded neural activity from the auditory cortex while the rats' performance was being tested in the light and dark and quantified the differences in neural activity between these conditions. Together, our findings suggest that self-generated footstep sounds encoded by the auditory cortex are used for navigation in the dark.

Disclosures: M. Kumar: None. **G. Rothschild:** None.

Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.20/M6

Topic: E.05. Auditory and Vestibular Systems

Support: ONR grant N000014-21-12065

Title: Auditory processing and response time in bottlenose dolphins performing a signal detection task: proof of principle neurobehavioral observations

Authors: *M. D. SCHALLES[1,2], J. COHEN[1], T. COMBE[1], K. HENSON[1], K. CHRISTMAN[3], J. MULSOW[4], D. HOUSER[3], J. FINNERAN[4], P. TYACK[5], B. SHINN-CUNNINGHAM[2]; [1]New Col. of Florida, Sarasota, FL; [2]Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA; [3]Natl. Marine Mammal Fndn., San Diego, CA; [4]US Navy Marine Mammal Program, NIWC Pacific, San Diego, CA; [5]Biol., Woods Hole Oceanographic Inst., Woods Hole, MA

Abstract: Dolphins navigating turbid waters, like San Diego Bay, rely on echolocation for foraging and navigation. At speeds up to 10 m/s, they have high demands for using auditory information to update motor plans and movement trajectories. Previous attempts to quantify behavioral response times for auditory tasks relied largely on acoustic recordings of dolphins producing a whistle when they detected a target. One of the standard electrode recording sites for dolphin auditory evoked potential (AEP) audiometry is just posterior to the blowhole, a thin lip of skin that covers the dolphin's airway. This site is sensitive to EEG and additional EMG signals produced by breathing and vocalizations. In the present study we asked 1. If it is possible to observe AEPs in the time window between target sound onset and a whistle response and 2. Is it possible to use the muscle activation from the same electrode to estimate behavioral response time? We recorded EEG from a single electrode, a hydrophone near the dolphin's head, and a hydrophone encased in a silicone suction cup placed on the dolphin's melon. Two male dolphins (*Tursiops truncatus*) performed a behavioral hearing threshold task with a descending staircase, whistling when they heard a 40 kHz tone that we modulated in amplitude. Preliminary results indicate that an AEP similar to passive listening conditions in previous experiments is present, followed by a longer latency, larger amplitude negative deflection that appears to peak around the time that muscles are engaged to produce a vocalization (~200 ms post stimulus onset). This method could be used for studying cognitive processes in dolphins for both stimulus-locked and subject response-locked neural activity, and for future studies of dolphin decision making in the moments leading up to a behavioral response.

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Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR121.21/M7

Topic: E.05. Auditory and Vestibular Systems

Support: CONAHCYT 1003309
UNAM PAPIIT BG200424

Title: Neural mechanisms underlying beat-based and single-interval time production in non-human primates

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Abstract: Precise estimation and production of time are essential to the control of many behaviors that can be either simple such as collision avoidance or highly complex such as dancing or performing music. Depending on the context, different types of time measurement can take place, and individuals should be able to flexibly alternate between them. The neural mechanisms behind these processes remain elusive. In the current study we focused on two types of time estimation: beat-based and single-interval. Single-interval timing requires the estimation of the elapsed time between two events (absolute duration). On the other hand, beat-based timing relies on the repetition of events, and individuals must measure the duration of time intervals relative to their temporal regularity. Studies in humans suggest that these two types of timing engage different cerebral circuits, with the cortex-basal ganglia circuit being more predominant during beat-based timing and the olivocerebellar circuit being more involved in single-interval timing. These circuits have cerebral structures in common, such as the medial premotor cortex (MPC). Previous studies have shown that MPC is closely related to time perception and production. In this study, we trained a macaque monkey to perform two auditory timing tasks: the perception-synchronization task (which requires beat-based timing) and the single-interval reproduction task. Neural activity from pre-SMA and SMA was recorded while the monkey performed both tasks. Preliminary results show that monkeys can perform both tasks and are able to switch from beat-based to single-interval timing depending on the context. Moreover, neural activity in both areas is heavily modulated by the task, with single units modulating their firing rates differently, according to the task performed. This suggests that beat-based and single-interval timing activate different neural mechanisms, even in premotor areas that are considered to be the core of the timing circuit.

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Poster

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.22/M8

Topic: E.05. Auditory and Vestibular Systems

Support: PAPIIT Grant BG200424

Title: Population dynamics in the primate audiomotor system for correct and incorrect trials during tapping synchronization

Authors: *J. P. MARQUEZ GUTIERREZ[1], Y. A. AYALA[2], L. PRADO LOEZA[1], G. MENDOZA[3], H. MERCHANT[4];
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Abstract: Audiomotor synchronization depends on the interaction between auditory and motor areas of the brain, including the pre-supplementary motor area (pre-SMA) and the basal ganglia. This auditory information may reach the pre-SMA and then the putamen through the posterior parietal cortex. However, during this process, errors may occur in: (1) information coding, (2) information transfer between areas, or (3) time coding, which may lead to incorrect synchronization. In this study we recorded the activity of the audiomotor circuit in two Rhesus monkeys with single-cell resolution while they performed an auditory synchronization task. Behavioral analysis revealed clear differences between correct and error trials, which were classified as early (large negative asynchronies) or late (large positive asynchronies) errors. Using pattern recognition methods and warping techniques, we identified clusters of cells whose responses were aligned to the metronome, to the tapping, or to a combination of both stimuli and movements. We found a gradient of increasing motor cell density and a decrease in sensory cell density from A1 to M1 and cells with responses associated with a top-down signal in auditory areas associated with the internal beat representation. We found differences in population activity between correct and error trials with activity patterns specific to each error category and the position of the error. Finally, using PCA to project the population activity of each area into a low-dimensional state space we compared the trajectories of correct and error trials using distance and tangling metrics within the shared subspace for each identified cluster.

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Poster

PSTR121: Auditory Processing: Animal Models

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.23/M9

Topic: E.05. Auditory and Vestibular Systems

Support: AARF-22-970734

Title: Revealing hidden knowledge in amnestic mice

Authors: *A. SANTI[1], S. Y. MOORE CORONA[2], K. FOGELSON[6], A. WANG[7], J. LAWLOR BLONDEL[3], K. BURKE[1], A. M. LAUER[4], K. KUCHIBHOTLA[5];
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Abstract: Alzheimer's disease is a form of dementia in which memory and cognitive decline is thought to arise from underlying neurodegeneration. These cognitive impairments are transient when they first appear and can fluctuate across disease progression. Here, we investigate the neural mechanisms underlying fluctuations of performance in amnestic mice. We trained APP/PS1+ mice on an auditory go/no-go task that dissociated learning of task contingencies

(knowledge) from its more variable expression under reinforcement (performance), while monitoring the activity of 6,216 excitatory neurons in 8 mice by using large-scale two-photon imaging in behaving mice. We found that auditory cortical networks were more suppressed, less selective to the sensory cues, and exhibited aberrant higher-order encoding of reward prediction when APP/PS1+ mice exhibited significant performance deficits compared to control mice. A small sub-population of neurons, however, displayed the opposite phenotype, reflecting a potential compensatory mechanism. Volumetric analysis demonstrated that deficits were concentrated near Aβ plaques. Strikingly, these cortical deficits were reversed almost instantaneously on probe (non-reinforced) trials when APP/PS1+ performed as well as controls, providing neural evidence for intact stimulus-action knowledge despite variable ongoing performance. A biologically-plausible reinforcement learning model recapitulated these results and showed that synaptic weights from sensory-to-decision neurons were preserved (i.e. intact stimulus-action knowledge) despite poor performance that was due to inadequate contextual scaling (i.e. impaired performance). Our results suggest that the amnestic phenotype is transient, contextual, and endogenously reversible, with the underlying neural circuits retaining the underlying stimulus-action associations. Thus, memory deficits commonly observed in amnestic mouse models, and potentially at early stages of dementia in humans, relate more to contextual drivers of performance rather than degeneration of the underlying memory traces. Future investigation will test whether amyloid disrupts the integration of long-range inputs, disturbing the delicate balance between inhibition (via PV+ interneurons) and disinhibition (via VIP+ interneurons) and thereby impairing the activation of the memory trace.

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Poster

PSTR121: Auditory Processing: Animal Models

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC018650
Kavli NDI Distinguished Postdoctoral Fellowship

Title: Role of the cholinergic system in early sensorimotor acquisition

Authors: *J. LAWLOR BLONDEL[1], S. E. ELNOZAHY[5], F. ZHU[2], Z. ZHU[3], A. WANG[6], F. DU[7], T. RAAM[8], K. KUCHIBHOTLA[4];
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Baltimore, PA; [7]Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA; [8]Dept. of Biol. Chem. and Dept. of Neurobiology, David Geffen Sch. of Med., UCLA, Los Angeles, CA

Abstract: During sensorimotor learning, animals link a sensory cue with actions that are separated in time using circuits distributed throughout the brain. 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 for reinforcement, termed '*expression*'. What role does cholinergic neuromodulation play in task acquisition? Here, we test the hypothesis that 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. We report both robust stimulus-evoked cholinergic activity to both S+ and S- and stable licking-related activity throughout learning. While this activity mildly habituates in a passive control, in behaving animals the S+ and S- stimulus-evoked activity is enhanced (S+: duration, S-: amplitude and duration) on the timescale of 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. In each case, 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

PSTR121: Auditory Processing: Animal Models

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.25/M11

Topic: E.05. Auditory and Vestibular Systems

Title: Compositional inference in the continual learning mouse playground

Authors: *A. BAL[1], A. SANTI[2], S. SOTO[2], P. H. JANAK[3], K. KUCHIBHOTLA[4]; [2]Psychological and Brain Sci., [3]Psychological and Brain Sciences, Neurosci., [4]Psychological and Brain Sciences, Neurosci. and Biomed. Engin., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: Humans exhibit the remarkable ability to continuously learn new things over their lives without forgetting previous information, an ability known as continual learning. Currently, the neural mechanisms underlying this ability remain unknown. Studying this phenomenon in biological organisms remains challenging, as the nature of the problem requires training experimental subjects on numerous tasks over time while simultaneously obtaining neural recordings. Given this constraint, we use mice as a model organism, given their amenability to longitudinal neural recording procedures and trainability on complex cognitive tasks. However, many assume that mice can only handle simple learning paradigms, successfully learning at most a few tasks. We contend that this limit is not a result of reduced cognitive capacity in mice, but rather from training procedures that ignore naturalistic behaviors. To that end, we built the Continual Learning Mouse Playground, a fully-automated home-cage training system where mice continuously complete cognitive tasks in a naturalistic setting. Using the Mouse Playground, we trained mice (n=12 across 3 cohorts) to sequentially learn 8 tasks that varied across the learned task structures (Go-NoGo, 2AFC) and perceptual dimensions (pure tone, sound duration, click rate, AM modulation, sweep direction, and sound intensity). Importantly, we defined a task as any unique combination of task structure and perceptual dimension. Mice exhibited expert performance on a sequence of 8 tasks, reaching at least 80% accuracy on each task in rapid fashion. Throughout training, we probed earlier tasks between new tasks and found strong retention with minimal relearning. So far, this data showed that mice can learn many tasks in sequence without forgetting, but an important aspect of continual learning is being able to leverage prior knowledge in new contexts, known as compositional inference. To assess this, the final two tasks combined a familiar task structure (2AFC) with previously-learned auditory dimensions, yet in an unencountered novel pairing. Strikingly, we observed that 6 out of 12 trained mice exhibited extremely rapid learning in Tasks 7 and 8, with some mice exhibiting over 80% performance in the first 50 trials of Task 8. A generalized linear model revealed that rapidly-learning mice utilized stimulus information earlier in Tasks 7 and 8 and relied less on a biased-response strategy compared to gradually-learning mice. Collectively, these results establish the Mouse Playground as a viable platform to study continual and compositional learning, providing rapid and scalable behavior results that were previously difficult to study.

Disclosures: A. Bal: None. **A. Santi:** None. **S. Soto:** None. **P.H. Janak:** None. **K. Kuchibhotla:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.01/M12

Topic: E.06. Vision

Support: Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 22KK0137 Ritsumeikan Global Innovation Research Organization （R-GIRO）

Title: Preserved retinal function in a severely disrupted retina: an electrophysiological study

Authors: *K. SAKUTA[1], A. UENO[7], H. ONO[2], A. HASHIO[3], H. TOKUMOTO[4], M. TACHIBANA[5], C. KOIKE[6];
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Abstract: Introduction:
Laminar architecture in the central nervous system is closely tied to neural circuit function. The mammalian retina, derived from the brain, also exhibits a highly organized laminar structure crucial for visual processing. However, the functional relationship between retinal lamination and visual circuit integrity remains incompletely understood. We investigated how visual functions are preserved when retinal lamination is disrupted by conditional knockout of Afadin, a cytoplasmic scaffold for the adhesion molecule Nectin, normally localized at the outer limiting membrane.

Methods:
We utilized retina-specific Afadin conditional knockout (cKO) mice generated using Dkk3-Cre. Visual function was assessed via in vivo electroretinography (ERG) and ex vivo multielectrode array (MEA) recordings from isolated retinas. We measured micro-electroretinograms (mERGs) and retinal ganglion cell (RGC) spike responses to full-field flashes and checkerboard stimuli. RGC light responses were classified using peristimulus time histograms, and receptive fields (RFs) were computed via spike-triggered averaging.

Results:
Retinas from Afadin cKO mice exhibited structural abnormalities in the outer retina, particularly in the photoreceptor layer, including reduced photoreceptor density and fewer synapses between photoreceptors and bipolar cells. In vivo ERG responses were nearly flat, indicating reduced retinal activity. However, ex vivo MEA recordings revealed small but detectable a-waves (photoreceptor-driven) and b-waves (bipolar cell-driven) in the mERGs. Although these responses were reduced in amplitude and delayed in onset compared to controls, they were consistently present.
Strikingly, many RGCs in cKO retinas exhibited light-evoked spiking activity, and the distribution of response types was largely comparable to controls. RFs were still detected in a subset of cKO RGCs, about one-third the number in controls, with slightly smaller spatial extent. Temporal analysis revealed a loss of fast-responding RGC subtypes. Additionally, periodic spontaneous RGC firing, commonly seen in degenerated retinas, was observed.

Conclusion:
Despite profound disruption of outer retinal architecture in Afadin cKO mice, RGC light

responses and receptive fields were preserved in a substantial subset of cells. These findings provide evidence that RGC receptive fields can form and function if residual photoreceptor-bipolar connectivity remains. This study highlights the resilience of retinal circuits and informs our understanding of retinal development, disease, and regenerative therapy design using stem cell-derived tissue.

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Poster

PSTR122: Photoreceptors and Retinal Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.02/M13

Topic: E.06. Vision

Support: NSF OIA-2121164
Internal funding from the USC Center for Neuronal Longevity

Title: Dendritic remodeling of retinal ganglion cell morphology at early stage of retinitis pigmentosa

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Abstract: Retinitis pigmentosa (RP) is a disease which causes impaired metabolic support to photoreceptor cells, resulting in their degeneration and eventual cell death, leading to irreversible vision loss. Due to the loss of neural inputs from degenerating photoreceptors, downstream bipolar and retinal ganglion cells (RGC) in the inner retina remodel their connectivity, but it's unclear how dendritic morphology changes during the early disease stages. Understanding how the inner retina changes in RP at early disease timepoints is critical to developing therapeutic devices that can accurately restore visual signaling in a remodeled inner retina. RGCs, whose axons comprise the optic nerve, are critical for the conveyance of visual information towards the brain for cognitive processing and visual perception. We hypothesized that RGC dendritic morphology is significantly changed at an early age timepoint (P49) where RP degeneration is primarily limited to the outer retina. To label RGC morphology in diseased retina at high resolution, we utilized N2c G-deleted rabies viral tracing by stereotaxic injections into the dorsal lateral geniculate thalamus (LGd) in Royal College of Surgeons (RCS) rats, a well established rodent model of RP. In wildtype (WT) Sprague Dawley and RCS rats, LGd-projecting RGCs were retrogradely-labeled via the optic nerve and fluorescently expressed green fluorescent protein (GFP) to visualize their full cellular morphology. Following 1 week survival time, rats

were transcardially perfused with paraformaldehyde fixative and retinas were extracted, processed for SHIELD tissue clearing, and flat-mounted onto microscope slides for 3D microscopy imaging. Cleared retina samples were imaged using a spinning disk confocal with 40X magnification to generate 3D images with 160 nm isotropic voxel resolution. Microscopy images of RGC morphology were reconstructed manually in 3D using Aivia reconstruction software and geometric features of these reconstructions were used for statistical comparisons of LGd-projecting RGC morphology in WT vs RCS. Reconstruction analysis found several significant changes in RGC dendritic morphology vs WT at P49 including decreased dendritic diameter, path length, and volume. Interestingly, RGC dendrite fractal dimensionality increased in the RCS vs WT, suggesting these dendritic changes promote connectivity, supporting their role in retinal remodeling rather than neurodegeneration at this early disease timepoint. Future studies will investigate dendritic changes to RGC morphology at progressive disease timepoints to understand how the inner retina continues to change across RP.

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Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Program #/Poster #: PSTR122.03/M14

Topic: E.06. Vision

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Title: On-direction selective ganglion cell function and the optokinetic reflex are sensitive to cone loss

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Abstract: In humans, visual acuity can remain unaffected after dysfunction of up to half of all cones, suggesting compensatory mechanisms within the visual system. In the mouse retina, partial cone loss causes compensation in ON-sustained alpha retinal ganglion cell (RGC) circuit, likely involved in conscious vision. It remains unknown how ganglion cells involved in nonconscious visual pathways react to cone loss. ON-direction selective ganglion cells (oDGSCs) in the retina drive a gaze stabilization reflex called the optokinetic reflex (OKR), and here, we test the impact of graded cone loss on both the OKR and oDSGC function. We used a mouse model (cone-DTR) that selectively ablates M-opsin expressing cones, where the dosage

of diphtheria toxin can induce different degrees of cone loss. We evaluated the OKR gain (ratio of eye velocity to stimulus velocity) across a range of cone densities from cone-DTR and wildtype mice using a grating stimulus oscillating vertically. For electrophysiology recordings of oDSGCs, we used retrograde labeling to target two types of oDSGCs in the retina, sensitive to upward- (Superior) and downward- (Inferior) motion. We observed responses of oDSGCs from dark-adapted retinas to stimuli moving in 8 directions using cell-attached and whole-cell patch clamp recordings. We then compared spike responses and direction selectivity of oDSGCs across cone density from both cone-DTR and wildtype retinas. For both physiology and behavior experiments, we quantified cone density using post-hoc immunohistochemistry.Our behavioral analysis found that OKR gains of cone-DTR mice with minor cone loss were significantly reduced ($p=0.008$) compared to wildtype mice. Consistent with this finding, we observed fewer spikes ($p=0.005$) and greater direction selectivity ($p<0.001$) in oDSGCs from cone-ablated retinas. These metrics were linearly correlated with cone density in Inferior oDSGCs, however Superior oDSGC responses had nonlinear relationships with cone density. Cone density was negatively correlated with the magnitude of Inferior inhibitory currents ($R=-0.53,p=0.03$) and the tuning of Superior inhibitory currents ($R=-0.61,p=0.02$), while excitatory currents were not correlated with cone density ($p>0.05$).These results demonstrate that: 1) the OKR and oDSGC function are sensitive to minor changes in cone density, 2) oDSGC types are differentially affected by cone loss, and 3) compensation in the oDSGC circuit occurs via altered inhibition, rather than excitation. The sensitivity of the accessory optic system to the degree of cone loss will be useful for better diagnostic tools for photoreceptor degeneration.

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Poster

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Topic: E.06. Vision

Support: AMED JP25ek0109726

Title: Functional longevity assessment of a photoelectric dye-coupled polyethylene film (OUReP) for retinal stimulation

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Abstract: Retinal degenerative diseases, such as retinitis pigmentosa, have prompted the development of prosthetic devices to restore visual function. Among these, OUReP—a light-

sensitive polymer film developed at Okayama University—offers a non-electrode-based strategy for retinal stimulation. The surface of OUReP is chemically coupled with photoelectric dye molecules, enabling photovoltage generation in response to light. Previous studies have demonstrated OUReP's safety and efficacy in a monkey model of age-related macular degeneration, as well as its ability to evoke spike discharges in retinal ganglion cells (RGCs) in isolated mouse retinas. To assess the functional longevity of this system, we conducted extracellular recordings from RGCs in isolated mouse retinas using both standard and photobleached OUReP films simulating implant durations of six months and several years in monkeys. All procedures followed the guidelines of the Japan Neuroscience Society and were approved by the Animal Experiment Committee of Senshu University (#2024-1, #2025-1). C57BL/6J mouse retinas were mounted on the film with the ganglion cell layer facing upward. A conventional tungsten electrode was inserted into the RGC layer to record multi-unit activity (MUA). Spatially uniform LED light stimuli were presented, and L-AP4 was applied to block synaptic transmission from photoreceptors to ON bipolar cells. Under these conditions, ON responses were abolished with control films but persisted with standard OUReP, indicating direct neural activation by the film. Even in a moderately photobleached state (~24% residual dye), corresponding to six months of implantation, OUReP continued to evoke ON responses despite the synaptic blockade. In contrast, a severely photobleached version (~5% residual dye), prepared to simulate several years of implantation, induced minimal or no RGC activity. These findings indicate that OUReP may retain its function for at least six months after implantation, but its effectiveness significantly declines after several years. Future refinements, such as increasing the density of dye molecules, may enable even more sustained and effective retinal stimulation.

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Poster

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Title: Role of early visual activity for regulating synaptic connectivity in the mammalian retina

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Abstract: The retina is a highly specialized and meticulously organized sensory epithelium which absorbs photon light signals, converting them into electrical signals. Retinal ganglion cells (RGCs), of which there are ~42 types, serve as the output cells of the retina and fire action potentials to connect the retina to higher-level brain areas. Approximately six types of the currently characterized RGCs can absorb photons by themselves via a specialized photopigment known as melanopsin. These RGCs can respond to light without input from traditional photoreceptors and are known as intrinsically photosensitive retinal ganglion cells (ipRGCs). ipRGCs are known to be implicated in many physiological behaviors such as light aversion, pupillary light reflex, encoding irradiance, and photoentrainment. However, little is known about the role of ipRGC signaling in retinal circuit assembly during development. ipRGCs, and RGCs more broadly, are one of the first neuronal classes to develop in the retina, with melanopsin signaling beginning before birth in the murine retina, over a week before photoreceptor signaling commences. ipRGCs are also the first cells to send visual information to the brain. Since early melanopsin driven signaling occurs at the same timepoint that retinal synapses begin to form, we asked how this early visual signaling in the retina shapes the structure and function of second order retinal neurons known as bipolar cells. Bipolar cells are crucial intermediaries in the retinal circuit that channel photoreceptor information from the outer retina to inner retinal neurons including RGCs. In this study, we used confocal imaging coupled with immunohistochemistry as well as serial block-face scanning electron microscopy (SBF-SEM) to determine changes in the development of bipolar cells in a melanopsin knockout (KO) mouse model which possesses ipRGCs that lack the photopigment melanopsin. We found that bipolar cell connectivity with both pre- and post-synaptic partners is altered when early melanopsin-driven activity is suppressed in the retina. In addition, both bipolar cell morphology and categorical segregation are perturbed in the KO mice. These findings point to a role of early melanopsin signaling for the proper development and formation of the mammalian retina.

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Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Program #/Poster #: PSTR122.06/N1

Topic: E.06. Vision

Title: One million retinal nuclei atlas generated by single nuclei RNA-seq reveals extensive unique cell subtypes in murine eye tissue

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Abstract: The retina is a highly complex tissue composed of several layers of interconnected neurons that enable visual perception. These layers facilitate the process of translating and

transducing light into electrical signals through the pathway of photoreceptor rods and cones, bipolar cells, horizontal cells, amacrine cells, and retinal ganglion cells. Each of these cell types can be further subdivided into subclasses with subtle differences, although previous attempts to accurately characterize these rare cell types through smaller scale snRNA-seq studies have been challenging for two main reasons: 1) Cell populations of subtypes in the system are relatively small. 2) Subtype characterization often relies on a few marker genes and can be missed due to poor gene detection. The retina represents a pinnacle of challenges for single nuclei RNA-seq. As a proof-of-concept, 1 million nuclei isolated from murine eyeballs were processed from two animals (male and female), put through the barcoding workflow, and sequenced. Clustering of the subsequent data reveals a diversity of expected cell types including (but not limited to) retinal ganglia cells (RGC), amacrine cells, horizontal cells, bipolar cells, astrocytes, and Muller cells. Further sub-clustering of amacrine cells and RGCs reveals even more distinct subtypes (46 RGC subtypes and >35 amacrine subtypes) whose markers are consistent with putative subtypes. With >100 profiled cell types, the number of profiled cells per type is very few and can be difficult to parse out with low starting cell amounts. Scaling to at least 1 million cells is necessary to detect as many types as possible since some populations represent <0.1% of the eye. Furthermore, high gene sensitivity allows for detection and sub-clustering of distinctive subtypes in RGC and amacrine cells. This combination of scaling and sensitivity is needed to achieve a comprehensive and robust atlas. This murine eye atlas is just the beginning of using single nuclei RNA-sequencing technology to study the mechanisms of ophthalmologic disease models.

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Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Title: Systems Genetics Analysis of Retina to Reveal the Early Molecular Mechanisms of Alzheimer's Disease in a Genetically Diverse multi-pathology Model

Authors: N. RAMESHKUMAR[1], S. SIVAKUMAR[1], J. MARTINS BOFF[1], M. KHAMRAI[1], X. WANG[1], M. JABLONSKI[1], D. ASHBROOK[1,2], ***T. VAITHIANATHAN**[1];
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Abstract: The retina, described as ‘a window to the brain’, is emerging as a potentially valuable medium for studying Alzheimer’s disease (AD) *in vivo,* and revealing disease mechanisms. However, we lack a comprehensive mechanistic understanding of the relationship between visual deficits in AD and normal aging and the biomarkers that predict later disease. This lack of understanding is partly attributable to the limited genetic diversity in animal models, with most mouse studies relying on a single inbred C57BL/6J genetic background. We used the highly diverse recombinant inbred panel derived from C57BL/6J and DBA/2J parental strains (BXD), which mirror the genetic and phenotypic variation of human populations. We found that AD-BXD65 transgenic (Tg) at 6 months exhibited a substantial reduction of electroretinography (ERG) responses compared to non-transgenic (Ntg) mice in all scotopic, photopic ERG, oscillatory, and patterned ERG responses. Similar results were found in female AD-BXD65, but the differences were comparatively lower. Fundoscopy shows drusen-like deposits of vasculature, loss, and attenuated blood vessels in the male Tg retina compared to females. Immunostaining of synaptic vesicle proteins and astrocytes exhibited substantial changes in synaptophysin, a synaptic vesicle protein, and increased activation of astrocytes in male Tg compared to female Tg and Ntg. Understanding the effects of concurrent visual impairment will have a major impact on our causal and mechanistic understanding of AD and on the highly complex and variable pathophysiology of human AD and early diagnosis. Our data and discoveries will catalyze more replicable and robust preclinical models for prevention and therapeutic targeting.

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Poster

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Title: Functional and Structural Impacts of TRPM1 Deficiency on Retinal Oscillations

Authors: *T. NISHIMOTO[1], S. HORIE[2], K. SAKUTA[3], K. TADA[4], H. TOKUMOTO[5], K. KITANO[6], M. TACHIBANA[7], C. KOIKE[8];
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Abstract: TRPM1 is a transduction channel regulated by mGluR6 and expressed in the dendrites of ON bipolar cells. Our group previously found that retinal ganglion cells (RGCs) in *Trpm1* knockout (KO) mice exhibit aberrant spontaneous firing activity (i.e., oscillations), whereas such activity is absent in *mGluR6* KO mice. On the other hand, it's known that RGCs in *rd* mouse, model mouse for retinitis pigmentosa, also exhibit oscillations, which are generally thought to be triggered by photoreceptor degeneration. Notably, the photoreceptors in *Trpm1* KO mice remain structurally intact, suggesting that the loss of TRPM1—rather than photoreceptor degeneration—may be a causative factor for the emergence of oscillations. In this study, we examined whether the properties of oscillations are shared between the retinas of *Trpm1* KO and *rd1* mice. Whole-cell patch-clamp recordings from αRGCs revealed that oscillations in *Trpm1* KO mice closely resemble those observed in *rd1* mice. These electrophysiological findings, together with computational modeling, suggest that the oscillations in the *Trpm1* KO retina originate from AII amacrine cells (AII ACs), and that a hyperpolarized shift in the resting membrane potential of AII ACs relative to wild-type mice is a critical factor contributing to the generation of oscillations. We directly confirmed that AII ACs in *Trpm1* KO mouse also exhibit oscillations and that their resting membrane potential is significantly more hyperpolarized compared to that in wild-type mice. In addition, we found that resting membrane potential of rod bipolar cells (RBCs) in *Trpm1* KO mouse were also hyperpolarized. Finally, we performed immunohistochemical analyses to assess common morphological changes in the retinas of both *Trpm1* KO and *rd1* mice. We found that TRPM1 puncta were poorly localized in the dendrites of RBCs in the *rd1* mouse retinas, and that the volume of RBC axon terminals was reduced in both mutant models compared to wild-type controls. The shrinkage of RBC's axon terminals and the hyperpolarization of resting membrane potential of RBCs may lead to a reduction in synaptic input from RBCs to AII ACs. Interestingly, although reduced or absent TRPM1 expression in RBC dendrites has been reported in other oscillatory mutant retinas, its functional role in the emergence of retinal oscillations has remained unclear. Our findings point to TRPM1 as a potential key factor in this process. Our findings suggest that reduction or absence of TRPM1 in

ON-cone bipolar cells dendrites may cause RGCs oscillations by hyperpolarization of resting membrane potential of RBCs and remodeling of RBC's axon terminals, leading hyperpolarization of its downstream AII Acs.

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Poster

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Title: Characterization of Retinal Degeneration and Molecular Pathway Alterations in a Novel Humanized PDE6B Knock-In Mouse Model

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Abstract: Retinitis Pigmentosa (RP) is a group of inherited retinal degenerative disorders characterized by progressive photoreceptor loss, ultimately leading to vision impairment and blindness. Despite recent advances, no curative treatment is available for most forms of RP. Among its genetic causes, mutations in PDE6B, a gene critical for phototransduction, are frequently implicated in autosomal recessive RP. This study aimed to generate a humanized PDE6B knock-in (KI) mouse model using CRISPR-Cas9 and to characterize the temporal progression of retinal degeneration and the involvement of cGMP-related molecular pathways. Using CRISPR-Cas9-mediated gene editing, we introduced disease-relevant mutations into the PDE6B gene to generate a humanized KI mouse model. Retinal structure was monitored via optical coherence tomography (OCT) at various developmental stages. Protein expression and molecular changes were assessed using immunofluorescence staining. To explore the contribution of cGMP signaling to photoreceptor degeneration, pharmacologic inhibitors of the cyclic nucleotide-gated (CNG) channel (L-cis-diltiazem) and protein kinase G (PKG) (Rp-8-Br-cGMPs) were administered intravitreally. OCT imaging demonstrated that ONL thickness in PDE6B KI mice was comparable to wild-type at postnatal day 20 (P20), followed by rapid thinning by P25, indicative of acute photoreceptor degeneration. Immunostaining revealed the absence of PDE6B protein as early as P7, with a concurrent accumulation of cyclic GMP (cGMP), suggesting early dysregulation of the cGMP pathway prior to structural degeneration. The humanized PDE6B KI mouse model faithfully recapitulates key features of early-onset RP, including early photoreceptor loss and dysregulation of the cGMP signaling cascade. This model

offers a valuable platform for mechanistic studies and for testing therapeutic interventions targeting cGMP-mediated pathways in PDE6B-associated RP.

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Poster

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Title: Type 6 cone bipolar cell's en passant synapse gates rod signaling of DACs and ipRGCs for non-image forming vision

Authors: *K. SZATKO[1], A. NATH[1], W. N. GRIMES[1], K. M. DALY[2,3], D. M. BERSON[4], S. HATTAR[2], J. S. DIAMOND[1];
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Abstract: The inner plexiform layer (IPL) of the mammalian retina exhibits a highly organized structure featuring functionally and anatomically distinct sublayers. Bipolar cells (BCs) that respond to light increments send their axons to the ON sublamina of the IPL, whereas BCs responding to light decrements project their axons to the OFF sublamina [Nelson et al., 1978]. More recent anatomical studies revealed an “accessory ON sublayer” within the OFF sublamina [Hoshi et al., 2009; Dumitrescu et al., 2009]. Here, the axons of some ON bipolar cell types, e.g., the type 6 ON cone BC (T6 CBC), confer ON signals to postsynaptic targets via *en passant* ribbon synapses. Serial block-face electron microscopy reconstructions of T6 CBC axons revealed specific postsynaptic partners at *en passant* sites - the M1 intrinsically photosensitive retinal ganglion cells (ipRGCs) and dopaminergic amacrine cells (DACs) [Sabbah et al., 2022]. T6 CBCs also project their axon terminals to the ON layer and contact sustained ONα (M4) RGCs. The functional role for the accessory ON sublayer and the biophysical properties of the T6 CBC’s *en passant* and terminal synapses have not been fully identified. Here, we have investigated the divergent output of T6 CBCs under dark-adapted conditions, making cell-attached and whole-cell recordings from identified neurons in whole-mount retina. Our experiments revealed that M4s, DACs, and M1s exhibit distinct sensitivity to flashes from darkness. M4s, which primarily project to image forming regions, responded to dim scotopic flashes, whereas a subpopulation of DACs and M1s, which are mainly involved in non-image forming vision, did not. Blocking inhibitory synaptic transmission significantly enhanced visual DAC and M1 sensitivity with less effect on M4s, indicating the involvement of wide-field ACs. These results, together with anatomical reconstructions of T6 CBC circuitry, suggest that

inhibitory inputs from ACs along T6 CBC axons attenuate passage of rod signals via T6 CBC's *en passant* synapses to M1s and DACs. We also tested whether intracellular Ca^{2+} dynamics in T6 CBC axons influence the differential sensitivities of the two divergent circuits. We measured Ca^{2+} signals in axons of T6 CBCs using either a genetically encoded Ca^{2+} sensor or a low-affinity Ca^{2+} dye. Electrical stimulation of the primary rod pathway elicited strong signals in T6 CBC terminals but only weak signals at the *en passant* synapses. These experiments, together with an isolated assessment of Ca^{2+} channel expression, suggest that axonal resistance and low Ca^{2+} channel expression also contribute to reduced scotopic sensitivity in non-image forming circuits.

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Poster

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Title: Distinct Phenotypes in Mouse Models carrying two Early-Onset Blinding CRX Mutations, Y191d1 and E168d2

Authors: *M. BROWN, C. SUN;
Dept. of Ophthalmology and Visual Sci., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Cone-rod homeobox (CRX) is a retinal transcription factor required for photoreceptor development and survival. Autosomal dominant mutations are linked to early-onset degenerative blinding diseases such as Leber Congenital Amaurosis (LCA) and Cone-Rod Dystrophy (CoRD). The most prevalent diseases are caused by frameshift mutations on the CRX C-terminal activation domain, producing truncated proteins interfering with normal CRX function. It is unknown why these truncation mutations produce distinct diseases, but our hypothesis is that late truncations are less toxic than early ones. To test this, a new mouse model carrying a late truncation has been characterized: CRXY191d1. This was compared to the phenotypes of the previously published CRXE168d2 model carrying an early truncation. E168d2 is associated with early-onset CoRD, and Y191d1 is associated with LCA. The homozygous and heterozygous mutant mice of both sexes were observed in comparison to C57BL/6J (WT) at time points ranging from P0-3mo, but no sex differences were observed. The sample size was 4 mice. To characterize morphological changes for each strain, H&E histology was performed at various ages. The Outer Nuclear Layer (ONL) and the Outer Segments (OS) in heterozygous mice of both mutant strains are significantly thinner than WT at 1mo - 2mo and become worse later, with

a larger and faster decrease in Y191d1/+. Immunohistochemistry (IHC) was then performed for cone/rod markers. In Y191d1/+ at P21, cone arrestin is barely seen while rhodopsin is present until 2mo, suggesting that cones degenerate before rods. E168d2/+ has more cones/rods than Y191d1/+ at these time points, but less than WT. To test rod function, Electroretinogram (ERG) was performed at 1mo when rods mature for light responses in mice. Y191d1/+ mice had null rod responses to light, essentially blind, while E168d2/+ still responded to light although slightly worse than WT. To examine CRX expression, Western Blots were executed, and surprisingly both models express more mutant protein than the WT, with Y191d1 expressing the most. Lastly, qPCR examined expression changes in CRX target genes. In Y191d1/+, cone genes expressed lower than WT at P10 and became severely reduced by 1mo, while E168d2/+ expressed slightly above the Y191d1/+ levels at both time points. Collectively, our results show the phenotypes are more severe in Y191d1 than E168d2, challenging the position hypothesis. Investigating these mutations in mouse models helps us understand disease initiation and progression, why some mutations are worse than others, and information that can be put towards potential treatments.

Disclosures: M. Brown: None. **C. Sun:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.12/N7

Topic: E.06. Vision

Title: The Investigation of the Mechanism of Action of Chloroquine Retinopathy: By prevention of lysosomal membrane permeabilization (LMP)

Authors: *H. KIM[1], J. CHOI[2], J.-Y. KOH[3], Y. HAN[1], Y. KIM[4], Y. YOON[4];
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[4]Ophthalmology, [3]ASAN MEDICAL CENTER, SEOUL, Korea, Republic of

Abstract: Chloroquine (CQ), originally developed as an antimalarial agent, has been repurposed for autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis (Eliise Laura Nirk et al., 2020). However, its use is limited by CQ retinopathy—a severe adverse effect causing irreversible vision loss through mechanisms involving lysosomal dysfunction. This study investigated strategies to mitigate chloroquine-induced retinal toxicity using ARPE-19 cells as a model system. CQ treatment (40 μM for 24 hours) induced widespread ARPE-19 cell death, with 84.42 ± 3.48% cytotoxicity measured by LDH release. Parallel MTT assays confirmed reduced cell viability. The toxicity correlated with lysosomal alkalization and subsequent lysosomal membrane permeabilization (LMP), evidenced by increased cytosolic cathepsin D levels, accumulation of galectin-3 puncta at damaged lysosomes, and loss of lysosomal integrity. A high-throughput screening of the LOPAC drug library (Sigma) was performed to find protective drugs against CQ-induced LMP and cell death in ARPE-19 culture. A total of three candidate

protective drugs were selected, amiodarone, nortriptyline and desipramine, amiodarone was selected as the most effective against cell death measured by LDH release (amiodarone: 27.65 ± 5.56%, nortriptyline: 64.30 ± 7.73%, desipramine: 67.30 ± 9.36%). Amiodarone was found effective in lowering the rise of cathepsin D levels in the cytosol, reducing galectin-3 staining in the lysosome, and protecting against cell death. Further supporting that these drugs protect against LMP in general, they effectively attenuated galectin-3 accumulation in cells treated with other LMP-inducing agents such as tamoxifen and LLOMe. These findings demonstrate that CQ retinopathy may arise through LMP-driven pathways. The identified compounds represent promising candidates for adjunct therapies to prevent vision loss in patients requiring long-term CQ treatment. Further validation in animal models and clinical studies is warranted to translate these protective effects into clinical practice.

Disclosures: H. Kim: None. **J. Choi:** None. **J. Koh:** None. **Y. Han:** None. **Y. Kim:** None. **Y. Yoon:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.13/N8

Topic: E.06. Vision

Support: KDDF Grant RS202300283544

Title: Exploring the Role of miRNA-146a-5p in Sodium Iodate-Induced Age-Related Macular Degeneration Model

Authors: *S. CHO[1,3], J. CHOI[2], Y. KIM[4];
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Abstract: Age-related macular degeneration (AMD) is a neurodegenerative retinal disease. Non-protein-coding RNAs have been implicated in the pathophysiology of various neurodegenerative diseases. Animal models induced by sodium iodide ($NaIO_3$) have been widely used to investigate the pathophysiology of retinal pigment epithelial (RPE) cell and photoreceptor cell dysfunction because they exhibit a phenotype like the retinal degeneration observed in AMD. In a previous study, we screened exosomal miRNAs differentially expressed in vitreous samples from dry AMD patients. In the present study, we used animal models to investigate the pathophysiology of dry AMD by the previously identified miRNA-146a-5p. C57BL/6J mice, male, 7-8-week-old, were administered with 25mg/kg $NaIO_3$ by intraperitoneal injection and 4 nmol miR-146a-5p inhibitor by intravitreal injection. After 24 hours, phenotypic and functional changes of RPE and retina were assessed by fundus imaging, Optical Coherence Tomography (OCT), Electroretinography (ERG), and H&E staining. The expression of miRNA was analyzed by real-

time PCR. In addition, RPE dysfunction-related molecules caused by altered miRNAs were evaluated by immunohistochemistry, TUNEL stain, and Dihydroethidium (DHE). After $NaIO_3$ administration, retinal tissue and RPE degeneration and decreased RPE layer density were confirmed with fundus and OCT photographs and H&E stain. ERG recordings showed a decrease in photoreceptor cell function by $NaIO_3$. The expression level of miR-146a-5p, a target miRNA discovered in a previous study, was increased in the RPE/choroid of mice injected with $NaIO_3$ compared with the vehicle group. $NaIO_3$ administration showed decreases of RPE tight junction-associated genes, such as ZO-1. Additionally, $NaIO_3$ administration resulted in more TUNEL-positive apoptotic cells and higher oxidative stress. Surprisingly, these $NaIO_3$-induced toxicities were reduced by injection of miR-146a-5p inhibitor. In conclusion, our study, utilizing a sodium iodate-induced mouse model, demonstrated that dysregulation of exosomal miRNA-146a-5p is associated with RPE dysfunction in dry AMD. The observed alterations in miR-146a-5p expression correlated with RPE degeneration, suggesting a potential role for miR-146a-5p in the pathogenesis of dry AMD.

Disclosures: S. Cho: None. **J. Choi:** None. **Y. Kim:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

Location: SDCC Halls B-H

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Program #/Poster #: PSTR122.14/N9

Topic: E.06. Vision

Support: NIH Grant EY019498

Title: Dissecting the contribution of retinal circuits to motion direction impairments associated with neurodevelopmental disorders

Authors: *E. Y. LIANG, R. SOMAIYA, K. BHATTACHARYA, M. B. FELLER;
Univ. of California, Berkeley, Berkeley, CA

Abstract: Sensory deficits are common in individuals with neurodevelopmental disorders and are increasingly recognized to result from disruptions in peripheral sensory neurons. Understanding how specific cell types and circuits at the sensory periphery contribute to these deficits will offer new avenues for diagnosis and intervention.
Here, we focus on optokinetic reflex (OKR), a behavior that involves reflexive eye movements that stabilize images during global visual motion. Disruptions in motion detection, including atypical OKR behavior, are frequently reported in individuals with neurodevelopmental disorders. Although these abnormalities are often attributed to dysfunction in cortical or subcortical areas, the contribution of the retina, which serves as the initial site of motion computation, remains underexplored.
In this study, we investigate OKR behavior in mouse models of Fragile X Syndrome and Phelan-McDermid Syndrome, which are neurodevelopmental disorders caused by mutations in Fmr1

and Shank3 genes, respectively. Our single-cell transcriptomic analysis revealed that both genes are expressed in key retinal neurons involved in motion encoding, including starburst amacrine cells, bipolar cells, and direction-selective ganglion cells. To assess OKR behavior, we obtained quantitative records of eye movements in head-fixed mice in response to drifting grating stimuli presented in the four cardinal directions. We quantified two features of eye movements: 1) the number of eye-tracking movements, which is defined by the number of saccades during visual stimulus presentation, and 2) OKR gain, which is defined as the ratio of cumulative eye displacement during slow pursuit tracking to total stimulus displacement. Fmr1 and Shank3 knockout mice exhibited an increased frequency of eye-tracking movements and elevated gain. These findings are consistent with the hypothesis that the visual hypersensitivity phenotypes associated with developmental disorders originate in the retina.

Disclosures: E.Y. Liang: None. **R. Somaiya:** None. **K. Bhattacharya:** None. **M.B. Feller:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.15/N10

Topic: E.06. Vision

Support: NIH grant EY028542

Title: Retinal ganglion cells show cell-type specific patterns of kinetic changes across light levels

Authors: *S. E. NAIDU[1], F. M. RIEKE[2];
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Abstract: The retina relies on adaptive mechanisms such as gain control and context-dependent feature selectivity to enable the efficient encoding of complex visual input across dynamic visual environments. Because of their rich spatial and temporal structure, natural images may engage these mechanisms differently than the simple artificial stimuli often used to study them. Prior work has demonstrated that rod-mediated gain control is a key mechanism shaping retinal ganglion cell (RGC) sensitivity under low to moderate luminance conditions in the mouse retina. Additionally, changes in ambient luminance can lead to reversible changes in preferred stimulus polarity. This suggests that luminance regulates the relative strength of the convergent ON and OFF pathways impacting these cells. However, much of this prior work was conducted in the mouse retina using artificial, uncorrelated stimuli and it is not known how the primate retina encodes natural, spatially correlated stimuli across scotopic light levels. In addition to adaptation in the rod photoreceptors, we hypothesize that such stimuli recruit cell-type-specific mechanisms that contribute to responses in more complex visual environments. We conducted extracellular

electrophysiology recordings in the primate retina using a 512-channel multi-electrode array while presenting a series of natural images across four scotopic light levels (0.5, 5, 50, and 500 R*/rod/s). We identified On and Off midget and parasol RGCs and quantified the luminance values within a cell's receptive field to examine how local image statistics modulate response dynamics. We found that changes in local luminance affected the time course of RGC responses in an unexpected way. If luminance dependence were solely determined by changes in photoreceptor signals, we would expect uniform, cell-type invariant changes in response gain and time course across RGCs. Instead, we found that local luminance modulates response timing in a structured, cell-type-specific manner. This indicates the presence of circuit-level computations that shape RGC dynamics in addition to those in the photoreceptors. Rather than a global luminance-dependent shift in response time course, the retina appears to implement differential temporal processing across cell types. These results highlight how retinal populations dynamically adapt to environmental luminance, refining our understanding of visual processing in complex conditions.

Disclosures: S.E. Naidu: None. **F.M. Rieke:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

Location: SDCC Halls B-H

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Program #/Poster #: PSTR122.16/N11

Topic: E.06. Vision

Support: ERC DEEPRETINA No. 101045253.

Title: Uncovering Amacrine Cells Function in Retinal Circuits with 2-Photon Holographic Stimulation

Authors: *V. CALBIAGUE, T. BUFFET, G. GLAZIOU, A. S. SENGER, M. A. GOLDIN, O. MARRE;
Inst. de la Vision, Paris, France

Abstract: Amacrine cells (ACs) are critical interneurons in the retinal neural circuit that orchestrate visual stimulus processing by modulating synapses between bipolar and ganglion cells that form the retinal output. However, understanding their specific roles in retinal computation is challenging due to the remarkable diversity of AC types (roughly 60 in total), making their circuit-level analysis difficult with conventional methods. Here, we targeted a sparse population of amacrine cell types by expressing optogenetic proteins under the control of the ProB13 promoter, with expression restricted to GABAergic neurons using an intersectional viral strategy in Gad2-Cre mice. We refer to these cells as GadB13 amacrine cells (GadB13 ACs). Confocal imaging revealed that approximately two-thirds of GadB13 ACs are located in the ganglion cell layer, suggesting that most are displaced ACs. Whole-cell patch-clamp recordings further showed that displaced GadB13 ACs are spiking ON-type cells. To investigate

their impact on downstream circuit dynamics, we employed single-cell two-photon holographic stimulation to selectively activate GadB13 ACs while recording ganglion cell activity with multielectrode arrays. Our data reveal that targeted activation of single GadB13 ACs inhibits the spontaneous activity of specific OFF retinal ganglion cells (RGCs), with the strength of inhibition decreasing beyond a distance of ~200 µm between GadB13 ACs and OFF RGCs. Pharmacological experiments confirmed that this inhibition is predominantly mediated by GABAergic neurotransmission.These findings suggest that the displaced population of GadB13 ACs are ON spiking cells that modulate ganglion cell activity through GABAergic inhibition. We now aim at combining optogenetic stimulation with visual stimuli to determine the specific visual features that recruit this inhibitory microcircuit.

Disclosures: V. Calbiague: None. **T. Buffet:** None. **G. Glaziou:** None. **A.S. Senger:** None. **M.A. Goldin:** None. **O. Marre:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Program #/Poster #: PSTR122.17/N12

Topic: E.06. Vision

Support: EY029259

Title: Optimizing Negative Contrast Encoding in the Degenerated Retina

Authors: *M. CARLETON[1], N. W. OESCH[2];
[1]UCSD, La Jolla, CA; [2]Univ. of California San Diego, La Jolla, CA

Abstract: Optoelectronics are a leading strategy to restore vision in patients diagnosed with retinal degenerative disorders. Prior optoelectronic prosthetics have had success in generating positive (bright) phosphenes in patients. However, patients do not report perception of negative (dark) phosphenes. This may be due to a lack of stimulation to the OFF retinal pathway. Using whole-cell current clamp electrophysiology we show that morphological OFF RGCs do not respond to single electrical pulses. Action potentials could be elicited in morphological OFF cells using high frequency pulse trains (100-500Hz), but most cells had functional ON responses to the stimulus. A small subgroup of morphological OFF RGCs displayed an OFF functional response. This group of cells displayed both functional and morphological characteristics of OFF alpha ganglion cells. We found that OFFα RGCs maintain OFF responses due to rebound excitation mediated via HCN channels following glycinergic inhibition from the AII amacrine cell network. Thus, we show that the majority of morphological OFF cells have ON responses to electrical stimulation, with the exception of the OFFα. These results show that aspects of the normal OFFα circuitry remain intact during degeneration. Moreover, this work provides insight into the lack of negative contrast perception in patients with prior optoelectronic prosthetics and

show that selectively driving the AII amacrine cell may be ideal for eliciting these responses in future vision restoration strategies.

Disclosures: M. Carleton: None. **N.W. Oesch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NanoVision Biosciences.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.18/N13

Topic: E.06. Vision

Title: Waveform-dependent calcium dynamics in retinal ganglion cells revealed by ex-vivo imaging and computational modeling

Authors: *O. SHARAFI[1,2], T. SILLIMAN[1,3], S. T. WALSTON[1,4], J.-M. C. BOUTEILLER[1,3], K. K. GOKOFFSKI[1,4], G. LAZZI[1,3,2,4];
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Abstract: Precise activation and monitoring of retinal ganglion cells (RGCs) are crucial for advancing retinal prosthetic systems. However, the impact of different electrical stimulation parameters on the response of the retinal network remains poorly understood. Here, we introduce a novel experimental-computational framework that quantitatively assesses neuronal spiking activity by combining population-level calcium imaging with horizontal electric field (EF) stimulation and detailed biophysical modeling. Using ex-vivo retinas from Thy1-GCaMP6f-expressing mice (P10-P20, n=5), we applied a series of EF waveforms—including a 50Hz 1:4 asymmetric charge-balanced (ACB) pulse and sinusoidal inputs spanning 1 Hz to 10 kHz—while recording real-time calcium dynamics via single-photon microscopy. Cell bodies were automatically segmented using a U-Net model, and the averaged normalized fluorescence signal ($\Delta F/F_0$) across >2000 RGCs per condition was integrated over time to compute an Averaged Induced Calcium (AIC) metric. The 1:4 ACB waveform at 50 Hz produced an 80% greater AIC than conventional 50 Hz sinusoidal input, suggesting superior spiking efficiency. Moreover, we identified a 5 kHz cutoff frequency beyond which sinusoidal EFs failed to elicit significant responses. A NEURON model incorporating realistic RGC morphologies and channel kinetics replicated these findings. Importantly, tissue viability and response consistency were validated across multi-hour recordings. Our approach demonstrates that stimulus waveform critically shapes neural responses, and that waveform optimization, guided by modeling and population imaging, can significantly improve the accuracy and effectiveness of neural stimulation. These

findings provide design principles for more effective retinal prosthetic strategies and support broader applications in brain-machine interfaces where precise neuromodulation is essential.

Disclosures: O. Sharafi: None. **T. Silliman:** None. **S.T. Walston:** None. **J.C. Bouteiller:** None. **K.K. Gokoffski:** None. **G. Lazzi:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Topic: E.06. Vision

Support: NIH Grant T32GM139780
Raymond & Beverly Sabbatical Fund
NIH Grant EY019498
Weill Neurohub Fellowship

Title: Investigating the impact of neurodevelopmental disorders on functional retinal development

Authors: *E. AKO[1], R. SOMAIYA[2], M. B. FELLER[2];
[1]Vision Sci., Univ. of California Berkeley, Berkeley, CA; [2]Dept. of Neurosci., Univ. of California, Berkeley, Berkeley, CA

Abstract: Visual abnormalities such as altered motion perception and light sensitivity are frequently reported in individuals with neurodevelopmental disorders. While these deficits are often attributed to changes in neural circuitry in the brain, the contribution of the retina, the first site of visual information processing, remains poorly understood. In this study, we examine whether spontaneous retinal activity, known as retinal waves, is disrupted in mouse models of neurodevelopmental disorders, Fragile X Syndrome (*Fmr1*-KO) and Phelan-McDermid Syndrome (*Shank3*-KO). Retinal waves occur before eye opening and are critical for refining visual maps in the brain's retinofugal targets. Recent work from our lab has shown that these waves are also crucial for the development of retinal circuits underlying the optokinetic reflex, a reflexive eye movement that stabilizes vision on the retina during global motion. Given that individuals with neurodevelopmental disorders frequently exhibit impaired optokinetic reflex, we investigate whether disruptions in retinal wave activity may contribute to these sensory deficits. Based on single-cell transcriptomic data, we know that both *Fmr1* and *Shank3* are expressed in key retinal neurons involved in wave generation and propagation, including starburst amacrine cells, bipolar cells, and ganglion cells. To characterize retinal wave activity in developing *Fmr1*-KO and *Shank3*-KO mice, we employ two-photon population calcium imaging. Here, we will present data comparing wave frequency, strength, and velocity. In addition, we will use immunohistochemistry to compare synaptic protein organization in the inner retina of *Fmr1*-KO and *Shank3*-KO mice. Overall, this work aims to uncover whether visual processing deficits

observed in neurodevelopmental disorders can be attributed to early disruptions in retinal activity, offering new insight into the mechanisms underlying sensory periphery dysfunction.

Disclosures: E. Ako: None. **R. Somaiya:** None. **M.B. Feller:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Program #/Poster #: PSTR122.20/N15

Topic: E.06. Vision

Support: FONDECYT REGULAR #1210790
ANID 21241487

Title: Evaluation of metformin, insulin, lixisenatide, and photobiomodulation treatments in two model of diabetic retinopathy.

Authors: *R. I. CÉSPEDES;
interdisciplinary center for neuroscience, Univ. de Valparaíso, Valparaíso, Chile

Abstract: Type 2 diabetes mellitus affects approximately 10% of the global population, and around 20% of these individuals already present with diabetic retinopathy (DR) at the time of their diabetes diagnosis. DR is a progressive microangiopathy characterized by oxidative stress, neuronal apoptosis, and eventual vision loss. Current treatments for DR are often invasive and do not address the underlying disease mechanisms, emphasizing the urgent need for more effective and less invasive therapeutic alternatives. Photobiomodulation (PBM) has shown promising potential in mitigating inflammation, oxidative stress, and neuronal death across various retinal diseases. However, its therapeutic role in diabetic retinopathy—particularly in comparison with established pharmacological treatments—remains relatively underexplored. The aim of this study was to evaluate the effects of PBM in conjunction with insulin, metformin, and lixisenatide—drugs commonly used to treat diabetes—on organotypic retinal cultures exposed to high glucose levels, as well as in *db/db* diabetic mice, thereby modeling the pathological environment of diabetic retinopathy. A variety of microscopy-based techniques were employed, including toluidine blue histology, MitoSOX assays to detect mitochondrial superoxide production, and immunofluorescence to assess the expression of NF-kB, VEGF, and GFAP. The results revealed that among the tested drugs, lixisenatide was most effective in preserving the ganglion cell layer and significantly reducing mitochondrial oxidative stress. Interestingly, PBM increased NF-kB expression, suggesting a potential activation of neuroprotective signaling pathways. In *db/db* mice, PBM also led to a reduction in neuronal apoptosis and inflammation, comparable to the effects observed with semaglutide treatment. These findings highlight PBM as a promising complementary therapy that could enhance the efficacy of existing pharmacological approaches for diabetic retinopathy.

Disclosures: R.I. Céspedes: None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Program #/Poster #: PSTR122.21/N16

Topic: E.06. Vision

Support: RM1NS140200

Title: Light stimulus of alternating long and short wavelengths causes analgesia and decreased fibromyalgia-like behavior in Dahl-S rats

Authors: *A. RAMIREZ[1], A. WILKINSON[2], N. TAYLOR[2];
[2]Anesthesiol., [1]Univ. of Utah, Salt Lake City, UT

Abstract: Light therapy delivered through the retina is a promising, non-invasive therapy has been shown in multiple rodent models of pain and human studies to produce robust anti-nociceptive effects. Despite the promise these studies show, the exact neuronal mechanism of light mediated analgesia remains incompletely understood, especially the visual system circuitry and specific retinal neurons that are activated. Green light has been specifically identified as a color that produces analgesia at lower intensities than white light. The color specificity of green light induced analgesia indicates a possible color-sensitive retinal mechanism. Color-sensitive ganglion cells receive excitatory and/or inhibitory input from short (S-), middle (M-), and long (L-) wavelength-sensitive cone photoreceptors (e.g. S vs L/M). There are several types of color-sensitive ganglion cells that have differential S vs. L/M inputs, so called color-opponent ganglion cells. In color-opponent ganglion cells, short vs longer wavelengths have different effects and in this study, we hypothesize that light-driven analgesia works through specific visual pathways involving S-cone color-opponent ganglion cells in the retina. To test this hypothesis, we created a light stimulus that specifically targets these S-cone color sensitive retinal ganglion cells through alternating 360 nm (short) and 540 nm (long) wavelengths, termed dynamic light. This study tests white, green, and dynamic light using Dahl-S rats as a model of inherited widespread hyperalgesia and fibromyalgia-like behavior as measured by the FAM index (Ferrari et al, 2022; Ferrari et al, 2025). Male and female rats were exposed to either white, green or dynamic light stimulus daily for 5 days (n=10/group) and then subjected to the FAM index battery of behavioral tests to determine the effects of each stimulus on fibromyalgia-like behavior. Both the green and dynamic light groups showed significantly decreased F-scores compared with the white light exposed group (white: 0.2636 ± 0.9356, green: -1.963 ± 1.363, dynamic: -2.361 ± 1.749). These results provide the first preliminary data suggesting that light driven analgesia is working specifically through the S-cone color opponent ganglion cell pathway.

Disclosures: A. Ramirez: None. **A. Wilkinson:** None. **N. Taylor:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Program #/Poster #: PSTR122.22/O1

Topic: E.06. Vision

Title: Chromatic and Spatial Encoding in the Foveal Bipolar Layer: Implications for Retinal Prostheses

Authors: *E. JOYCE[1], M. BEYELER[2];
[1]UC Santa Barbara, Santa Barbara, CA; [2]Psychological & Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Bipolar cells play a critical role in transforming photoreceptor signals into spatially and chromatically structured input to the inner retina. Yet their contribution to color encoding remains underrepresented in computational models, particularly in the context of retinal prostheses that now directly target this layer. We present a biologically grounded model of the human foveal bipolar cell mosaic, including realistically tiled L-, M- and S-cone driven ON and OFF midget and diffuse bipolar subtypes. Subtype distributions and model parameters were informed by recent human retinal connectomics data. The model incorporates center-surround interactions via horizontal and amacrine cell inhibition and transforms natural image input into bipolar cell responses. Using an encoder-decoder framework, we simulate visual percepts under different electrode resolutions and stimulation radii. These findings suggest that colored percepts may emerge naturally at the resolution scales enabled by next-generation arrays. Our model provides a computational tool to predict the conditions under which color is likely to be evoked, offering new design constraints for next-generation retinal prostheses. By identifying stimulation regimes that leverage chromatic coding, this work opens the door to richer, more informative artificial vision. As more human data becomes available, the model's architecture allows for flexible refinement and potential tuning to match the perceptual experience of next-generation implant users.

Disclosures: E. Joyce: None. **M. Beyeler:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Topic: E.06. Vision

Support: Italian Ministry of University and Research Grant P202299C3L

Title: Three-dimensional multiscale and multimodal X-ray neuroimaging: an advanced technique to quantify potential neuroprotective strategies for retinal ganglion cell degeneration in an experimental mouse model of glaucoma

Authors: F. LIBERATORE[1], K. NURELIGN[2], D. BUCCI[1], G. MASCIO[1], M. BOSSI[2], V. RODRIGUEZ MENENDEZ[2], P. MARMIROLI[2], G. CAVALETTI[2], V. BRUNO[3,1], F. NICOLETTI[3,1], P. COAN[4], A. BRAVIN[2,5], ***G. BATTAGLIA**[3,1];
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Abstract: Glaucoma is a chronic neurodegenerative disease and the leading cause of irreversible blindness worldwide due to the progressive degeneration of retinal ganglion cells (RGC). To date, there are no drugs to counteract the death of RGCs. Thus, neuroprotection remains a major unmet need in the treatment of glaucoma. We have developed and applied multi-scale synchrotron-generated X-ray phase contrast imaging computed tomography (X-PCI-CT) to perform a virtual histology of mouse brains. This technique enabled the identification and quantification of cellular and sub-cellular neurodegeneration in CNS cell populations in a transgenic model of Alzheimer's disease (Barbone et al, Eur J Nucl Med Mol Imaging, 2022). Here we used this technique, along immunohistochemistry, to evaluate the potential neuroprotective effects of JNJ16259685, a negative allosteric modulator of mGlu1 metabotropic glutamate receptors, and of Idebenone, a synthetic analogue of coenzyme Q10 with antioxidant activity, in the DBA/2J mice, a genetic experimental model of glaucoma associated with neurodegeneration. Moreover, we used X-ray fluorescence and transmission electron microscopy (TEM) for a detailed structural examination at nanometric resolution. Control C57Black mice and DBA/2J mice were treated with vehicle or idebenone (10 mg/kg/day) by gavage; with vehicle or JNJ16259685 (1 mg/kg/day) by subcutaneously implanted osmotic minipumps; and with the combination of both drugs, either in the pre-symptomatic phase as prophylaxis or in the symptomatic phase as therapy after intraocular pressure (IOP) increase, for 2 months. We measured IOP by a rebound tonometer to identify the time point of its increase and the effects of drug treatments in DBA/2J mice, and evaluated the motor performance by the rotarod test as mGlu1 receptors are expressed in the cerebellum. At the end of treatments, to identify and quantify RGC degeneration, ocular bulbs were used for immunohistochemistry and Serial Block Face-SEM. X-PCI-CT imaging was carried out at SOLEIL, Paris and at European Synchrotron Radiation Facility, Grenoble, France. Treatments with drugs did not affect IOP values in DBA/2J mice, and treatment with JNJ16259685 did not affect motor performance either in C57Black mice and DBA/2J mice. This advanced 3D multiscale and multimodal imaging method allowed visualizing the complex retinal structure and distinguishing the retina layers with different levels of detail, along with the complete representation of mouse ocular bulbs. These data are also used to quantitatively characterize the retina layers and the effects of drug treatments at different time points. Results will be presented.

Disclosures: F. Liberatore: None. **K. Nurelign:** None. **D. Bucci:** None. **G. Mascio:** None. **M. Bossi:** None. **V. Rodriguez Menendez:** None. **P. Marmiroli:** None. **G. Cavaletti:** None. **V. Bruno:** None. **F. Nicoletti:** None. **P. Coan:** None. **A. Bravin:** None. **G. Battaglia:** None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.24/O3

Topic: E.06. Vision

Support: NIH Grant R01EY033905

Title: Mitochondrial reactive oxygen species act as autaptic neuromodulators regulating gain control and encoding strategies during variance adaptation in sustained alpha RGCs

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Abstract: Sensory input varies across timescales that exceed the limited dynamic range of neural input-output functions. Efficient coding suggests that adaptation optimizes response gain to match input statistics, preventing both saturation and insensitivity to small inputs to maximize mutual information between stimulus and response. Information rate may not be the only function optimized by neurons. Metabolically efficient coding proposes that neurons balance information transmission against energy constraints. Neuronal energy demands fluctuate with input changes. ATP production increases rapidly with elevated spike rates, and electron leakage during ATP synthesis generates reactive oxygen species (ROS). We investigated whether ROS produced by changes in activity actively modulates gain adaptation and encoding strategy in retinal ganglion cells (RGCs). In sustained αRGCs, elevating ROS steepened the relationship between gain and input variance. At low input variance, information efficiency (bits/spike - information per action potential) increased while information transmission rate (bits/s - total information flow) decreased. Conversely, reducing ROS with antioxidants flattened the gain-variance relationship, and increased information transmission rate while reducing efficiency. These effects were absent in transient αRGCs. Voltage clamp recordings showed that H_2O_2 caused a hyperpolarizing shift in Na_V channel steady-state inactivation and reduced peak Na_V current specifically in sustained αRGCs. These cells showed greater current reductions when $Na_V1.1/1.3$ channels were blocked specifically compared to transient αRGCs. Blocking $Na_V1.1/1.3$ channels prevented further H_2O_2 modulation in both voltage clamp recordings of Na_V current and current clamp recordings of variance adaptation. We propose that ROS serve as autaptic neuromodulators indicating recent metabolic expenditure in sustained αRGCs, adjusting both adaptation and encoding strategies accordingly. At baseline a standing level of ROS favors an encoding strategy that balances information rate against efficiency. High variance recent input elevates ROS levels, promoting a high-gain input-output relationship that prioritize information efficiency (bits/spike) at the cost of information transmission rate when input variance drops. Low variance recent input shifts the balance toward lower-gain input-output relationships with higher information transmission rates (bits/s) but reduced metabolic efficiency. Recent metabolic expenditure dynamically regulates both adaptation and encoding strategies in sustained αRGCs with high baseline metabolic costs.

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Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Program #/Poster #: PSTR122.25/O4

Topic: E.06. Vision

Title: Ocular trigeminal innervation contributes to light-mediated behavior

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Abstract: Purpose Photoallodynia is a clinical condition in which light induces or enhances pain to normal or even dim levels of light. Previously, we showed a mouse model of migraine with a bilateral optic nerve crush retains light aversion, a rodent surrogate for photoallodynia, which was dependent on the presence of melanopsin-expressing neurons. Melanopsin is expressed in a class of retinal ganglion cells (mRGCs) as well as in trigeminal ganglion neurons, providing a potential mechanism for trigeminal circuits to influence light aversion. Here, we investigate the role of melanopsin and ocular trigeminal innervation in light aversion. **Methods**Light aversion was assayed using a dark/light box with LED illumination of 1000 lux and quantitated as an aversion index (0=no aversion; 1=complete aversion) in wild type C57Bl/6J mice and melanopsin knockout mice (mKO) in a B6129 genetic background with and without atropine dilation. Partial trigeminal axotomy (PTAx) lesions removing some of the nasociliary nerve bundle were performed in surgically anesthetized mice. **Results**In C57Bl6/J wild type mice, light aversion was minimal without dilation (AI=0.11±0.04, n=22) compared to with dilation (AI=0.41±0.10, n=22). PTAx significantly reduced light aversion with dilation (AI=0.19±0.07, n=11) compared to sham controls (AI=0.59±0.07, n=11) seven days post-surgery but had no effect at three days post-surgery (PTAx AI=0.41±0.17, n=7 versus sham AI=0.57±0.09, n=7). Preliminary results from mKO mice indicate a similar increase in light aversion after dilation (undilated AI=0.02±0.05, n=14 versus dilated AI=0.12±0.12, n=14). However, mKO mice exhibited retained light aversion seven days post-surgery (PTAx AI=0.72±0.09, n=7 versus sham AI=0.76±0.09, n=7). Analysis of mKO mice in the C57Bl/6J genetic background is ongoing. **Conclusions**Behavioral responses to light are not solely dependent on the optic nerve communicating with the brain. The major peripheral nervous system dedicated to pain perception also drives robust light-driven behavioral responses. The time-dependent changes in light aversion in wild type mice suggests an adaptive mechanism that is at least in part driven by melanopsin.

Disclosures: M.Z.R. Rasheed: None.

Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Program #/Poster #: PSTR122.26/O5

Topic: E.06. Vision

Support: NIH EY024265
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Title: Runx1 is a molecular marker of a conserved ganglion cell type in mouse and macaque retina

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Abstract: Purpose: The macaque retina contains at least 18 ganglion cell (GC) types that differ in their morphology and gene expression profiles, yet the function of most types remains unknown. By mining existing single-cell transcriptomic data (Peng et al., 2019), we identified an uncharacterized macaque GC type that selectively expresses the transcription factor, RUNX1. The orthologous cell type in mouse also expresses RUNX1 and corresponds to the high definition (HD1) GC, an On-Off cell that exhibits object motion sensitivity (Hahn et al., 2023; Jacoby & Schwartz, 2017). Here, we test the hypothesis that RUNX1-GCs have conserved morphology and function in mouse and macaque retina.
Methods: Retinas from C57BL/6J mice and rhesus macaques were collected post-mortem. RUNX1-GCs were immunolabeled for spatial distribution analysis, and cell morphology was obtained by filling immunolabeled cells with DiI. Light responses were measured using two-photon calcium imaging with Cal-590 AM or GCamp6f followed by immunolabeling for RUNX1. Data are reported as mean ± s.d.
Results: Macaque RUNX1-GCs comprised 0.6 ± 0.2% of GCs with a density of 12 ± 3 cells/mm^2 in peripheral nasal retina (n=4 retinas). Somas formed a non-random mosaic (Voronoi domain regularity index: 4.3 ± 0.5, n=4), supporting transcriptomic evidence that they comprise a single cell type. The mean dendritic arbor diameter ranged from 118 ± 6µm in the fovea (< 1.5 mm ecc., n = 3 cells) to 355 ± 25µm in peripheral retina (6-15µm ecc., n = 13 cells). Foveal RUNX1+ cells were encountered infrequently. Mouse RUNX1-GCs constituted 3.2 ± 0.3% of GCs with a density of 103 ± 21 cells/mm^2 (n=3 retinas) and had a mean dendritic diameter of 147 ± 30µm (n=4 cells). Both macaque and mouse RUNX1-GCs were narrowly stratified in the inner plexiform layer (IPL S3, ~56% and ~52% depth, respectively) and had a “thorny” dendritic structure, consistent with the reported morphology of mouse HD1-GCs. Calcium imaging of macaque RUNX1-GCs revealed ON-OFF responses to 500 µm spot stimuli, non-directional responses to drifting bars, and band pass temporal tuning (peak frequency 3.3 Hz) to drifting

gratings (n=4-5 cells). Preliminary data suggests mouse RUNX1-GCs are object motion sensitive, consistent with reported HD1-GC function.
Conclusions: RUNX1 is a selective molecular marker of a genetically conserved GC type in macaque and mouse retina. These cells have similar morphological features and exhibit ON-OFF physiology. Ongoing studies are assessing whether macaque RUNX1-GCs are object motion sensitive, similar to their mouse GC counterparts.

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Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Topic: E.06. Vision

Support: NIH grant EY026817

Title: Distinct roles of CaBP4 and Ca_v alpha2delta-4 in the organization and structural plasticity of mouse photoreceptor synapses

Authors: W. KAUNG[1], J. W. MADDOX[1], J. DE LA ROSA[2], *A. LEE[3];
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Abstract: Voltage-gated $Ca_v1.4$ Ca^{2+} channels are essential for glutamate release from photoreceptor synapses and play a critical role in synapse formation and structural plasticity. Mutations in the genes encoding $Ca_v1.4$ and its interacting proteins, $\alpha_2\delta$-4 and CaBP4, lead to vision disorders including congenital stationary night blindness type 2 (CSNB2). Although these disorders are all characterized by impaired photoreceptor synaptic transmission, clinical visual phenotypes are heterogeneous. To better understand this clinical variability, we compared the retinal defects in knockout (KO) mice lacking either $\alpha_2\delta$-4 or CaBP4. Using immunofluorescence and confocal microscopy, we analyzed molecules in the presynaptic terminals of rods and cones and postsynaptic elements in bipolar cells and horizontal cells.While presynaptic $Ca_v1.4$ levels in the outer plexiform layer were significantly reduced in both KO strains compared to wild-type (WT) mice, $\alpha_2\delta$-4 KO mice exhibited a five-fold greater reduction in $Ca_v1.4$ levels than CaBP4 KO mice. Postsynaptic cone bipolar cell dendrites sprouted minimally in the outer nuclear layer (ONL) in both KO mice. Rod bipolar cell dendrites extended into the ONL in both KO mice but were more vertically oriented in $\alpha_2\delta$-4 KO mice than in CaBP4 KO mice. Additionally, rod bipolar cell dendrites occupied less of the ONL while horizontal cell axons occupied more in $\alpha_2\delta$-4 KO mice than CaBP4 KO mice.Compared to WT mice, light adaptation-induced shortening of rod and cone synaptic ribbons was significantly blunted in $\alpha_2\delta$-4 KO mice, yet still present. However, photoreceptor synaptic ribbons in CaBP4 KO mice were completely resistant to light-dependent changes.These results demonstrate that the

loss of function of $\alpha_2\delta$-4 or CaBP4 has distinct effects on presynaptic $Ca_v1.4$ channels, ribbon plasticity, and postsynaptic abnormalities. Our findings highlight how dysregulation of different components of the $Ca_v1.4$ complex leads to divergent retinal phenotypes, providing insights into the spectrum of visual phenotypes that typify CSNB2 and related visual disorders.

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Poster

PSTR122: Photoreceptors and Retinal Circuitry

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Program #/Poster #: PSTR122.28/O7

Topic: E.06. Vision

Support: BBSRC G4001-04

Title: Diurnal modulation of information transfer through the retina

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Abstract: The fundamental function of the retina is to extract and transmit information about the visual world. All this information flows through bipolar cells (BCs), which are the only neurons connecting photoreceptors to the inner retina. How efficiently does this bottleneck operate? And how does this change when the circuit is modulated during the diurnal cycle? To investigate, we aimed to simultaneously record the synaptic input and output from individual bipolar cells *in vivo* and quantify information received from cones and transmitted to the IPL. We achieved this through multiphoton imaging of glutamate in larval zebrafish sparsely expressing the glutamate reporter iGluSnFR in BCs. A rotating scan path simultaneously recorded glutamate transients on BC dendrites and axonal compartments (1 kHz). A stimulus set of 11 contrasts (0-100%, full-field) delivered at 5 Hz provided an information rate of 17.3 bits s^{-1}. The mutual information was calculated between i) the iGluSnFR signal at individual cone synapses and the stimulus; ii) the *total* glutamate input signal and the stimulus; iii) total synaptic input and BC output, and iv) BC output and stimulus. In the afternoon, when retinal gain is at a maximum, an individual cone synapse transmitted an average of 3.31 ± 0.12 bits s^{-1} (information efficiency = 19%). The total cone input carried 5.36 ± 0.32 bits s^{-1} (31% of maximum) which was significantly higher than the morning (3.84 ± 0.35 bits s^{-1}; $p = 0.01$). The mutual information between the BC output and visual stimulus also increased from morning to afternoon (1.99 bits s^{-1} ± 0.12 to 2.82 bits s^{-1} ±0.18) but this was not simply because of enhanced cone signals: the mutual information between the excitatory input and output of BCs also increased by 56% (1.48 bits s^{-1} ± 0.11 to 2.22 bits s^{-1} ±0.16). These results provide a quantitative overview of the retinas' performance as an information transmitting device. Diurnal modulation of retinal function adjusts information flow through both cones and BCs.

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Poster

PSTR123: Visual Motion

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Program #/Poster #: PSTR123.01/O8

Topic: E.06. Vision

Support: Medical Research Council (UK) Grant MR/Y004000/1

Title: Compensation for reafferent visual signals in functional neurological disorder subtype PPPD

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Abstract: Persistent Postural Perceptual Dizziness (PPPD), a subtype of Functional Neurological Disorder (FND), presents without structural abnormalities but with symptoms of chronic dizziness and the sense of an unstable environment. STARDUST (STudy to Assess and Reduce Dizziness Using Sensory Theory) investigates whether PPPD symptoms stem partly from changes in mechanisms that compensate for visual reafferent signals during self-movement and thus facilitate assessment of environmental motion/stability. One such mechanism, flow parsing (FP), involves analysing retinal motion to subtract optic flow components arising from self-movement. Here, we present preliminary data in two tasks from a pre-registered study to compare FP performance in control (N=9) and PPPD (N=9) groups. On each 250ms trial in Task 1, seated, stationary participants fixated centrally and viewed a hemifield of expanding/contracting optic flow, simulating forward/backward observer movement at 0.75 m/s through a cloud of 300 dots. In the opposite hemifield, a target dot, displaced 5° horizontally from fixation, had horizontal velocity controlled via interleaved adaptive staircases. Participants reported perceived target motion direction (left/right). Psychometric functions mapping physical target velocity to perceived target direction were fit to response data. FP induces a bias in perceived target movement, which can be recovered from the psychometric function, and reflects the magnitude of the globally subtracted optic flow component. On each 1s trial in Task 2, the same participants fixated centrally and viewed (via active shutter glasses) a complex 3D scene of 55 scene-stationary wireframe objects, while judging scene-relative movement of a target dot displaced 3.5° horizontally from fixation. We measured target direction discrimination thresholds (psychometric function slopes) in two conditions: no observer movement vs. simulated 0.125m/s forwards observer movement. Better flow parsing performance is characterised by a smaller FP Index (FPI = moving/static psychometric function slopes). In Task 1 we observed typical FP biases across conditions for all controls, but more mixed results in PPPD. Three PPPD

participants failed to exhibit consistent FP. The rest exhibited FP-consistent biases but larger than controls ($F(1, 13)=16.7$, $p=.001$, $\eta p^2=.56$), suggesting stronger FP. In Task 2, the same PPPD participants had lower FPIs than controls ($t(13)=2.27$, $p=.04$), again suggesting stronger FP. If confirmed with larger samples, these data suggest altered compensation for reafferent optic flow in PPPD, which could contribute to dizziness and instability symptoms.

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Poster

PSTR123: Visual Motion

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Program #/Poster #: PSTR123.02/O9

Topic: E.06. Vision

Support: NIH R01EY026286

Title: Decoding visual motion via distinct molecular cell types in the mouse superior colliculus

Authors: *C. CHEN[1,2], Y. LIU[3], H. CHEN[4], J. CANG[1,3,2];
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Abstract: Identifying a moving object and responding to it appropriately is one of the most important visual functions for animal's survival. The superior colliculus (SC) as a major retinal recipient is a key node to process visual motion information and mediate such behaviors. How exactly the features of visual motion, such as direction, speed, and size, are encoded by specific molecular cell types in the SC is largely unknown. Here, we identified three transgenic mouse lines that each label a distinct transcriptomic neuron type and studied their responses to a range of motion stimuli using 2-photon calcium imaging. All three populations, including *Cbln4*+, *Vip*+, and *Grp*+ neurons, encode combinatory features of moving objects but display divergent preferences. *Cbln4*+ neurons prefer medium-size stimuli, vertical direction, and slow motion. *Vip*+ neurons also respond to medium-size stimuli and slow motion but prefer horizontal direction. In contrast, *Grp*+ neurons prefer small stimuli, fast motion, and vertical axis. Next, we asked whether these distinct motion detections are transformed differently by mapping the spatial distribution and anatomical projections of these three populations. *Cbln4*+ neurons mark an inhibitory subtype in the surface of the SC and project to the parabigeminal nucleus (PBG). *Vip*+ neurons are located at the same depth, but they are excitatory neurons innervating the lateral geniculate nucleus (LGN). *Grp*+ neurons are distributed slightly deeper and send excitatory fibers to the PBG. Together, our results demonstrate that three molecular cell types encode distinct features of visual motion, indicating a genetic code for precise motion processing in the mouse SC. The distinct spatial organization and projection patterns of the three transcriptomic

types suggest that they may play different roles in mediating visual behaviors. The tools that we identified to label these types of neurons will facilitate future developmental and behavioral studies of visual processing in the SC.

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Poster

PSTR123: Visual Motion

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Topic: E.06. Vision

Support: NIH EY022122
NIH R01EY035807

Title: Proto-tuning, visual response properties in the ferret prior to natural eye opening

Authors: *M. K. SEVERSON[1], A. JORDAN[1], R. SIERRA[1], S. D. VAN HOOSER[1], K. J. NIELSEN[2];
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Abstract: Sensory systems in the brain exhibit an organization that is, in part, hierarchical. Cells in the first processing stages exhibit selectivity to basic features, and cells in subsequent stages build on this selectivity to generate selectivity to more complex features. In the visual system of adult carnivores such as the cat or ferret, there is a progression of selectivity from spot-detectors (lateral geniculate nucleus, LGN) to orientation-and-direction-tuned neurons (primary visual cortex, V1), to pattern-motion-tuned cells (posterior bank of the suprasylvian sulcus, PMLS). One might naively imagine that these chains of selectivity would unfold progressively across these stages, from LGN to V1 to PMLS, during early development. However, recent studies in ferrets have found that direction selectivity arises in PMLS earlier than V1, raising questions as to how these hierarchical chains of selectivity are constructed. Further, very early development, before eye opening, was thought to proceed in a largely experience-independent manner. However, recent work shows that artificial introduction of premature visual experience causes aberrant development of motion processing in V1, raising questions about what activity is produced by premature visual stimulation that could alter receptive fields. Both questions are further motivated by previous observations that reliable visual responses can be evoked in ferret LGN and V1 up to a week before eye opening. Yet, little is known about the tuning properties at these very early stages of life. To understand the early developmental state of the visual system, we studied receptive fields of multiple visual areas, including the LGN and V1, of the anesthetized ferret in the week before natural eye opening. At this early stage, LGN exhibited substantial direction selectivity that is not present around the time of eye opening. Many LGN cells exhibited stronger modulation to stimulus luminance rather than stimulus contrast. Similarly, V1 exhibited direction selectivity during this time, although tuning widths were much

wider than are found at eye opening, when cells exhibit orientation selectivity but not direction selectivity. In summary, LGN and V1 appear to go through a transient developmental stage of direction selectivity that is lost around the time of eye opening. This period may serve as an important scaffold for sculpting initial orientation selectivity and/or functional architecture, even though direction selectivity is then lost and finally rebuilt a few weeks later, after the onset of visual experience.

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Poster

PSTR123: Visual Motion

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Program #/Poster #: PSTR123.04/O11

Topic: E.06. Vision

Support: R01EY024831

Title: Spatiotemporal Dynamics of Population Responses to Moving Targets in the Monkey Superior Colliculus

Authors: *F. YANG, N. J. GANDHI;
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Abstract: The superior colliculus (SC) is a subcortical structure essential for converting visual input into motor commands for eye movement generation. Visuomotor neurons in the SC exhibit both visual bursts following target onset and motor bursts preceding saccade initiation. Across its topographic map, each neuron has a preferred spatial location, producing peak activity for targets or saccades at that location and reduced activity for more distant stimuli or movements. This spatial tuning, shaped by intra-collicular connectivity, gives rise to a population activity pattern as a Gaussian mound centered on the locus encoding the target displacement during visual stimulation and on the intended saccade vector during motor execution. While SC population dynamics for stationary targets are well characterized, how the SC encodes moving targets remains poorly understood.Two major factors complicate SC population responses during target motion. First, a continuously moving target maps onto a larger area of the SC across space and time, raising the question of whether the population response retains its Gaussian structure. Second, due to visual transduction delays—caused by the time it takes retinal signals to propagate—it remains unclear whether the SC represents the current location of a moving target or its lagged position.Here, we recorded simultaneous population activity across SC layers using an N-form array (Plexon, Inc.) implanted in the monkey performing interceptive saccades. We compared the SC population response at each moment of a moving target to the activity evoked by a static target presented at the same instantaneous location. Using both vector summation and vector averaging models, well-established models for population activity of the stationary target,

we decoded the represented location from population activity and compared it to the actual target position and the lagged position by applying a fixed transduction delay.We found that SC population activity systematically morphs in both shape and magnitude during target motion, with effects dependent on target speed and direction. While vector averaging reliably estimated target location for both stationary and moving stimuli, vector summation was only reasonable in the stationary case. The represented location during motion fell between the lagged and actual target positions, suggesting a continuum from non-predictive to semi-predictive to fully predictive encoding depending on target speed and direction. In summary, our results show that SC population activity dynamically adapts during target motion and supports a semi-predictive representation of the moving target's position.

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Poster

PSTR123: Visual Motion

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Program #/Poster #: PSTR123.05/O12

Topic: E.06. Vision

Support: 1UF1NS116377

Title: Consistency between visual motion and locomotion modulates responses in primate area MT

Authors: *P. S. CHEN[1], D. P. ROWLEY[2], A. HUK[3];
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Abstract: Primate area MT has been extensively studied for visual motion processing, but often with animals being constrained and passively viewing simple motion stimuli. It is therefore hard to demonstrate whether MT's responses take account of active, naturalistic behaviors that can generate retinal motion. Previous studies have shown that behavioral states can modulate the processing and transmission of sensory signals in rodent and primate V1 (Niell & Stryker 2010; Liska et al., 2024). Here, we investigated whether MT's responses were modulated by the consistency between self-generated visual motion and concurrent locomotion.
We trained head-fixed common marmosets to run or stay stationary on a wheel-based treadmill. Moving dot stimuli simulated realistic optic flow patterns, with a flat ground plane and an upper zone with sparser and less regular structure. In the "closed-loop" condition, the stimulus was updated in real time to be consistent with the animal's concurrent treadmill locomotion- the optic flow expanded when the animal was running forward and contracted when running backward. The same visual patterns from the "closed-loop" were then displayed in a "replay" condition

(where the stimulus was no longer yoked to the treadmill velocity). We simultaneously recorded from area MT, as well as foveal and peripheral V1 and V2, using Neuropixels 1.0 probes. Eye movements were recorded using high-precision digital Dual-Purkinje Image eye-tracking.
As expected, the MT population response was correlated with locomotion direction and magnitude in both conditions (n = 1172 units). But surprisingly, the average firing rate was higher during the replay condition, and responses were correlated with stimulus velocity only during the closed-loop condition. These different response dependencies seen in closed loop versus replay were not explained by initial analyses of eye movements, running or arousal states. These results suggest that MT might carry mismatch and/or other signals' computation during replay but have better visual motion encoding during closed-loop. In contrast, in V1/V2, responses were more modulated by running as the population activity was higher during running in the periphery (1308 units) and slightly suppressed in the foveal region (279 units). Altogether, these results show that area MT's activity was suppressed when the self-generated visual motion was consistent with concurrent locomotion. Thus indicating area MT as a potential locus for the computation and processing of sensorimotor interactions and dynamics.

Disclosures: P.S. Chen: None. **D.P. Rowley:** None. **A. Huk:** None.

Poster

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Title: Encoding and combining naturalistic motion cues in the ferret higher visual cortex

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Abstract: The perception of a coherent moving flow relies on the integration of a variety of visual signals across orientation, spatial, and temporal frequencies. Yet, how these visual attributes are encoded in late visual cortex for scenes containing a rich content remains poorly understood. Here, we performed single-neuron recordings in the motion-selective area PMLS (posteromedial lateral suprasylvian sulcus) of awake ferrets to examine neuronal responses to a class of naturalistic stimuli with parametrically controlled spatiotemporal statistics, namely

motion clouds.
We found that individual neurons encoded motion features in a temporally staggered sequence: orientation and spatial frequency emerged early, within 50 to 90 ms after stimulus onset, while temporal frequency and direction followed at later latencies. Decoding analyses showed that this selectivity evolved over time within neurons and was distributed across the population.
To understand how neurons integrate concurrent motion signals, we presented compound motion clouds composed of two or three components of localized spatiotemporal energies. Neuronal responses were well predicted by a linear model that summed responses to the individual components. Moreover, a subset of neurons exhibited selectivity to differences in speed content, consistent with receptive fields differentiating along the speed gradient.
These findings reveal a temporally structured and population-distributed coding strategy for motion processing in higher-order visual cortex, and provide mechanistic insights into how visual systems parse the motion property of natural scenes.

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Poster

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Title: Neural evidence of serial dependence in ocular tracking

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Abstract: Serial dependence is a phenomenon where perception is biased toward recent experience. While this effect is well documented in behavior, its underlying neural processes remain unclear. To investigate this, we combined eye-tracking and EEG recordings while participants tracked the step-ramp motion of a moving target. On each trial, participants clicked the mouse to start the trial and then tracked a target spot moving at 16°/s in a randomly chosen direction (12° steps, covering the full 360° range). Behavioral analysis revealed a serial dependence effect: pursuit directions were systematically attracted toward the target motion

direction in the previous trial at pursuit initiation, followed by a later repulsion adaptation effect. This dynamic pattern suggests that serial dependence in ocular tracking occurs at early stages of visual processing.To uncover its neural signatures, we performed time-resolved multivariate pattern analysis (MVPA) on EEG signals. Motion direction in the current trial could be reliably decoded from EEG signals. More importantly, motion direction in the previous trial could be decoded starting around 100 ms after stimulus onset. Scalp topographies indicated that electrodes over occipital and parietal regions contributed most to decoding accuracy during the 100-300 ms window, suggesting that recent perceptual history is reflected in activity over visual cortical areas.To further explore how past motion information is processed in the brain, we modeled EEG signals as a linear combination of current and previous motion directions. Interestingly, the regression weight for previous directions showed a rhythmic fluctuation at ~10 Hz, beginning before stimulus onset. This alpha-band oscillation was most prominent over occipital and parietal electrodes. These findings suggest that visual cortical regions dynamically modulate the influence of past motion information on upcoming sensory processing through preparatory rhythmic activity.Together, this study provides converging behavioral and neural evidence that serial dependence in ocular tracking occurs early in visual processing and is linked to rhythmic alpha-band oscillations in the visual cortex, offering insight into how the brain temporally integrates recent motion history to guide ongoing behavior.

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Poster

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Title: Distinct neural processing of real versus unreal optic flow in the human brain: evidence from fMRI and EEG

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Abstract: During self-motion in a rigid 3D environment, optic flow conveys both 3D structural information (e.g., motion perspective) and 2D features (e.g., radial velocity field). However, many studies have confused radial motion patterns lacking 3D cues as real optic flow. Our previous work found that decoding accuracy of motion coherence in human MST was high for expansion than contraction patterns in real optic flow but this pattern reversed for unreal optic flow, aligning with behavioral sensitivity. While this suggests that MST may be modulated by

the “realness” of optic flow, its ability to directly distinguish between real and unreal optic flow has not been explicitly tested. To address this, we conducted an fMRI experiment to directly examine whether human MST can differentiate between real and unreal optic flow, and a complementary EEG experiment to investigate the temporal dynamics of this distinction. In the fMRI experiment (N=20), we used a block design with six conditions: 2 flow types (real and unreal optic flow) × 3 motion coherence levels (0%, 30% and 60%). Participants completed two sessions (expansion and contraction motion patterns), each with eight runs. Each run had 24 stimulus blocks (6 conditions × 4 times) and 3 fixation blocks. A task-irrelevant fixation point color change detection task was used during scanning. ROI-based MVPA showed that MST decoding accuracy for real versus unreal optic flow increased significantly with coherence levels in both motion patterns. In the EEG experiment (N = 20), we used the same stimuli and tested eight conditions (2 optic flow types × 2 motion patterns × 2 motion coherence levels), with 100 trials per condition presented in randomized order. Participants also performed a fixation point color change detection task during EEG recordings. Time-resolved MVPA revealed that the decoding accuracy for real versus unreal optic flow was significantly above baseline between 180 and 320 ms after stimulus onset. Furthermore, for real optic flow, decoding accuracy of motion coherence was significantly higher for expansion than contraction from 205 to 235 ms; whereas for unreal optic flow, decoding accuracy was significantly higher for contraction than expansion from 175 to 220 ms. These findings provide converging evidence that real optic flow modulates neural responses across spatial and temporal dimensions, underscoring the importance of real optic flow in shaping neural response to stimuli about self-motion.

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Poster

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Title: Neural responses to form and motion cues for heading perception in the human brain

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Abstract: When moving around in the world, the human visual system uses both form and motion information to estimate the direction of self-motion (i.e., heading). However, the underlying neural mechanism of their temporal integration remains unclear. Here we conducted an EEG experiment to investigate the temporal course of neural response to motion and form cues for heading perception. In the experiment (N=18), we used stimuli consisting of 200 randomly distributed dot pairs oriented toward a locus on a screen (the form-defined focus of expansion, fFoE]) but moved away from a different locus (the motion-defined FoE, mFoE) to simulate observer translation. The fFOE and mFOE were independently positioned at −4°, 0°, or 4° relative to the display center, resulting in three levels of cue discrepancy (0°, 4°, or 8°). Participants made a heading judgement task during EEG recordings. Behaviorally, a mixed-effects linear model revealed that the bias in heading judgments away from the fFoE increased with the difference between the fFoE and the mFoE. This result suggests that participants integrated both cues to perceive heading direction. We used a support vector machine (SVM) classifier to decode both form- and motion-defined FoEs. Decoding accuracy of fFoEs was significantly above chance at ~50 ms after stimulus onset, while decoding accuracy of mFoEs reached significance at ~100 ms. We further performed representational similarity analysis (RSA) to assess motion and form cue integration. We constructed two model representational dissimilarity matrices (RDMs) for each participant: one based on perceived heading (derived from behavioral responses) and the other based on the discrepancy between mFoEs and fFoEs (defined by stimulus parameters). These RDMs represent either the integrated heading estimation or the degree of conflict between cues. We then computed neural RDMs from EEG signals across time and and correlated them with each model RDM to assess when neural representations reflected either heading integration or cue discrepancy. Neural representations correlated significantly with the perceived heading model beginning at ~110 ms, closely following motion decoding, suggesting that integration occurred in parallel with motion processing. In contrast, neural correlations with the FoEs-discrepancy model were not significant during the stimulus presentation period, suggesting that early integration does not rely on explicit detection of conflict between cues. Together, our findings suggest that the brain processes form earlier than motion cues and integrates both cues rapidly and automatically, without requiring explicit evaluation of their discrepancy.

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Poster

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Topic: E.06. Vision

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Title: Neural correlates of causal inference in motion perception

Authors: *Y. DONG[1], G. F. DIRISIO[2], B. RABAH[3], Z. B. XU[4], A. ANZAI[1], S. SHIVKUMAR[5], G. LENGYEL[6], R. M. HAEFNER[1], G. C. DEANGELIS[1];
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Abstract: Retinal image motion arises from the combined effects of self-motion and object movement, posing a challenge for the visual system to infer causal relationships. Previous studies (Peltier et al., 2020) have demonstrated that, when self-motion differs substantially from object motion, the brain subtracts self-motion to perceive object movement, which produces perceptual biases that are reflected in neuronal responses in area MT. Conversely, when local optic flow motion is similar to object motion, the observer may infer that the object's motion on the retina is caused by their self-motion, leading to motion integration to reduce perceptual noise. To further explore these processes, we trained two rhesus macaques on a motion discrimination task. The task involved discriminating the leftward or rightward motion of a patch of random dots relative to a reference direction. Optic flow simulated three self-motion conditions in which the optic flow vector at the object's location was either leftward, rightward, or aligned with respect to the task reference. As expected for motion integration, the monkey's choices were biased towards optic flow direction in the leftward and rightward flow conditions compared to the neutral condition, with systematic dependence on flow angle and eccentricity. Neural recordings in area MT using 32-channel linear arrays aimed to identify corresponding changes in neural responses. Analyses from one monkey revealed that some MT neurons exhibit response modulations that depend on optic flow conditions. Furthermore, applying a population decoder to simultaneously recorded neurons (single-session decoding) showed attractive shifts in predicted psychometric curves in the same direction as, but substantially weaker than, behavioral biases. To further investigate how causal inference is represented in the brain, we developed a Bayesian model that could explain the monkeys' causal inference behavior. Next, we will evaluate how area MT reflects causal inference by comparing model predictions with neural encoding of object motion. Our findings from monkeys' behavior establish a shift in perceptual biases from repulsive (i.e., flow parsing) to attractive (i.e., motion integration) as the image motion of an object becomes more similar to background optic flow resulting from self-motion. This suggests a causal inference process underlying motion perception in macaques, partially reflected in neural activity in area MT.

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Poster

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Title: Mesoscopic and volumetric calcium imaging in the marmoset MT visual area

Authors: *S. OTERO CORONEL, D. G. HILDEBRAND, W. FREIWALD, A. VAZIRI; Rockefeller Univ., New York, NY

Abstract: The primate brain exhibits complex spatial patterns of functional specialization that have been studied using techniques with either large spatial coverage or single-cell resolution, but not both. Here, we implemented next-generation calcium indicators and optimized microscopy techniques to achieve mesoscopic and volumetric two-photon calcium imaging in the marmoset cortex. By recording from cortical volumes of up to $4 \times 4 \times 0.3$ mm^3, we simultaneously captured the activity of over 40,000 stimulus-responsive neurons. Our results reveal frequency-tuning granularity in the auditory cortex and direction-tuning pinwheels in the visual area MT+. Response correlations and neuronal tuning in MT showed a lateral spatial frequency of 500 μm and low variability across depths. Trial-noise correlations between cells decayed exponentially with distance, but were significant even for cells over 2 mm apart. These advancements open the door for large-scale, single-cell investigations of functional organization and population dynamics in the primate brain.

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Poster

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Title: Beyond Magnocellular: Koniocellular Contributions to Motion Sensitivity Linked to Reading Skill

Authors: *J. CADENA-VALENCIA, S. RIMA, N. CHAMANI, Y. SOUICI, M. C. SCHMID; Dept. of Neurosciences and Movement Sci., Univ. of Fribourg, Fribourg, Switzerland

Abstract: Reading is a high-level cognitive skill that depends on a range of low-level visual processes, including motion perception. According to the magnocellular theory of dyslexia, reading difficulties are linked to dysfunction in the magnocellular (M) layers of the lateral geniculate nucleus (LGN) and their downstream projections through primary visual cortex (V1) to motion-sensitive area MT. However, recent evidence suggests an alternative thalamocortical route: a V1-bypassing pathway in which koniocellular (K) neurons project directly from the LGN to MT. A key distinction between these pathways lies in their input characteristics—while the M pathway is primarily driven by luminance contrast, the K pathway predominantly processes chromatic information, particularly from short-wavelength sensitive (S-) cones.
To examine the relative contributions of these pathways to reading ability, we developed a chromatic speed-change detection paradigm. Detection thresholds were measured under S-cone isolating (K pathway), L-cone isolating (parvocellular [P] pathway), and high-contrast achromatic (M pathway) conditions, using stimuli defined in DKL color space. Reading proficiency was assessed using a Rapid Automatized Naming (RAN) task.
Twenty-nine adult readers (18-35 years, normal or corrected vision) completed a two-alternative forced-choice speed-change detection task. Gratings were presented peripherally (18° eccentricity), drifting at 1°/s before undergoing a randomly selected instantaneous speed increase (0.1-1.0°/s). Psychometric functions were computed for each participant and condition.
Motion detection thresholds were lower for luminance contrast stimuli compared to isoluminant stimuli (repeated measures ANOVA, $p = .002$; Bonferroni-corrected pairwise $p < .05$). Crucially, thresholds for achromatic stimuli correlated with better RAN performance ($r = -0.52$, $p = 0.013$), consistent with M-pathway involvement in reading-related motion processing. S-cone isolating thresholds also predicted RAN scores ($r = -0.45$, $p = 0.035$), implicating the K-pathway. No significant correlation was found for L-cone isolating stimuli ($r = -0.30$, $p = 0.173$), suggesting limited P-pathway involvement.
These results indicate that reading-related visual motion sensitivity involves both M and K pathways. Our findings support an expanded model in which multiple parallel visual pathways—especially those engaged in temporal processing—contribute to reading proficiency.

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Poster

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Topic: E.06. Vision

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Title: Object Recognition from Dynamic Cues; Examining the Inversion Effect

Authors: *N. FARIDANI[1], S. MAQSOOD[1], M. VAZIRI PASHKAM[2];
[2]Psychological and Brain Sci., [1]Univ. of Delaware, Newark, DE

Abstract: Humans have the ability to identify and categorize objects in a dynamic visual scene with remarkable accuracy. To achieve this accuracy, our visual system relies not only on static information but also on dynamic cues. In static images of objects, it has been shown that turning the image upside down hinders recognition. Similar effects have been found in dynamic videos of human action. However, this inversion effect has not been investigated for a broader set of categories when only dynamic cues are available. Here, we used object kinematograms to investigate the inversion effect on object recognition using dynamic cues. We used videos of four animate and four inanimate categories of objects, extracted motion cues from the videos, and projected them on randomly moving dots to create object kinematograms that only contain dynamic information. We showed the videos either upright or inverted to participants in an online experiment. For each video, participants were asked to answer three questions: 1) identify if the stimulus was an animal or an object, 2) identify the category to which the object belonged, and 3) name the object. We also provided the "I don't know" option for all three questions. Our results showed that, for the first question (animacy classification), animals were easier to classify ($p < 0.01$) and showed a strong inversion effect ($p < 0.05$). We did not observe a significant inversion effect for objects ($p > 0.05$). For the second question (basic level categorization), some categories did not have a significant inversion effect ($p > 0.05$ for tools, swings, reptiles, and balls), while others showed a strong inversion effect ($p < 0.05$). Lastly, when subjects chose to provide a name for the objects, their ability to name the objects was not significantly hindered when the videos were inverted ($p > 0.1$). These results demonstrate that inversion disrupts categorization accuracy; however, this inversion effect varies across categories. Most animate categories showed a strong inversion effect, which is consistent with prior research on the advantages of upright position for biological stimuli. This variation may be related to the natural orientation of objects in our visual environment (stronger inversion for objects that typically appear in a particular orientation) or the symmetries in the patterns of movement that would reduce the change in the pattern upon inversion.

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Poster

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Title: Neural encoding of visual reliability in mouse cortex

Authors: *E. M. FRAZIER[1], A. B. SERENO[2], M. C. DADARLAT[1];
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Abstract: Accurate perceptual decisions require encoding of both stimulus features and their reliability. Under a Bayesian framework, the brain computes optimal perceptual decisions by weighting sensory evidence according to its reliability to infer the most probable interpretation of noisy sensory input. Probabilistic population coding theories propose that neural populations representing the identity of a sensory variable (e.g., the movement direction of a visual stimulus) simultaneously encode the uncertainty over that variable by modulating response gain. Previous work has investigated these ideas in primate sensory cortices and using artificial neural networks, but it remains unclear whether these principles generalize across species. Here, we tested this framework in the mouse visual system using a motion discrimination task. Head-fixed mice were trained to report the global motion direction of random dot kinematograms (RDKs) by rotating a wheel. We manipulated stimulus reliability by varying the fraction of coherently moving dots. After training, mice achieved a mean psychometric threshold of 33% ± 6% coherence at 70% accuracy, indicating motion integration. Further, behavioral performance improved as a function of RDK coherence. Using mesoscopic two-photon calcium imaging from thousands of layer 2/3 neurons across visual cortex, we identified a distributed population significantly responsive to the presentation of RDK stimuli. Population decoding of motion direction from these neurons produced an average neurometric threshold of 25% ± 4% coherence, substantially below the behavioral threshold - suggesting precise sensory information is available even at stimulus levels too weak to support perception. We found that individual neurons were specifically tuned to the RDK movement direction and that the amplitude of their responses increased with coherence. At the population level, higher coherence stimuli also elicited stronger responses and more accurate encoding of motion direction, consistent with theoretical predictions from probabilistic coding models. Taken together, these findings demonstrate that the mouse visual cortex robustly encodes both the direction and reliability of visual motion signals and that these features are multiplexed within single neurons and across spatially distributed populations. These results align with probabilistic coding and mirror inferences from primate sensory cortices. Ultimately, this supports a neural implementation of probabilistic inference in mouse visual circuits and provides new insights into how the brain achieves stable perceptual decisions under sensory uncertainty.

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Poster

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Title: Development of direction selective input and output in the Xenopus tadpole midbrain tegmentum and optic tectum

Authors: *K. ZHENG[1], U. G. UDOH[2], K. G. PRATT[3];
[2]Zoology and Physiol., [1]Univ. of Wyoming, Laramie, WY; [3]Zoology and Physiol., Univ. of Wyoming Grad. Program In Neurosci., Laramie, WY

Abstract: There are two direct projections from the tadpole retina to the midbrain: the retinotectal projection and the retinotegmental projection. The retinotectal projection is homologous to the mammalian superior colliculus (SC). The retinotegmental projection is part of the highly conserved accessory optic system (AOS). Tegmental neurons within the AOS are direction selective: they respond optimally to slow-velocity motion and elicit compensatory optokinetic and optomotor reflexes - eye and head/body movements that stabilize the visual world as the organism moves. Because the tadpole midbrain tegmentum is part of the AOS, we hypothesized that tegmental neurons should exhibit direction selectivity. In this study, we measured the development of direction selectivity in tadpole tegmental neurons and, for comparison, in tectal neurons. Slow-moving bars of light, moving in four directions (upward, downward, temporal to nasal, nasal to temporal), were projected onto one eye of tadpoles from developmental stage 42, approximately 5 days postfertilization (dpf), when retinal ganglion cell axons first innervate midbrain targets, to stage 48/49, 10 to 18 days dpf, when projections are more mature. To measure direction selectivity in contralateral tectal and tegmental neurons, moving bar-evoked synaptic currents (input) were measured in whole-cell voltage-clamp mode, and action potentials (output) were measured in loose cell-attached mode. For each neuron, a direction selectivity index (DSI) was calculated for each direction; neurons with DSI > 0.2 were considered direction selective. We found direction selective tegmental neurons, consistent with their role in the AOS. We also found direction selective tectal neurons, perhaps homologous to the direction selective neurons of the mammalian SC associated with saccades. Overall, the percentage of tectal neurons receiving direction selective input increased over development. While the percentage of tectal neurons displaying direction selective output decreased, the remaining ones became strongly direction selective (i.e., more narrowly tuned). In contrast, the percentage of tegmental neurons displaying direction selective input and output and the strength of the direction selectivity remained stable over development. The observed differences between direction selective tectal and tegmental neurons suggest distinct functional roles: tectal neurons refine direction tuning during later development, while tegmental neurons establish stable tuning early to support reflexive stabilization. We are currently testing the requirement for NMDA receptors in the development of direction selectivity.

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Poster

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Topic: I.05. Working Memory

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Title: Degradations of spatiotopic visual working memory across eye movements are observed with oculomotor responses

Authors: *S. R. BASS[1], A. H. HARRISON[1], T. C. SPRAGUE[2];
[2]Psychological and Brain Sci., [1]UC Santa Barbara, Goleta, CA

Abstract: Every eye movement, or saccade, shifts visual input, requiring the brain to update spatial representations to keep perception stable. A previous study showed that spatiotopic memory - memory for object locations relative to the world - degrades with each saccade away from the encoding gaze position (Golomb & Kanwisher, 2012). However, using a mouse click to report a remembered object location may incur performance costs due to the need to convert spatiotopic representations across oculomotor movements into motor plans. To investigate whether the previously seen memory degradation reflects fundamental limitations in spatiotopic updating rather than modality conversion costs, we conducted an experiment in which participants reported a spatiotopic remembered location with an eye movement, rather than mouse click, after zero, one, or two saccades. Our results replicate previous studies showing that spatiotopic memory error increases with more saccades unless gaze returns to the original encoding location. This suggests that the degradation arises from inherent limitations in spatial updating mechanisms, not from response modality constraints. Thus, the cumulative error may be attributed to the cost of converting spatial locations from our native retinotopic coordinate system into spatiotopic coordinates. When the two coordinate systems realign by returning gaze position to the encoding location, the preserved memory trace may bypass remapping costs. Future work will seek to further examine how spatiotopic and retinotopic coordinate systems act in tandem to impact visual working memory performance and guide our behavior.

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Poster

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Program #/Poster #: PSTR123.17/P8

Topic: E.06. Vision

Title: Preserved sensitivity to visual threats in peripheral compared to central vision

Authors: *J. GUO, J. DAI, J. HU, Y. WANG;
Zhejiang Univ., Hangzhou, China

Abstract: Detecting moving visual threats, such as imminent collisions, is crucial for human survival. Unlike static stimuli, moving threats can pose significant danger even when they appear in the peripheral visual field, demanding rapid and precise discrimination despite dynamic trajectories and high velocities. However, direct evidence is lacking regarding whether humans can detect such threats with high sensitivity in peripheral vision. Notably, because the cortical visual system exhibits reduced sensitivity to peripheral stimuli, such capability may rely on a subcortical magnocellular pathway specialized for rapid threat detection.
To investigate this possibility, we conducted five experiments using either desktop displays (Experiments 1 - 4) or immersive virtual reality (Experiment 5). In each experiment, human participants (N = 12 per experiment, 42 females in total) judged whether looming spheres would "hit" or "miss" their head. These spheres approached from various starting positions spanning different eccentricities across the visual field (from 2° to 14.25°). Psychometric functions revealed that increasing eccentricity systematically decreased the likelihood of perceiving an impending collision. However, contrary to the traditional view that peripheral vision is poor at resolving visual details, we found undiminished and uniform sensitivity within the central 28.5° of the visual field, as reflected in the slope of point of subjective equality and Just Noticeable Difference (JND). Eye-tracking data ruled out the possibility that these results were due to compensatory eye movements. Additionally, pupillometric analysis - an indirect measure of emotional arousal - was used to support the engagement of threat-processing mechanisms. A control experiment involving non-colliding but physically similar trajectories was further included to rule out low-level visual factors unrelated to threat as explanations for the observed effects.
Together, these findings provide converging evidence for enhanced peripheral sensitivity to moving visual threats. They further offer indirect support for the role of a subcortical visual pathway in detecting moving visual threats.

Disclosures: J. Guo: None. **J. Dai:** None. **J. Hu:** None. **Y. Wang:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.01/P9

Topic: E.08. Multisensory Integration

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Title: Single-cell projectome of sensory cortex: circuit organization and multisensory integration pathways

Authors: *W. SONG[1,2,3,4,5], Y. SUN[2,3], H. YAO[2,3];
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Abstract: Sensory cortices are critical for perception and sensorimotor behavior, yet the principles of their single-cell projection patterns remain poorly understood. Here, we reconstructed the brain-wide projections of 5,357 single neurons of mouse somatosensory, visual, and auditory cortices, identifying 95 projectome-defined subtypes with distinct projection to sensory, motor, and association areas, as well as thalamic areas. Motor area-projecting neurons exhibited subregion preference, topographic organization, and an ipsilateral bias with some neurons exhibiting symmetric bilateral targeting. Thalamus-projecting neurons showed focal or divergent targeting pattern, laminar-dependent co-innervation, and modality-specific collateralization in the thalamic reticular nucleus. Neurons with cross-modal projection were diverse in targets and branching; association area-projecting neurons exhibited cross-modal terminal convergence within specific subregions. Sensory cortices also formed hierarchical network, with a subset of neurons in intermediate regions projecting both upstream and downstream. Together, our study provides a comprehensive anatomical framework for understanding sensory processing and multisensory integration at single-neuron resolution.

Disclosures: W. Song: None. **Y. Sun:** None. **H. Yao:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

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Program #/Poster #: PSTR124.02/P10

Topic: E.08. Multisensory Integration

Support: Canadian Institutes of Health Research
Natural Sciences and Engineering Research Council of Canada.

Title: Age-related modulation of visually-evoked LFP responses in auditory cortex

Authors: *Y. MERRIKHI[1], C. SABOURIN[1,2], S. G. LOMBER[1,2];
[1]Physiol., McGill Univ., Montreal, QC, Canada; [2]Psychology, Univ. of Texas at Arlington, Arlington, TX

Abstract: One of the fundamental roles of the cerebral cortex is to assimilate and synthesize information from various sensory modalities, creating an integrated perception of the environment. While it is well established that auditory areas of cats develop multisensory capabilities within the first six months, the progression of these multisensory functions into adulthood, beyond six months, remains less characterized. This study investigated age-related changes in visually-evoked local field potentials (LFPs) in the primary auditory cortex (A1) and the higher order auditory area, the dorsal zone (DZ). Using laminar arrays of electrodes, we recorded LFP responses in A1 (n=741 recording sites) and DZ (n=525 recording sites) of 6 cats aged 9-36 months under light ketamine anesthesia in response to visual stimulation (80 lux, 500 ms). Our analysis focused on the power and phase consistency of LFP responses, critical indicators previously shown to be affected by cross-modal visual inputs. Our results indicate non-significant and inconsistent correlations between the power of LFP signals and age in DZ across various frequency bands. In contrast, A1 showed consistently positive, though non-significant, correlations across all frequency bands, with notable strength in the theta (θ; r=0.7, p=0.211) and alpha (α; r=0.726, p=0.102) bands. Significantly, the power of visually-evoked LFP responses in A1 increased relative to DZ with age, particularly in the θ (r=0.822, p=0.045) and α (r=0.902, p=0.012) bands. Similarly, phase consistency of LFP responses in DZ displayed inconsistent, non-significant correlations across frequencies. Conversely, A1 exhibited consistently positive, non-significant correlations, with stronger effects in θ (r=0.635, p=0.175) and α (r=0.643, p=0.169) bands. Notably, as cats aged, the phase consistency of LFP responses in A1 significantly outpaced DZ in the θ (r=0.872, p=0.023) and α (r=0.934, p=0.006) bands. These observations suggest a progressive enhancement in A1's ability to integrate visual stimuli with age, indicative of augmented multisensory processing capabilities in older cats. The increase in LFP response properties (i.e. LFP power and phase consistency) mainly reflects greater synaptic input from visual pathways in A1 as cats age. Our data suggest that this trend does not occur in DZ, highlighting potential regional variations in how the aging auditory cortex adapts to multisensory inputs. This work was supported by grants from the Canadian Institutes of Health Research and the Natural Sciences and Engineering Research Council of Canada.

Disclosures: Y. Merrikhi: None. **C. Sabourin:** None. **S.G. Lomber:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

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Program #/Poster #: PSTR124.03/P11

Topic: E.08. Multisensory Integration

Support: NIH Grant R01-EY014882
Johns Hopkins University 2025 Summer PURA Award

Title: Adaptations of Visual Detection Following Adult-onset Hearing Loss in Mice

Authors: *B. SEO[1], H. PHAM[3], B. KIM[1], R. LEE[1], M. KOMMU[1], R. JEONG[1], L. MESIK[1,2], H.-K. LEE[1,3,2];
[1]Mind/Brain Institute, Krieger Sch. of Arts and Sciences, Johns Hopkins Univ., [2]Kavli Neurosci. Discovery Inst., Johns Hopkins Univ., Baltimore, MD; [3]Dept. of Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Hearing loss has been shown to induce cross-modal adaptations across multiple brain regions, even after the closure of the critical period of cortical plasticity. For example, ex vivo recordings from the primary visual cortex of deafened mice have demonstrated potentiation of the feedforward visual pathway. Current literature suggests that such neural changes may help organisms maintain or more effectively guide behavior through their remaining senses. Here, we performed two psychophysics experiments to assess how deafening affects the visual acuity and contrast sensitivity of central and peripheral vision using awake head-fixed adult B6 mice of both sexes. Auditory deprivation (AD) was done via ototoxic lesioning 7 days prior to behavioral training. Age-matched littermate controls (Normal Reared, NR) were prepared in parallel. After water deprivation and habituation, the mice were trained to detect Gabor patches of various spatial frequencies and contrast levels presented in either the central or peripheral visual fields, and to report their detection by licking for water rewards. The detection rate was measured as the lick rate during the response time window following stimulus onset. The detection threshold for the central and peripheral visual fields was calculated for each mouse by fitting a logistic function to the detection rate plotted against either the spatial frequencies or contrast levels. Our preliminary data show the detection threshold for both NR and AD mice did not differ significantly for central vision. For peripheral vision, a two-way ANOVA test revealed a statistically significant improvement in the visual acuity of AD mice compared to NR mice. There was only a marginal improvement in contrast sensitivity in the peripheral visual field of AD mice. Our current results suggest that select visual functions are improved following deafening and prompt further investigation using other visual detection tasks, as well as mechanisms of such selective improvement in visual function. Our findings have implications for improving visual function in adults.

Disclosures: B. Seo: None. **H. Pham:** None. **B. Kim:** None. **R. Lee:** None. **M. Kommu:** None. **R. Jeong:** None. **L. Mesik:** None. **H. Lee:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

Location: SDCC Halls B-H

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Topic: E.08. Multisensory Integration

Support: NIH R01 DC 019348
NSF IOS 1652432

Title: Contralateral corticothalamic projections from cortical layer 6b

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Abstract: Higher forebrain operations are mediated through an extensive network of corticothalamic, thalamocortical and corticocortical connections. Within the corticothalamic network, two projection systems have been classically regarded to have complementary roles; the layer 5 corticothalamic pathways are considered 'drivers' of thalamic activity, while the layer 6a pathways are considered 'modulators' of thalamic activity. Recently through, a third corticothalamic pathway, originating from layer 6b, has received increased attention, in part due to its laminar role in mediating forebrain wake states. Moreover, we have shown that this sublayer may be a significant source of *contralateral* corticothalamic projections originating from limbic/prefrontal cortical areas. As such, layer 6b is uniquely poised to influence *contralateral* forebrain operations via overlooked ipsicortico-contrathalamocortical loops. Thus, to assess the organization of this circuit, we characterized the corticothalamic projections from cortical layer 6b of three cortical areas: primary auditory cortex (A1), insular cortex (IC), and prefrontal cortex (PFC). We employed the *Drd1a-Cre* mouse lines, which specifically expresses Cre-recombinase in layer 6b corticothalamic neurons. We stereotaxically injected floxed anterograde adeno-associated virus expressing various fluorophores, EYFP (green) and mCherry (red), and examined the terminations of *ipsilateral* and *contralateral* corticothalamic projections to specific thalamic nuclei. These projections differ according to the area injected, topographic segregation of terminal fields, characteristic morphological features, with no contralateral projections observed from A1. Our experiments addressed overlooked neuronal pathways involved in forebrain processing, which could offer insights into deficits in neurological disorders mediated by these pathways.

Disclosures: O.A. Ayanshina: None. **C.C. Lee:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

Location: SDCC Halls B-H

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Program #/Poster #: PSTR124.05/Q1

Topic: E.08. Multisensory Integration

Support: R01NS116598
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Title: Input circuitry of infragranular auditory cortex from diverse visual areas in the mouse

Authors: *T. SUZUKI, T. R. OLSEN, A. R. HASENSTAUB;
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Abstract: Recent studies have revealed that the auditory cortex (AC) not only processes auditory information but is also modulated by other sensory information. We have previously shown that

the mouse AC contains a group of cells that respond to or are otherwise influenced by visual information (1). These neurons are mainly found in the deep layers, but their inputs remain poorly characterized. Thus, the present study aimed to identify primary sources of visual information in AC using retrograde viral tracing experiments. We first performed localized microinjection of retrograde tracers using iontophoresis. C57BL/6 mice were injected with a viral mixture (AAV2retro-hsyn-EGFP and AAV9-hsyn-ChR2-mCherry) in the right AC (for deep layer: n = 8, depth -0.75mm; for shallow layer: n = 6, depth -0.25mm), and after 3-4 weeks, we perfused and sliced their brains. EGFP-positive cells were analyzed using Aligning Big Brains & Atlases (BioImaging And Optics Platform), with reference to the Allen Brain Atlas (2017 CCF v3). For each injection, most input came from the ipsilateral cortex, especially from the temporal association areas, somatosensory cortex, and visual cortex. EGFP-positive cells were distributed across visual cortices, with a greater number observed in mice that had deep-layer AC injections - notable areas include the primary visual cortex, lateromedial, lateral intermediate, and anterolateral visual areas. These EGFP-labeled cells were predominantly located in the deep layers of the visual cortexBecause AAV2retro seemed to spread less toward the subcortical region than we expected, we conducted additional experiments using G-deleted Rabies viral tracing. C57BL/6 mice were injected with a viral mixture (AAV8-hsyn-DIO-TVA(E66T)-EGFP-oG and AAV1-hsyn-Cre) in the right AC (n = 5, depth -0.75mm) by iontophoresis injection. Three weeks later, EnvA-RVdG-mCherry was injected in the same place. We perfused the brain 10 days after the Rabies injection. mCherry-positive cells, which indicated the postsynaptic cells from the EGFP-positive starter cells, were also observed in the temporal association areas, somatosensory cortex, and visual cortex, but also thalamic regions, including the medial geniculate complex and visual/multimodal thalamic nuclei: the lateral posterior and suprageniculate nuclei. Together, our findings suggest deep layers of the mouse AC receive convergent inputs from multiple visual cortical areas and thalamic regions, expanding our understanding of multisensory integration in the AC.
1. Morrill and Hasenstaub. (2018). Visual Information Present in Infragranular Layers of Mouse Auditory Cortex. J. Neurosci. 38, 2854-2862.

Disclosures: T. Suzuki: None. **T.R. Olsen:** None. **A.R. Hasenstaub:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

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Program #/Poster #: PSTR124.06/Q2

Topic: E.08. Multisensory Integration

Support: NIH DC 011579

Title: Noxious spinal input affects taste neurons in the mouse parabrachial nucleus

Authors: *J. LI, C. H. LEMON;
The Dept. of Biol., Univ. of Oklahoma, Norman, OK

Abstract: The parabrachial nucleus (PbN) in the brain stem is responsible in part for integrating sensory information from diverse modalities, such as taste, somatosensory and visceral sensations. Our lab recently found that taste-excited neurons in PbN were activated by oral trigeminal somatosensory stimulation. It is unknown whether taste neurons in this area would respond to a broader array of somatosensory stimuli such as spinal (body) somatosensory circuits that reach the PbN. Here, we have used in vivo neurophysiological recordings combined with optogenetics in TRPV1;Ai32 mice to monitor evoked activities in individual PbN cells under anesthesia during oral chemical and thermal stimulation, and stimulation of spinal nociceptive pathways. Taste responses (in spikes/sec) were indexed using temperature-controlled solutions of (in mM) 100 NaCl (salty to humans), 500 sucrose (sweet), 10 quinine (bitter), 0.1 cycloheximide (bitter), and 10 citric acid (sour). Oral somatosensory stimuli included delivery of thermal ramps to oral epithelia using water at 8 different temperatures (from cold near 7°C to heat at 51°C), 1 mM allyl isothiocyanate (AITC; agonist of TRP ankyrin 1 [TRPA1] and TRPV1), 1.28 mM menthol (TRPM8) and 1 mM capsaicin (TRPV1). Spinal input was stimulated by hind paw and tail pinch with calibrated forceps. Focused 473 nm optical stimulation was applied to the receptive field, defined by pinch stimulation, to transcutaneously excite TRPV1-lineage fibers. Analysis of 58 recorded PbN neurons revealed that 24 cells were taste-selective, 11 were activated exclusively by spinal input, and 9 responded solely to oral somatosensory stimuli. Additionally, 14 cells (24%) were activated by more than one stimulus modality, including two neurons that responded to bitter taste, AITC, and pinch stimulation of the hindpaw/tail. We also found 4 taste neurons activated by pinch to the hindpaw/tail but not oral somatosensory stimuli, indicating lack of hierarchy ranking for their possible convergence. Our findings provide neurophysiological evidence that spinal somatosensory information converges with taste onto single neurons in the PbN. These neurons would be defined as unimodal “taste” cells under traditional methods but display multisensory repertoires that agree with the integrative functions of the PbN supported by the literature.

Disclosures: J. Li: None. **C.H. Lemon:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

Location: SDCC Halls B-H

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Program #/Poster #: PSTR124.07/Q3

Topic: E.08. Multisensory Integration

Support: Fonds national suisse
Fondation De Reuter
Fondation Gertrude von Meissner

Title: From behavior to circuits: cortical substrates of cross-modal generalization

Authors: *M. GUYOTON[1], G. MATTEUCCI[1], C. FOUCHER[1], M. GETZ[2], J. GJORGJIEVA[2], S. EL BOUSTANI[1];

[1]Basic neuroscience, Univ. of Geneva, Genève, Switzerland; [2]Computation in Neural Circuits Group, Max Planck Inst. For Brain Res., Freising, Germany

Abstract: The ability to generalize learned behaviors across varying sensory conditions requires cortical mechanisms that integrate modality-specific signals into abstract supramodal representations. To study the neural basis of this cognitive function, we developed a Go/No go cross-modal task switching paradigm in which mice are first trained to discriminate between two vertically arranged stimuli presented in one modality (i.e. visual or tactile) and then are switched to a similar task in the other modality. We observed that mice can seamlessly generalize spatial task rules between vision and touch suggesting the use of abstract, modality-independent representations of peri-personal space. Multi-scale calcium imaging revealed distributed associative areas across dorsal and ventral streams containing aligned visuo-tactile maps, ideally poised to support this generalization. Anatomical tracing confirmed that these regions were embedded within topographically organized feedforward and feedback loops connecting the associative cortex with primary visual and somatosensory areas. At the single-cell level, multisensory domains demonstrated the hallmark properties of a supramodal representation of space: they exhibited congruent visual and tactile positional tuning. Causal manipulations further showed that one of these areas in the mouse dorsal steam, rostrolateral area (RL), plays a critical role in cross-modal generalization. Silencing RL selectively impaired the ability to generalize across modalities without affecting unisensory performance, while optogenetic substitution of physical stimuli with direct neuronal stimulation of spatially defined RL subdomains was sufficient to induce generalization. Altogether, these findings highlight RL as a key cortical locus supporting the abstraction and flexible deployment of learned knowledge across modality. Ongoing work investigates whether synaptic clustering and nonlinear dendritic integration within RL neurons contribute to neuronal computations yielding these supramodal representations.

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Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

Location: SDCC Halls B-H

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Program #/Poster #: PSTR124.08/Q4

Topic: E.08. Multisensory Integration

Support: NIH Fellowship 1F32MH134455-01

Title: Context-dependent processing of self-motion in primate vestibular cortex

Authors: *L. J. GÓMEZ[1], K. E. CULLEN[2];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Dept. of Biomed. Engin., The Johns Hopkins Univ., Baltimore, MD

Abstract: Forming a stable percept of self-motion requires the brain to 1) integrate multiple streams of sensory input, and 2) distinguish between self-generated (active) and externally generated (passive) movement. In the vestibular thalamus and cerebellum, for instance, vestibular and proprioceptive input during passive movement is integrated linearly, whereas during active movement, responses to these inputs are markedly suppressed. Although such sensorimotor transformations are well characterized in subcortical areas, it remains unclear whether similar processing occurs at the level of neocortex—specifically within the parieto-insular vestibular cortex (PIVC), a key area for self-motion perception. Here, we used high-density electrophysiology in behaving non-human primates to examine how PIVC neurons process vestibular and proprioceptive cues during passive and active head motion. We first characterized sensory integration during passive motion. Each neuron's sensitivity to passive vestibular stimulation was assessed by delivering whole-body rotations, whereas its sensitivity to passive proprioceptive stimulation was assessed by delivering body-under-head rotations. Overall, PIVC neurons displayed diverse responses dynamics to both stimulation types. To examine vestibular-proprioceptive integration, we tested neurons during combined stimulation via the delivery of passive head-on-body rotations. We then predicted a given neuron's response based on the linear sum of sensitivities to vestibular and proprioceptive stimulation alone. In general, our model prediction overestimated the sensitivity of PIVC neurons to combined stimulation. These results indicate that, unlike the thalamus, PIVC likely integrates vestibular and proprioceptive input sub-additively. Finally, we recorded during matched passive and active head movements and found that PIVC responses were attenuated during active motion, with an average ~50% reduction in sensitivity and substantial variability across neurons. In contrast, our prior work in vestibular thalamic neurons shows stronger (>80%) and more consistent suppression. Like thalamic neurons, PIVC cells were insensitive to motor-related signals, indicating that the observed suppression is inherited rather than computed locally. This suggests that cancellation of self-generated vestibular input likely occurs in the cerebellum and/or in other cortical areas—or within a distributed cortical network—that then projects to PIVC. These findings highlight continued transformation of multisensory signals from thalamus to cortex and clarify PIVC's role in supporting self-motion perception.

Disclosures: L.J. Gómez: None. **K.E. Cullen:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

Location: SDCC Halls B-H

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Program #/Poster #: PSTR124.09/Q5

Topic: E.08. Multisensory Integration

Support: Stanley Center Family Fund

Title: Multisensory Pavlovian conditioning for the efficient detection of hallucination-like false perceptionin mice

Authors: *N. D. HARTLEY[1], J. TIAN[2], Z. FU[3];
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Abstract: Hallucination, a positive diagnostic criterion in schizophrenia (SCZ), is defined as an experience involving the conscious perception of something not physically present. In psychosis patients, these experiences are otherwise characterized as high-confidence false percepts (most commonly auditory), distinguishing them from moments of perceptual ambiguity that can occur in the general population. Here, we modified traditional discriminatory Pavlovian fear conditioning procedures to induce incidents of false auditory perception during a 4-day multisensory associative learning paradigm, hereafter referred to as the False-Percept Procedure (FPP). We then validated our FPP using a pharmacological method to induce false percepts via administration of a sub-anesthetic dose of the pro-hallucinatory compound ketamine (KET). We demonstrate that the 4-day FPP paradigm can be used in both between-groups and within-subjects designs, making it an efficient behavioral readout of hallucination-like behavior. Given its efficiency, the FPP may be suitable for exploring the biological mechanisms behind hallmark positive symptoms of Schizophrenia using genetic mouse models and may be usefully implemented in therapeutics development pipelines.

Disclosures: N.D. Hartley: None. **J. Tian:** None. **Z. Fu:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

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Program #/Poster #: PSTR124.10/Q6

Topic: E.08. Multisensory Integration

Support: SK1234556

Title: Dorsal root potentials evoked by pcm electrical stimulation in female wistar rats

Authors: *M. A. LARA GARCIA[1], M. K. SERRANO[2], A. REYES[3], E. DORANTES[4], O. LARA-GARCÍA[5], P. PACHECO[6];
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Abstract: Pubococcygeus muscle (Pcm) is a multi-functional muscle, whose reflex activity is highly related to mechanical stimulation of clitoral sheath; however, EMG recordings commonly displayed afterdischarges while female is on late proestrus. The origin of this activity remains unknown. Dorsal root potentials (DRP) can be induced by electrical stimulation of striated muscles, such as Pcm by activating sensory neurons. Hence, in the present study we recorded DRPs from L6-S1 dorsal roots when Pcm was electrically stimulation, before and after dorsal root transection in female rats during proestrus phase. Dorsal root recordings before L6 transection displayed activity correlated to Pcm stimulation, which was modified but not lost

after dorsal root transection from peripheral region. Likewise S1 recordings displayed a similar pattern after transection. As it stands, Dorsal root potentials are apparently contributing to these afterdischarges later recorded in Pcm.

Disclosures: M.A. Lara Garcia: None. **M.K. Serrano:** None. **A. Reyes:** None. **E. Dorantes:** None. **O. Lara-García:** None. **P. Pacheco:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

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Program #/Poster #: PSTR124.11/Q7

Topic: E.08. Multisensory Integration

Support: Whitehall Foundation: 2021-12-007
NIH: NS128079

Title: Ndnf interneurons in layer 1 facilitate audiovisual performance enhancement in visual discrimination tasks

Authors: *G. ZOOK, I. SMITH;
Neurosci. Res. Inst., UC Santa Barbara, Santa Barbara, CA

Abstract: Performance in visual detection and discrimination tasks is heightened in the presence of concomitant audio stimuli, even if the audio encodes no task-relevant information. This performance enhancement has been shown to be present even for mice under the effects of anesthesia. However, the neural mechanisms underlying this enhancement have not yet been identified. Here, we investigate the role of neuron derived neurotrophic factor expressing interneurons in the layer 1 visual cortex (L1 NDNF INs) for their role in this enhancement effect. L1 NDNF INs are well-suited to mediate this effect due to their broad top-down modulatory influence and widespread distribution throughout L1. To this end, we overexpress DREADD in the mouse primary visual cortex (V1) L1 NDNF INs in a Cre-dependent manner (AAV-hSyn-DIO-hM4Di) in order to chemogeneticaly silence these neurons during a visual task. After the AAV injection, mice are trained on a freely-moving two-choice visual discrimination task. During training, they will be exposed to two stimuli at a time, consisting of gratings moving either horizontally or vertically. Once they reach criterion performance of 85% correct rate, their performance at varying levels of contrast in the presence and absence of concomitant audio stimuli is evaluated. This contrast-sensitivity test provides the baseline psychometric curves, enabling us to quantify how the mouse's task performance is affected in the presence of concomitant auditory stimuli. These baseline curves are then compared to the performance in the same regime but with L1 NDNF INs silenced. We expect that silencing L1 NDNF INs will eliminate the auditory enhancement effect, such that performance with silenced interneurons will match baseline performance without auditory stimuli, regardless of whether audio is present.

Disclosures: G. Zook: None. **I. Smith:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

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Program #/Poster #: PSTR124.12/Q8

Topic: E.08. Multisensory Integration

Support: IBS-R002-A2

Title: Sharpening of cross-modal inhibition mediates contingency learning-dependent multisensory integration in mouse parietal cortex

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Abstract: Effective decision-making in animals relies on the integration of previously learned multisensory information. Previous studies have shown that animals' behavioral responses to multisensory stimuli vary depending on the combination of modality-specific stimuli and their distinct contingencies. However, it remains unclear how contingency learning shapes cortical circuits to drive such specific behavioral responses. Here, we found that learning shapes inhibitory circuits in the posterior parietal cortex (PPC) to form modality- and contingency-specific inhibition. We trained mice on an audiovisual Go/No-go discrimination task and measured the neural activity of layer 2/3 neurons in the PPC and primary visual cortex (V1) using *in vivo* two-photon calcium imaging. In naïve mice, PPC neurons exhibited broad auditory-to-visual inhibition across all stimulus pairs. In contrast, expert mice displayed selective auditory-to-visual inhibition in the PPC, specifically between incongruent stimulus pairs, but not between congruent ones. This cross-modal inhibition was not observed in the V1. Using targeted optogenetic activation of single neurons during calcium imaging, we found that auditory-responsive parvalbumin-expressing (PV^+) interneurons in the PPC broadly inhibited visual neurons in naïve mice. In contrast, in expert mice, auditory-responsive PV^+ interneurons preferentially targeted visual neurons with opposite Go/No-go preferences. Collectively, these findings demonstrate that contingency learning across sensory modalities sharpens cross-modal inhibitory circuits in the PPC, enabling behavioral enhancement for coherent multisensory stimuli and cross-modal competition under audiovisual incongruency.

Disclosures: I. Choi: None. **Y. Kim:** None. **S. Lee:** None.

Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

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Program #/Poster #: PSTR124.13/Q9

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Title: Ins-fmri in macaque pulvinar reveals distinct and topographic mesoscale networks

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Abstract: Motivation: In human and nonhuman primates, the pulvinar is a major thalamic nucleus which integrates multiple sensory inputs from the environment and disseminates this broadly to provide context for goal-directed behaviors. Our previous work, using INS-fMRI, demonstrated that the PL/PI (inferior/lateral pulvinar)-to-visual cortex (V1, V2, V3) networks are topographically organized at mesoscale. Here, we extend this investigation to explore brain-wide mesoscale networks associated with medial pulvinar PM and PI/PL. **Method**: We used a novel mesoscale functional connectivity mapping method (INS-fMRI: Infrared Neural Stimulation in 7T fMRI) in macaque monkey. INS evokes neural response at the fiber tip via short pulse trains of light (1875nm, 200 Hz, 200 μm optical fiber), which leads to neural activation at connected sites, detected by BOLD (EPI, 1.5mm isotropic), resulting in a brain-wide network mapped with 7T fMRI. Different statistical thresholds were examined to show stability of activation sites. We systematically evaluated the resulting brain-wide networks (GLM, FDR-corrected) from PM and compared to the PL/PI networks. **Results**: (1) INS in each of pulvinar PI, PL, and PM subnuclei induced brain-wide functional networks consisting of

patchy mesoscale activations. Activations from adjacent stimulation sites were largely non-overlapping. (2) Consistent with anatomical studies, the mesoscale functional connections of PI, PL and PM are distinct. INS in PI and PL revealed robust connections with visual cortical areas (V1-V4), dorsal pathway (LIP, VIP), ventral pathway (TPO, TEO), as well as connections with frontal areas (8Bs, 46v). In contrast, INS in PM revealed strong connections with limbic areas (e.g., cingulate, insula, amygdala) and medial wall cortical areas; connectivity patterns to limbic areas from consecutive sites in PM were organized with respect to known topography in target areas, resulting in a 3-tier hierarchy. (3) PM-to-prefrontal connections also exhibited mesoscale topographic organization. **Conclusion**: We reveal pulvinar subnuclei are embedded in distinct and topographically organized mesoscale functional networks. Our study lays the foundation for submillimeter pulvinar networks, which may be relevant for therapeutic interventions.

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Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

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Topic: E.08. Multisensory Integration

Support: NIH/NINDS grant #R01-NS071785-15 (to S.C.B.).

Title: Aberrant Sensory-Driven Behavior and Network Oscillations in a Complement C1qa-Deficient Mouse Model of Epilepsy

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Abstract: Epilepsy is one of the most common chronic neurological disorders in childhood, affecting approximately 0.5-1% of children. Beyond seizures, children with epilepsy frequently exhibit neurobehavioral comorbidities, including impaired sensory processing. These have traditionally been attributed to seizures or medication side effects; however, emerging evidence suggests that deficits in inhibitory network function may independently contribute. However, the mechanistic basis linking inhibitory dysfunction to sensory-driven behavioral impairments remains poorly understood. Here, we evaluated sensory-driven behaviors and inhibitory circuit function in mice lacking C1qa - a complement protein involved in synaptic pruning and neurodevelopment - to investigate how inhibitory function contributes to comorbid phenotypes in epilepsy. In addition to behavioral assessments, oscillatory network activity was evaluated by implanting 16-channel silicon probes (NeuroNexus) into somatosensory cortex, to assess circuit-level changes. We conducted textured Novel Object Recognition Test (tNORT) and Whisker Nuisance (WN) test in C1qa knockout (KO) and wild-type (WT) mice. Both sexes were tested at 2 months of age (n = 4-8 per group) under consistent light-phase conditions. To examine a

therapeutic role for interneuron-mediated circuit modification, embryonic medial ganglionic eminence (MGE) progenitors were transplanted into KO and WT mice, and behavioral testing was repeated. Experiments conducted and analyses were blinded to genotype, sex, and treatment condition. In this study, KO mice showed significant deficits in tNORT, with reduced object exploration and discrimination (unpaired *t* test, $p < 0.05$), but no differences in WN or individual behavioral responses (two-way ANOVA, $p > 0.05$), indicating preserved basic tactile responsiveness. MGE transplantation at postnatal day 2 rescued tNORT performance in adult KO mice (two-way ANOVA, $p > 0.05$). These findings demonstrate that inhibitory networks play a crucial role in spontaneous sensory-driven behavior, highlighting a mechanistic link between interneurons and behavioral comorbidities in epilepsy. This work also underscores the therapeutic potential of targeting inhibitory circuits and supports further investigation into novel cell-based interventions for comorbid behavioral deficits.

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Poster

PSTR124: Cross-Modal Processing: Neural Circuitry and Development

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Program #/Poster #: PSTR124.15/Q11

Topic: E.08. Multisensory Integration

Support: NIDCD R01 DC020892-03

Title: Complex Effects of Multimodal Inputs in the Antennal Lobe of the Honeybee Apis mellifera

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Abstract: Multimodal sensation is the process by which an organism integrates information from multiple sensory modalities to maximize the information about a stimulus and generate the optimal response. This information can be integrated at many different neurological levels, from a single sensillum to large regions of the brain, often occurring in multiple stages throughout the processing pipeline. Thus, sensory integration is a complex process whose neurological underpinnings we are only beginning to understand. We studied this integrative process in the honeybee olfactory system, which utilizes both olfactory and mechanosensory inputs from an odor plume to aid in odor identification and the subsequent behavioral response. To do this, we exposed bees to various combinations of air speed and odor concentration while simultaneously recording extracellular spike activity from within the antennal lobe (AL), which receives direct antennal input and serves as the first layer of processing within the bee brain. Responses were analyzed based on several factors including the spiking rate, length, and latency. We additionally

developed machine learning algorithms to categorize the response's shape, including the number of peaks, their locations, and any inhibitory responses. Integration occurred throughout the AL, showing some evidence within the local interneurons, but far more at the level of the projection neurons. This difference suggests a change in representations of sensory components depending on processing level. Future projects will further explore this change, and how it carries over to other levels of processing such as the mushroom bodies or lateral horn.

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Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

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Program #/Poster #: PSTR125.01/Q12

Topic: F.05. Brain-Machine Interface

Support: FWO Postdoctoral Fellowship Junior 1264926N
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Tianqiao and Chrissy Chen Brain-Machine Interface Center
Boswell Foundation

Title: Representational Geometries for Intended and Observed Actions in Human Parietal and Motor Cortex

Authors: *V. BOUGOU[1,2], J. GAMEZ[1,2], E. R. ROSARIO[3], C. LIU[4], K. PEJSA[1,2], A. BARI[5], R. A. ANDERSEN[1,2];
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Abstract: Understanding how the brain represents actions is a central question in motor cognition and brain-machine interfaces. One approach is to analyze the representational geometry of neural population responses, defined as the spatial structure of activity patterns evoked by different task conditions. We examined how these geometries reflect action encoding during two cognitive formats: intention (internal generation) and observation (viewing the same action). Using intracortical recordings from two tetraplegic participants (N1, N2) with Utah arrays, we analyzed neural activity during a fully crossed task varying hand (left, right), action type, and movement direction. We recorded 421 units in motor cortex (MC) and 326 in superior parietal lobule (SPL) from N1, and 441 and 479 units from two nearby MC regions in N2 (a more medial, posterior site (MCM) and a more lateral, anterior site (MCL)), along with 532 in SPL. Single-unit analyses revealed format-specific tuning in motor cortex. In N1, 70% of MC units, and in N2, 48% of MCM and 67.9% of MCL units responded only during intention, with

fewer than 34% per area active during observation or both. In contrast, SPL showed robust cross-format encoding, with 48.1% of units in N1 and 36.3% in N2 responsive in both formats. Linear model analysis confirmed a higher proportion of shared models in SPL, with shared action tuning most common (27.7%), in contrast to the predominance of single-format or idiosyncratic models in motor cortex (46.6%). At the population level, representational similarity analysis revealed strong cross-format correlations in SPL across action (R^2 = 0.59-0.79), hand (0.63-0.78), and direction (0.63-0.79). Motor cortex showed only partial or feature-specific overlap (e.g., MC/N1 rotation: R^2 = 0.31; MCM/N2 right hand: R^2 = 0.71) or none in MCL/N2 (R^2 < 0.12). Time-resolved cross-format decoding confirmed these patterns: SPL decoded action above 75% bidirectionally, while MC and MCM showed asymmetric generalization, limited to the observation-to-intention direction (MCM/N2 hand: 88.2%; MC/N1 action: 62.5%). MCL showed no generalization. PCA and Procrustes analysis revealed that only SPL supported shared low-dimensional geometry across formats (Procrustes distance d < 0.1), with partial overlap in MC (rotation) and MCM (right hand), and none in MCL. These findings show that at the single-unit level, SPL supports consistent, format-invariant encoding, while motor cortex is more format-dependent. At the population level, three representational geometries emerge: SPL supports format-general codes; MCM shows conditional overlap linked to intention tuning; and MCL remains format-specific.

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Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

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Program #/Poster #: PSTR125.02/Q13

Topic: F.05. Brain-Machine Interface

Support: NIH NEI UG1EY032039
T&C Chen Brain-Machine Interface Center
James G. Boswell Foundation

Title: Multi-phasic neural population dynamics during human intracortical BMI control

Authors: *F. YIN[1], C. GUAN[1], T. AFLALO[1], J. GAMEZ[1], K. PEJSA[1], E. R. ROSARIO[2], C. LIU[3], A. BARI[4], R. A. ANDERSEN[1];
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Abstract: The autonomous dynamical systems hypothesis (aDSH) posits that the motor cortex (MC) functions as an intrinsic pattern generator: once preparatory activity establishes an initial neural state, the ensuing neural trajectory unfolds according to fixed internal dynamics with

minimal influence from incoming sensory signals. This framework has been comprehensively demonstrated in reaching experiments with motor-intact non-human primates. In contrast, intracortical brain-machine interface (BMI) control in tetraplegic participants is guided solely by vision and lacks proprioceptive feedback, offering a cleaner test environment. If aDSH is correct, neural dynamics during BMI control should match the behavior of those reported in able-bodied reaching despite the absence of proprioceptive feedback. Here we present evidence inconsistent with aDSH. First, we show discrepancies in neural population dynamics across trials initialized in the same manner, which cannot be explained unless the MC accounts for inputs during movements. Second, we demonstrate that switching dynamical systems can more effectively capture neural population dynamics.
We recorded single-unit activity from two tetraplegic human participants implanted with intracortical NeuroPort Arrays as part of a clinical trial. Participant 1 was implanted with one array in the hand knob area of the left MC and one in the left posterior parietal cortex (PPC). Participant 2 was implanted with two arrays in the hand knob area of the left MC and two in the left PPC. Only data from their motor cortices were used for this study.
We utilized two variations of visually guided cursor BMI tasks, based on the center-out task: a ballistic-sustained version, where the decoder gain varied by trial, and a near-far version, where the target distance varied by trial. We found that the number of neurons tuned to target directions differs significantly across reach conditions in the latter phase of the trial but not in the beginning. We modeled aDSH with linear dynamical systems (LDS). LDS fits similar trajectories to reaches of different conditions at the beginning of ballistic-sustained trials, but the trajectories diverge as trials progress. Near-far trials produced similar outcomes. Furthermore, we found that recurrent switching linear dynamical systems (rSLDS) capture the multi-phasic nature of neural population dynamics during movements. Since visual feedback is the only form of external stimulus perceived by the participants, our results suggest that task-relevant inputs from beyond the MC influence MC dynamics during movements, creating discrepancies that vary over time across different task conditions.

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Poster

PSTR125: BMI Movement, Cognition, and Perception

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Program #/Poster #: PSTR125.03/Q14

Topic: F.05. Brain-Machine Interface

Support: UG1EY032039
Tianqiao and Chrissy Chen Brain-Machine Interface Center
Boswell Foundation

Title: Distinct Motor Representations of Facial Expressions in Human Posterior Parietal and Motor Cortices

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Abstract: Facial expression encoding in the human cortex is a central component of social communication. Functional imaging studies have implicated distributed cortical regions—including the superior temporal sulcus, fusiform area, and prefrontal cortex—in face perception. In contrast, motor and parietal cortices have been associated with the generation and control of facial expressions, as described by Bleichner et al. (J. Neural Eng., 2015). Recent intracranial recordings in the ventral motor cortex have provided finer-grained evidence of encoding the spatial displacement of facial features—such as lateral mouth movement—and shape-related changes, including mouth opening or smiling, as described by Kern et al. (Commun. Biol., 2019). However, the encoding of individual facial features such as mouth-shape has not been systematically examined at the level of single-neuron population in the posterior parietal cortex in human brain. To study this, we recorded single-unit activity from the posterior parietal cortex (PPC) and motor cortex (MC) of two tetraplegic participants. As part of brain-machine clinical trials, participants were implanted with two NeuroPort Arrays. Participant N1 had one array in the superior parietal lobule (SPL) of the PPC and one array in the MC, located close to the hand knob. Participant N2 had two arrays implanted in the PPC-located in the supramarginal gyrus (SMG) and SPL—and two arrays implanted in MC, also near the hand knob. In this study, participants viewed images of mouth shapes during the cue phase. Following a delay period, a signal prompted them to produce the corresponding mouth shape expression. Using a linear discriminant analysis (LDA) on the population neural activity, we found robust and differentiable activation patterns in PPC for each mouth shape during both cue and go production phases. In contrast, the MC showed activation patterns only during the go production phase. Importantly, PPC regions showed discriminable neural responses across both phases suggesting a shared representational substrate that supports both the planning and production of facial expressions. Furthermore, real-time decoding of neural activity reliably classified mouth shapes, underscoring the potential of these signals for affective communication in future brain-computer interfaces (BCIs). These findings provide direct evidence that both PPC and MC contribute to the representation of mouth shape—underpinning the neural basis of facial expression.

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Poster

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Topic: F.05. Brain-Machine Interface

Support: NIH Grant 1R01NS123663-01
Della Martin Fellowship

Title: Decoding motor and value information through a functional ultrasound-based BCI

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Abstract: We are investigating a new approach for brain-machine interfaces (BMIs) that uses functional ultrasound (fUS) to indirectly image neural activity by capturing hemodynamic signals at a high spatiotemporal resolution (100µm; 100ms). fUS imaging is minimally invasive because the probe sits on the dura outside of the brain, which may confer greater long-term stability and higher safety for chronic use. Additionally, in contrast to electrode recordings that only offer a local signal around each contact point, fUS imaging offers a wide and deep field of view and is a promising method for studying the distribution of neural activity across networks at the mesoscopic scale. Our group previously showed we could decode saccade direction and amplitude in a center-out task through fUS imaging of posterior parietal cortex (PPC) in a macaque model, establishing the feasibility of a fUS-based motor BMI. This work was based on planar fUS (which acquires 2D images of a slice of cortex) of the lateral intraparietal area (LIP), which plays a critical role in planning eye movements. We have recently developed volumetric fUS imaging using a row-column array probe, which represents a step change in the amount of neural activity we can simultaneously capture. Our preliminary results suggest volumetric fUS permits higher decoding accuracy of movement direction by exploiting the functional organization of saccade direction in LIP along three dimensions instead of two. While most BMI research focuses on motor restoration, there is mounting interest in developing BMIs to aid patients afflicted with neuropsychiatric disorders (for instance anhedonia, the inability to experience pleasure). Unlike motor applications, these BMIs would monitor neural activity for information related to mood and cognitive state. Numerous electrophysiological experiments have shown that PPC activity contains value- and motivation-related activity. To manipulate motivation, we modified our task to include variable target desirability. Some targets would yield higher juice rewards than others, increasing the target value and the motivation of the animal on a trial-by-trial basis. We were able to decode value and saccade direction simultaneously, and found that whereas information about direction was localized to LIP, the value signal appeared as a broad rise in activity across PPC. This demonstration of cognitive information decoding with fUS imaging suggests that the range of fUS-BMI applications may be broadened to include the treatment of debilitating neuropsychiatric disorders.

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Poster

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Topic: F.05. Brain-Machine Interface

Support: Tianqiao and Chrissy Chen Brain-machine Interface Center, Caltech
Merkin Institute of Translational Research, Caltech

Title: Functional ultrasound neuroimaging through a human cranial window for mapping and decoding of movement parameters in primary motor cortex

Authors: *L. J. LIN[1,6], T. CALLIER[2], C. LIU[7,2,8,9], M. G. SHAPIRO[3,4,10], R. A. ANDERSEN[2,5];
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Abstract: Brain machine interfaces (BMIs) can help patients with disabilities achieve greater independence by using their thoughts to control assistive devices. However, they commonly require highly invasive brain surgery for electrode implantation while conventional non-invasive imaging techniques like fMRI and EEG lack sufficient spatial resolution for high-bandwidth BMI use. Functional ultrasound (fUS) is a unique neuroimaging technique that balances these tradeoffs and can image epidurally with high sensitivity, high spatial resolution, and large field of view, demonstrating potential for use in less invasive BMIs. Previous studies demonstrated that fUS can be used to decode movement intention in non-human primates and task state through a polymeric acoustic skull window in a human patient - the first steps toward enabling a minimally invasive fUS BMI. Preliminary work has demonstrated that fUS is able to map and decode effector state across different body parts, including intralimb movement. In this study, we show that fUS can further be used to map movement direction information from primary motor cortex (M1) in a human participant with an acoustic window implant, demonstrating the growing applications of fUS for BMIs.

Experiments were performed on a human participant who had previously undergone a hemicraniectomy procedure and polymeric skull reconstruction including an acoustic window. The participant was asked to perform a center out target tracking task in 8 directions (0°, 45°, 90°, 135°, 180°, 225°, 270°, 315°) using a trackpad in which they followed a moving target to a set endpoint and back to the center while we acquired fUS data from the left M1.

Using fUS, we were able to identify activity correlated to subsequent movements toward the target and back to center. Based on this information, we then identified maps of significant task-correlated activity for each of the 8 movement directions in M1, in which activity effect size increased as the target angle approached 90°.

This work demonstrates that fUS can be used to map movement direction information and potentially detect directional preference in the motor cortex in a human subject with an acoustic window implant and presents significant progress in the development of a fUS-based BMI for decoding higher-level functions in humans.

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Poster

PSTR125: BMI Movement, Cognition, and Perception

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Topic: F.05. Brain-Machine Interface

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T&C Chen Brain-machine Interface Center
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Title: Spatial integration of intracortical microstimulation-elicited artificial sensation and natural vision

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Abstract: Intracortical microstimulation (ICMS) of primary somatosensory cortex (S1) evokes tactile percepts in humans. Consistent with S1's somatotopic organization, reported locations (projected fields, PFs) associated with these percepts depend on the stimulating electrode's cortical location. Here we investigate the effect of spatial visual context on ICMS-evoked PFs in three human subjects with cervical spinal cord injury. Previous studies have characterized the temporal binding window between ICMS and vision, and explored how visual cues can guide ICMS-parameter design. Understanding the spatial aspects of this integration is critical for developing sensory neuroprostheses that combine artificial touch with natural sensory feedback.
Three human subjects were implanted (years 2016, 2022, 2024) with two NeuroPort microelectrode arrays each in S1. Subjects had additional arrays implanted in posterior parietal, primary motor (P3/P2), pre-motor (P2/P1), and pre-frontal (P3) areas. Neural recordings were obtained from all implanted arrays. Single-channel ICMS was delivered via 35 (P3/P2) or 12 channels (P1) on one of the S1 arrays. ICMS parameters were fixed at 100 μA amplitude, 300 Hz frequency for a duration of 250 milliseconds.
Subjects performed trials inside a virtual reality environment depicting a first-person view of the palmar side of the right hand (P3/P2) or anterior surface of the right arm (P1). In 10 sessions per subject, baseline (BL), visual (V), and catch trials were interleaved. In BL trials, ICMS was delivered alone; in V trials, ICMS coincided with one of three white-sphere stimuli projected onto locations selected from each subject's prior PF map (P3: index and middle fingertips, index

middle phalanx; P2: index fingertip, proximal index and thumb phalanxes; P1: forearm, antecubital fossa, biceps). In catch trials, ICMS was withheld. After each trial, subjects reported perceived PFs on a hand-arm grid.
We observed changes in ICMS PFs when the ICMS was paired with a visual stimulus. Integrated percepts tended to shift toward the visual cue location. These shifts were consistent across most channels, stimuli, sessions, and subjects. Additionally, V trials elicited PFs not seen in BL trials, indicating novel percept locations driven by vision. These results show that the location of ICMS-evoked touch is strongly modulated by co-occurring vision, highlighting the need to consider multisensory context when designing future sensory neuroprostheses.

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Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.07/R2

Topic: F.05. Brain-Machine Interface

Support: Boswell Foundation
T&C Chen Brain-machine Interface Center
NIH/NINDS Grant U01NS098975
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Neilsen Postdoctoral Fellowship Research Grant 731621

Title: Can neurons sing? A participant-centered study of neuronal tones

Authors: *J. BUCKWALTER[1,2], S. S. DARCY[3], D. A. BJANES[2], K. PEJSA[2], B. LEE[4], C. LIU[4], R. A. ANDERSEN[5];
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Abstract: This presents a participant-centered application of intracortical brain-computer interfaces (BCI) in a 68-year-old C6-7 tetraplegic who has been implanted for 17 months with six Utah arrays. Studies on implanted BCI's often prioritize restoration of functional deficits. This investigates the psychological effects of creative expression from participant driven BCI use. Motivated by an interest in music, the participant and researchers developed a real-time tone generation feedback system responsive to firing rates of neurons. Neural spikes from motor and sensory neurons are mapped to dynamic tones. This allows the participant to "play" his neurons through sensory stimulation, physical and imagined movements.
The system assigns each channel a unique musical tone and starting pitch. Baseline measurement establishes the average firing rate for a channel. In real-time, the system monitors differences between the observed firing rate and the average. If the rate is greater, the pitch of the tone rises;

if it fires less, the pitch lowers. Pitch changes are smoothed for a continuous sound.
This allows the participant to generate and modulate sounds based on the activity of neurons, creating biologically based, personally expressive music. The team has generated rhythmic and percussive patterns, with plans to layer harmonic tones from multiple channels. While volitional control has not been found for all channels tested, the participant reports an increased sense of agency, increased awareness of neural modulation ability, and an emotional connection with the music when control is established. This suggests aesthetic feedback develops a sense of engagement and ownership amongst BCI participants.
Prior work indicated volitional control of neurons is responsive to generated feedback (Fetz, 2007, Moritz, et al., 2008). Music is an effective feedback mechanism for non-invasive BCI, such as enhancing emotional synchrony between participants (Ceccato, et al., 2023). Our data suggest participant-controlled musical generation is an effective feedback modality for intracortical BCI's. Further, using music has implications for participant satisfaction, motivation, neuroplasticity, and long-term adoption of the technology. By centering on participant creativity and identity, BCI's may exceed the goals of functional restoration to include self-expression, opening new avenues of both neuroscientific and artistic exploration.

Disclosures: J. Buckwalter: None. **S.S. Darcy:** None. **D.A. Bjanes:** A. Employment/Salary (full or part-time): Caltech. **K. Pejsa:** A. Employment/Salary (full or part-time): Caltech. **B. Lee:** A. Employment/Salary (full or part-time): USC. **C. Liu:** A. Employment/Salary (full or part-time): USC. **R.A. Andersen:** A. Employment/Salary (full or part-time): Caltech.

Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.08/R3

Topic: F.05. Brain-Machine Interface

Support: Boswell Foundation
T&C Chen Brain-machine Interface Center
NIH/NINDS Grant U01NS098975
NIH/NINDS Grant U01NS123127

Title: Investigating Touch Perception with Near-Threshold Stimulation During Human Single-Neuron Recordings

Authors: *B. LIU[1], D. A. BJANES[1], L. SHE[1], K. PEJSA[1], B. LEE[2], C. LIU[2], R. A. ANDERSEN[1];
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Abstract: Touch is a foundational sensory modality that underlies dexterous motor control and adaptive interaction with the environment. The primary somatosensory cortex (S1) and posterior parietal cortex (PPC) are central to somatosensory processing, yet their distinct contributions to

the emergence of conscious tactile perception in the human brain remain unclear.
To examine the contributions of S1 and PPC to somatosensory perception, we conducted a near-threshold vibrotactile study in a clinical trial involving three tetraplegic participants. Vibrotactile thresholds were determined using a one-up three-down adaptive staircase procedure. Mechanical stimuli were delivered to discrete sensate regions on the hand and arm. Simultaneous single-neuron recordings were obtained from chronically implanted Utah arrays targeting the somatosensory cortex, supramarginal gyrus (SMG), anterior intraparietal area (AIP), as well as motor and prefrontal cortices. To assess sensory encoding, a vibrotactile ramping task was employed to probe neuronal responses across a range of stimulus amplitudes.
Single-neuron recordings in humans reveal widespread somatosensory responses. Stimulation amplitude was encoded through modulated firing rates and we observed a clear enhancement of global firing as stimulus amplitude increases in the ramping task. We found the neural correlate of perception in both the PPC and S1, with PPC exhibiting significantly greater choice probability than S1 in distinguishing felt from not-felt conditions across vibrotactile trials during the vibrotactile near-threshold task. In catch trials where no vibrotactile stimulation was delivered, we also found that PPC exhibited greater choice probability than S1 in differentiating felt from not-felt conditions, suggesting PPC exceeds S1 in reflecting sensory perception. For the ramping task, S1 showed a stronger preference for physical input amplitude over perceptual outcome compared to PPC, and S1 also responded with faster latencies to supra-threshold inputs. These findings provide direct single-neuron evidence for the distinct and complementary roles of the PPC and S1 in human somatosensory processing. By uncovering the neural substrates underlying conscious tactile perception, this study reveals that PPC is more involved with the conscious percept, while S1 is more closely linked to the physical stimulus. These findings not only advance our understanding of somatosensory encoding but also offers critical insights for the development of neuroprosthetic technologies aimed at restoring somatosensation through artificial touch.

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Poster

PSTR125: BMI Movement, Cognition, and Perception

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Topic: F.05. Brain-Machine Interface

Support: NIH NINDS U01NS123127
Boswell Foundation
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Title: Functionality of the posterior parietal and motor cortex regions in the cortical grasping network in tetraplegic humans

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Abstract: The act of grasping requires creating a goal, planning hand geometry, and executing the movement. To accomplish these tasks, we rely on the sensorimotor processing capabilities of the brain. The posterior parietal cortex (PPC) is involved in early stages of movement planning, with specific sub-regions playing crucial roles in grasp and object processing. The cortical grasping network (CGN) includes the supramarginal gyrus (SMG) and anterior intraparietal cortex (AIP) of PPC and the primary motor cortex (M1). Here, we use human electrophysiology to reveal how grasps and objects are encoded in SMG, AIP, and M1. Two tetraplegic participants were implanted with microelectrode arrays, P1 in SMG, AIP, and M1; P2 in SMG. Single-unit neural activity was recorded during a motor imagery task, where participants were asked to imagine holding unique objects with a given hand position. Two variations of this task were performed. Task 1 used static images of 4 grasp types (Lateral (L), MediumWrap (MW), PalmarPinch (PP), Sphere3Finger (S3F)), each paired with a unique object. Small and large variations of each unique object were shown, in the smallest and largest feasible apertures. Participants were cued to imagine grabbing a small or large object by images which showed either: grasp alone, object alone, or the grasp holding the object. Task 2 disentangled the pairing between each grasp type and unique object, such that participants imagined grasping each object, with each grasp type. We identified the different functions of the CGN throughout Planning and Action phases of both tasks. Information about grasp type is seen in both PPC and M1 during Planning and strongly in M1 during Action. Size differences in hand aperture can be classified in SMG during Planning, and M1 during Action. Encoding of the object type is seen strongly in PPC during Planning, and very little in M1. Additionally, we see the size of the S3F grasp strongly encoded in all brain regions, MW in SMG, and L in M1. This implies that these regions encode unique features of grasps, such as number of effectors in SMG or thumb involvement in M1. Taken altogether, we see SMG demonstrating partial mixed selectivity by encoding grasp, size, and object during the Planning phase, while AIP encodes object type at the highest rate during Planning, and M1 appears to encode information relevant to hand shape (grasp and size) during Action. Each brain region encodes distinct features of grasp and hand aperture. These findings support the literature of these regions proposed roles and provide deeper understanding of the CGN.

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Poster

PSTR125: BMI Movement, Cognition, and Perception

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Program #/Poster #: PSTR125.10/R5

Topic: F.05. Brain-Machine Interface

Support: NIH Grant R01 NS109257

Title: Bridging BCI tasks: a proposed adaptive-difficulty assessment to facilitate standardized cross-study comparisons of cursor control performance

Authors: *J. D. CARDUCCI[1], Z. C. DANZIGER[1,2];
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Abstract: Intracortical brain-computer interfaces (iBCI) for point-and-click cursor control are typically evaluated using target-selection tasks tailored to address an individual study's question or designed to maximize performance on a system's specialized user interface. While sensible, this approach makes pooling data across studies for rigorous comparisons between design choices (like neural decoders) very difficult; it is unclear how to distinguish if differences in user ability are due to iBCI design or details of the task itself that make control more or less difficult. Data pooling would be especially useful for iBCI design, where invasive implants result in fewer subjects.

To address this, we propose a new cursor control task that has enough dynamic range to evaluate systems with simple, low-performing decoders up to able-bodied control of a standard computer mouse on the same scale without attenuation effects, and that is short enough to be unobtrusively appended to ongoing BCI studies. If adopted, this could facilitate pooling data across a wide range of cursor control studies.

The key aspects of the task are that it 1) features an adaptive difficulty scheduler that scales target size and allotted time based on user performance to provide dynamic range without floor or ceiling effects, 2) simply requires a 2D position state from a cursor decoder (with optional clicks/holds), 3) runs for less than 10 minutes, and 4) does not need other main protocol details. These aspects enable the benchmark to help pool results better compared to other tasks like center-out reaching and Webgrid.

We validate this task by implementing an example protocol beforehand on healthy participants. We emulate neural firings for decoding by processing finger motions from a 19-dimensional data glove through a validated non-invasive human-in-the-loop iBCI model. One of 3 decoder types (velocity Kalman, ReFIT Kalman, and Discrete Direction Selection), with known performance differences in prior literature, were assigned to each participant in a between-subjects design. We mimicked typical decoder familiarization by having participants reach targets for 40 minutes before the benchmark task. In preliminary 1-way ANOVA findings of $N = 12$ (age: 24.8 ± 5.4, 4M/8F), the benchmark scores the BCI decoders differently ($p = 0.003$), confirming previous findings. The benchmark also distinctly scores computer mouse and trackpad performance on the same scale as the BCI decoders ($p < 0.001$) without ceiling effects. Therefore, this benchmark task is a promising tool to help researchers share performance data that will help speed up proper decoder design and selection through fair comparison.

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Poster

PSTR125: BMI Movement, Cognition, and Perception

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Program #/Poster #: PSTR125.11/R6

Topic: F.05. Brain-Machine Interface

Support: NIH Grant R01 NS109257

Title: Fewer Choices, Better Control? Comparing Discrete and Continuous Cursor Decoders

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Abstract: *Objective.* Traditional invasive brain-computer interface (iBCI) decoders translate neural activity into continuously varying velocity commands, allowing selection from an infinite set of 2D movement directions. In prior work, we demonstrated that restricting decoders to select from a limited set of discrete velocity commands significantly improves cursor control performance. Our discrete decoder—Discrete Direction Selection (DDS)—operates by choosing from a predefined set of velocities rather than predicting continuous commands. Using a human-in-the-loop model with 48 participants across four sessions each, we showed that DDS consistently outperformed standard continuous decoders (like the ReFIT Kalman filter) in a Center-Out task. This result was replicated in a monkey iBCI experiment where the same monkey used both DDS and a traditional continuous decoder. To explore why DDS outperforms continuous decoders, we tested whether post-hoc discretization of continuous decoder outputs using a discrete filter could replicate DDS's benefits. *Approach.* We compared DDS with two discretized variants of continuous decoders: Discrete velocity Kalman Filter (DvKF) and Discrete DR-A (DDR-A)**.** These were produced by applying discrete filters to the outputs of vKF and DR-A (an affine map from neural activity to velocity). In a Center-Out task, we plan to use a between-subjects design with 36 participants per group (DDS, DvKF, DDR-A). Our goals are to determine: (1) if discrete-filtered continuous decoders outperform their native forms, and (2) whether these filtered decoders approach DDS's performance. *Results.* DvKF and DDR-A achieved 52% and 65% mean targets hit, respectively, compared to 17% and 43% by their continuous counterparts vKF and DR-A. However, DDS still outperformed these discrete decoders with a mean target hit rate of 93% (N per group <= 9). DvKF and DDR-A outperformed their continuous counterparts and showed similar performance to DDS on multiple metrics. Discretized decoders reached targets faster and produced cursor trajectories similar to DDS. These findings suggest that discrete filtering enhances continuous decoder performance. *Significance.* These findings highlight discrete filtering as a viable and practical method for improving continuous decoders. Nonetheless, DDS maintains superior performance, likely due to its native classification-based architecture that better decodes neural firing patterns. This work supports discrete decoding as a compelling strategy for enhancing the accuracy and reliability of iBCI control systems, while sacrificing fine-grained precision.

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Poster

PSTR125: BMI Movement, Cognition, and Perception

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Program #/Poster #: PSTR125.12/Web Only

Topic: F.05. Brain-Machine Interface

Support: NIDCD R01 DC016343-01A1
NCATS, Selecting and evaluating a brain computer interface for communication for individuals with severe dystonic cerebral palsy

Title: Kinesthetic motor imagery strategies used by participants during a BCI speech task

Authors: *C. KOSIROG[1], J. S. BRUMBERG[2];
[1]Speech Language Hearing Sci., [2]Speech-Language-Hearing, Univ. of Kansas, Lawrence, KS

Abstract: The use of brain computer interfacing (BCI) to access augmentative and alternative communication devices offers hope to people who suffer from progressive neurological diseases such as ALS or Parkinson's Disease. Utilizing motor imagery to control BCIs with imagined (covert) movements has been established (Brumberg et al., 2018, Blankertz et al., 2007) but little is known about individual, internal kinesthetic strategies used for motor imagery (MI).In this study we analyze MI strategies used by eighteen adult participants (21-36 years, m=27.5 years; 14 female; 4 left-handed) across 3 sessions collected during a BCI speech study. All participants are native English speakers with no reported speech, language or hearing deficits or known neurological disorders. Participants completed three EEG-based training sessions to learn to create target vowels by controlling a formant speech synthesizer. The BCI was controlled via upper and lower motor imagery tasks in one of three ways: 1) left-hand for UW /hud/, 2) right-hand for AA /hod/, and 3) bilateral feet for IY /hid/. Participants were randomly placed in one of three feedback groups to make corrections of the vowel attempt in real time: visual only, auditory only, and multimodal auditory and visual. EEG data was collected via a 64-channel acquisition system (g.HIAmp, g.tec) using 64 active electrodes, two earlobe electrodes designated as reference and one stimulus trigger channel for alignment of recorded signals. EEG signals were sampled at 256 Hz with a notch filter from 58-62 Hz to eliminate powerline artifact (see Brumberg et al., 2018 for full procedures).After each session participants categorized MI strategies they used for each trial into one of four categories based on classifications currently in the literature: novel task (Halder et al., 2011), familiar task (Olsson et al., 2008), simple task (Kuhtz-Buschbeck et al., 2013), or resistance training (Yao et al., 2013). They also reported what internal kinesthetic motor imagery they employed to assist them with completing each trial such as playing the piano, petting a cat, etc. Overall, we found participants were biased toward using familiar imagery tasks and used novel imagery tasks the least. Following this initial analysis, we

are examining data to determine if certain types of MI were most associated with feedback modalities and/or performance. Results will inform teaching and training of BCI users and fill a current gap in the literature on control measures for MI. Understanding of the impact of MI strategy on eliciting sensorimotor rhythms has the potential to provide critical information for increasing early performance.

Disclosures: C. Kosirog: None. **J.S. Brumberg:** None.

Poster

PSTR125: BMI Movement, Cognition, and Perception

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Program #/Poster #: PSTR125.13/R7

Topic: F.05. Brain-Machine Interface

Support: NIH NINDS R35NS122333

Title: Human sensorimotor cortex encodes interaction forces during active texture exploration

Authors: *N. DARABI[1], A. M. EMONDS[1], C. RAMAN[1], S. E. PALMER[2], A. R. SOBINOV[1]; [2]Organismal Biol. and Anat., [1]Univ. of Chicago, Chicago, IL

Abstract: Humans explore textures by actively moving their fingers across surfaces and modulating applied forces. Signals from skin mechanoreceptors are transmitted to the somatosensory cortex (SC), shaping texture perception and guiding the changes in exploration strategy. However, it remains unclear how and where in the cortex the perception of texture features is formed, important for designing brain-computer interface robotic arms that allow realistic tactile sensation. To investigate this, we worked with a participant with a spinal cord injury and multielectrode implants in both motor (MC) and sensory cortices. Because the participant still has limited arm and hand mobility as well as residual sensation in parts of the hand, they were able to use their index finger to explore the textures - hidden from view - and rate the perceived roughness, slipperiness, or hardness. The textures were mounted on a six-dimensional force sensor, and the finger movements were recorded using a camera focused on the texture. Each texture was presented three times in each perceptual task. We trained dynamic recurrent neural networks (long short-term memory) to predict the time-varying forces or the participant's perceptual ratings from neural activity in MC or SC during active exploration. Models were evaluated on held-out trials and compared to the performance on shuffled trials, which combined the neural activity of one trial with rating or forces from another trial. We found that normal forces could be predicted with high accuracy from both MC and SC across all perceptual tasks. In contrast, we could not reliably extract information about the perceptual rating from the neural activity. These findings indicate that sensorimotor cortex robustly encodes volitional forces during natural texture exploration, while perceptual judgments likely arise in other cortical areas.

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Poster

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TUM Innovation Network for Neurotechnology in Mental Health
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Title: Human intracortical neural responses to actively controlled and passively observed cursor movement errors

Authors: *V. DIMOVA-EDELEVA[1], G. ALKAN[2], I. XYGONAKIS[1], J. GEMPT[4,3], B. MEYER[3], S. HADDADIN[5], S. N. JACOB[2], M. ZAVAGLIA[1];
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Abstract: Intracortical Brain-Computer Interfaces (iBCI) are developed to assist patients with motor and speech impairments. Joint control between a human with a BCI and a computer assistant is often used to increase precision; however, discrepancies between the patient's intention and executed actions may occur. Many non-invasive and invasive studies have demonstrated that the human brain responds to errors. Importantly, EEG studies have shown that neural signatures discriminate between i) **interface errors** made by misinterpretation of user's active command, and ii) **autonomous assistant errors** that are only passively observed by the user [1]. Here, we used recordings from chronically implanted intracortical microelectrode arrays (64 channels per brain region) to provide deeper insights into these error-related potentials (ErrPs). A 51-year-old woman (with a large left-hemispheric ischemic stroke) collaborated with an autonomous assistant to follow a trajectory in a grid world game [1]. To reflect the concept of joint control, the cursor movements were in parts controlled by the user with a keyboard, and otherwise by the assistant. We report data from one recording session with 1125 cursor movements, from which 21% were **interface errors** (i.e., movements toward a direction other than the keyboard user input) and **assistant errors** (i.e., deviations from the trajectory). We analyzed local field potentials (LFPs, low-pass filtered at 90 Hz) cursor movement responses from the right inferior and middle frontal gyrus (IFG, MFG) and supramarginal gyrus (SMG)

using ANOVAs, and trained an SVM to discriminate between i) correct movements, ii) interface errors, and iii) autonomous assistant errors. Around 200 ms after cursor movement, we observed significant differences in the LFP between errors and correct movements in IFG ($p = 6.42e-53$) and SMG ($p = 1.29e-10$). Interestingly, in MFG, LFPs were different ($p = 0.00014$) only for interface errors. These ErrPs followed the responses in IFG and SMG, occurring around 250 ms and 440 ms after cursor movement. The SVM classification was significantly above chance level, reaching accuracy above 55%. Our results suggest that ErrPs related to misinterpreted user command and faulty autonomous support can be intracortically recorded with high temporal and spatial resolution. We believe that these preliminary results warrant further investigations into the suitability of these responses for joint control iBCI.
[1] Dimova-Edeleva, V., Ehrlich, S. K., & Cheng, G. (2022). Brain computer interface to distinguish between self and other related errors in human agent collaboration. Sci Rep, 12(1), 20764

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Poster

PSTR125: BMI Movement, Cognition, and Perception

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Program #/Poster #: PSTR125.15/R9

Topic: F.05. Brain-Machine Interface

Title: Improvement of motor imagery classification using deep residual convolutional neural networks for Brain-Computer Interface

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Abstract: Advances in deep learning have greatly improved brain-computer interface (BCI) decoding techniques. Visual decoding in functional magnetic resonance imaging (fMRI) has become more sophisticated. Auditory and electromyography (EMG) signals decoding have also advanced in local field potentials (LFP) and electrocorticogram (ECoG). Convolutional neural networks (CNNs) are often used in electroencephalography (EEG) to improve the classification accuracy of brain activity within the same subject. However, conventional EEG-based BCI studies have the following problem. Conventional BCI models are trained, validated, and tested using within-subject cross-validation on a small number of subjects. Therefore, their applicability to unknown subjects is uncertain, raising concerns about their practicality. In particular, classifying motor imagery rather than motor execution poses a significant challenge. To improve the practicality of the BCI prototype, this study developed and validated a generalization model, focusing on improving its suitability for unknown subjects. This study's generalization model consists of a multi-layered residual CNNs that takes an appropriately preprocessed EEG as input. The model was trained using a large dataset of over 100 subjects and

evaluated by cross-validation with cross-subjects to eliminate subject overlap and confirm its applicability to unknown subjects. Twenty participants from 105 participants were randomly assigned as test data. Five-fold cross-validation was performed on the remaining 85 participants data, and the model was evaluated by averaging the accuracy for the 20 participants test data. The constructed generalized model performed significantly better than the conventional open-source models for three tasks (mean = 83.54%, std = 0.291%). Significant differences were confirmed, with a considerable increase in performance from the accuracy of Shallow-ConvNet (mean = 74.99%, std = 0.936%) and Deep-ConvNet (mean = 76.55%, std = 0.106%) in the famous conventional open source software models. For these validations, we used electroencephalography (EEG) during rest and motor imagery tasks for left-hand and right-hand grasping. Additionally, Grad-CAM was used to visualize reasons for BCI classification and identify locations and timings of neural activity contributing to the classification of brain activity. This study supports the effectiveness of generalizing the model and inserting residual networks into the CNNs for BCI.

Disclosures: Y. Fujiwara: None.

Poster

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NSF Graduate Research Fellowship

Title: Toward recalibration-free intracortical decoders: Intracortical neural representation of finger movements in a nonhuman primate preserved over 400 days

Authors: *M. MENDER[1], H. TEMMAR[2], J. COSTELLO[1], M. WILLSEY[1];
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Abstract: Motor intracortical brain-computer interfaces (iBCIs) typically require daily calibration. To reduce this burden, decoding algorithms—which map neural activity to control signals—can be realigned across days or subjects. Latent Factor Analysis via Dynamical Systems (LFADS) has been previously used to identify neural dynamics that are consistent across many days and thus allows a static decoding of single effector movements (Karpowicz et al., 2025). We explored whether stable neural dynamics can be identified in neural activity during individuated finger movements enabling neural activity to be aligned to a stable representation across days. We also explored whether this representation could be inferred

without recalibration using only channel statistics.
Over 12 sessions spanning 427 calendar days in an nonhuman primate performing finger tasks, we recorded both finger movements (index and middle-ring-small groups) and intracortical activity from microelectrode arrays placed in the hand area of precentral gyrus. To determine whether a consistent latent representation exists, we trained a multiday LFADS model (mLFADS) with day-specific input and output layers for all sessions. The model revealed stable, movement-related latent factors across all 12 sessions/427 calendar days (correlation 0.8 ± 0.01 [S.E.M.]). These factors supported accurate decoding of finger velocities on prospective days using a static ridge regression decoder, with minimal decline in performance over time (−9.8e-5 corr/day; $p = 0.07$).
We then tested whether alignment could be automated without dedicated training on heldout sessions. We developed a static read-in network conditioned with day-specific channel means, termed Conditioned LFADS (cLFADS). Trained across all sessions, cLFADS and mLFADS were used to compute latent factors during validation trials and in 8 held-out sessions. Ridge regression predicted finger velocities from these factors. In held-in sessions, cLFADS achieved 0.68 ± 0.02 correlation, which was not significantly different from mLFADS ($p = 0.18$). On held-out days, cLFADS maintained high accuracy (corr = 0.517 ± 0.04), outperforming smoothed spikes by 29.3% ($p = 0.005$). Ongoing work includes quantifying effect size, improving generalization of mean-conditioning, and extending the approach to state-of-the-art decoders.
In summary, we demonstrate a stable latent representation of finger movements over 427 days using LFADS and introduce a pretrained decoding approach that may provide insights into reducing the reliance on daily recalibration.

Disclosures: M. Mender: None. **H. Temmar:** None. **J. Costello:** None. **M. Willsey:** None.

Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.17/R11

Topic: F.05. Brain-Machine Interface

Title: A complex-valued neural network to decode motor behavior from EEG recordings.

Authors: *G. A. MENDOZA FRANCO[1], X. SUN[1], G. AGARWAL[2];
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Abstract: How can behavior be decoded from oscillatory brain signals? Oscillatory signals, like those captured in electroencephalograms (EEGs), can carry information through patterns of phase and amplitude across electrodes. These patterns can be revealed by Hilbert transforming the signal, resulting in complex-valued signal representations. Our lab has developed a neural network, known as TIMBRE (Tracking Informative Multivariate Brain Rhythms Efficiently), capable of learning these behaviorally informative patterns from multi-channel brain wave

recordings (Agarwal et al., 2023). Unlike traditional models, TIMBRE learns complex-valued projections of multivariate signals and allows researchers to infer phase relationships. When applied to hippocampal local field potentials (LFPs) known as theta rhythms, TIMBRE outperformed Common Spatial Patterns (CSP), a common benchmark in oscillation decoding. While CSP is typically applied to real-valued signals (which we denote as rCSP), we have adapted the algorithm to function on complex-valued signals (cCSP).
This study asks how TIMBRE's superior performance relative to rCSP and cCSP generalizes to EEG recordings, from a motor imagery task (BCI Competition III dataset IVa, 100Hz sampling rate). Contrary to LFP performance expectations, we found that TIMBRE underperforms both CSP models on a per-sample basis (mean accuracy at 2 components per model=0.59 [TIMBRE], 0.65 [cCSP] 0.61 [rCSP]), see figure. We speculate that the differences between LFP and EEG, such as electrode density and reference schemes, differentially affect the performance of the algorithms. We are currently testing modifications of TIMBRE, including its initialization and regularization, with the goal of improving its performance for EEG signals. Nonetheless, our results speak to the utility of using complex-valued representations for decoding oscillations using CSP.

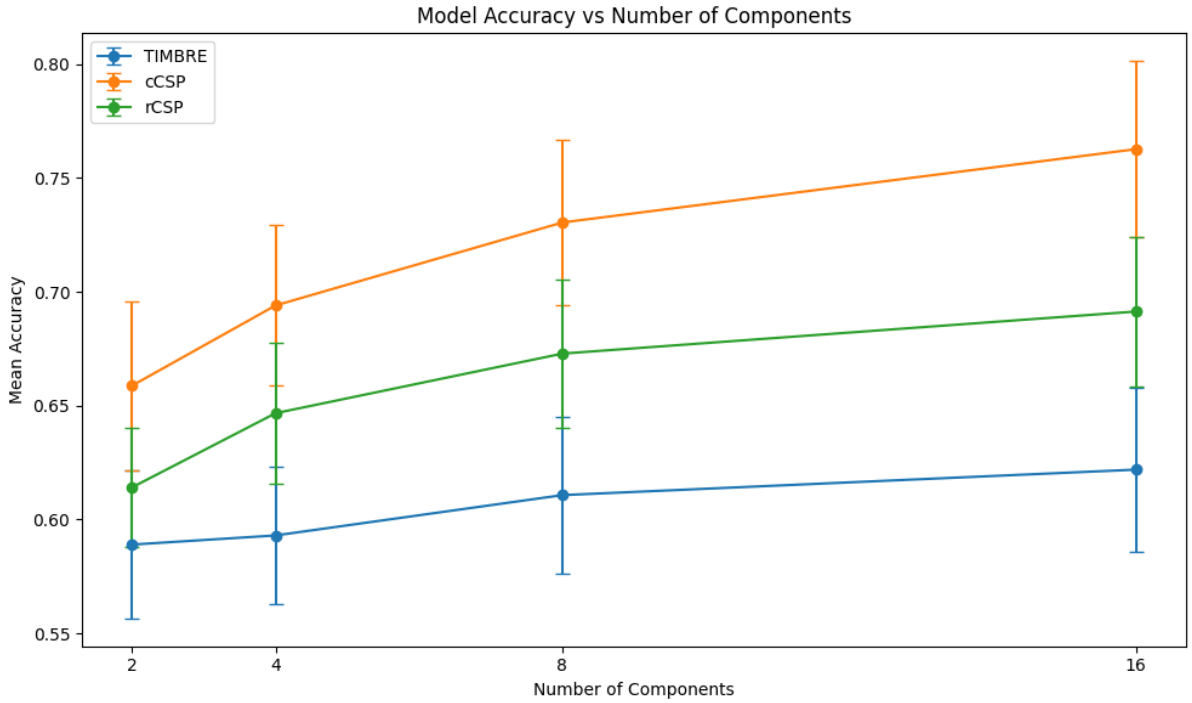


Figure. Comparison of mean accuracy across models against total number of components learned by each algorithm. Error bars indicate standard error across subjects (n=5).

Disclosures: G.A. Mendoza Franco: None. **X. Sun:** None. **G. Agarwal:** None.

Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.18/R12

Topic: F.05. Brain-Machine Interface

Title: Preferential Subspace Identification Extracts High Gamma Driven Latent Spaces That Are Highly Correlated With Movement Speed In Human M1 ECoG Recordings

Authors: *K. SARGUR[1], Q. QURESHI[2], P. BORGES[3], T. J. PISANO[3], B. WANG[1], B. I. RAPOPORT[4], B. PESARAN[3], I. CAJIGAS[3];
[1]Bioengineering, [3]Neurosurg., [2]Univ. of Pennsylvania, Philadelphia, PA; [4]Mount Sinai, New York, NY

Abstract: Decoding movement from high density electrocorticography (ECoG) arrays is essential to restore motor function in individuals with paralysis, however, high channel counts introduce computational costs that limit real time decoding. Algorithms that extract latent states from neural features are a promising avenue to reduce latency and increase accuracy. Specifically, preferential subspace identification (PSID) projects past neural activity onto future behavior to isolate latent states that drive movement. We aimed to identify the most informative ECoG channels and apply PSID to extract low dimensional latent dynamics that accurately mirror continuous finger speed.

We recorded 1024-channel ECoG signals (Layer 7, Precision Neuroscience) temporarily implanted over the hand-knob area of M1 in a single adult. They transitioned between 3 hand gestures, and index and pinky speed was derived from a capacitive glove (StretchSense Pro Fidelity, StretchSense). ECoG data was band passed into high gamma (100-200 Hz), gamma (65-100 Hz), beta (11-30 Hz), and local motor potential (<3.5 Hz) and band power was computed in 50ms windows. We selected 20 channels whose high gamma power had the highest Pearson correlation (r) with finger speeds. PSID was applied to extract latent states from those channels. To assess which feature drove performance, we shuffled each feature over time and recomputed PSID 50 times to measure the drop in r. We also compared PSID decoding performance to XGBoost and Support Vector Regression (SVR).

The first latent state negatively mirrored speed ($r = -0.33$). Permuting high gamma had the largest drop in r (median $\Delta r = -0.31$, $p = 5.6e\text{-}49$). PSID with just three latent states, achieved $r = 0.43$, and onset accuracy $a = 89\%$, outperforming XGBoost ($r = 0.37$, $a = 89\%$) and SVR ($r = 0.35$, $a = 81\%$).

High-gamma correlation enabled channel reduction without sacrificing performance. PSID yields a compact latent representation that accurately tracks continuous finger speed driven by high gamma and can support low latency, high accuracy decoding, advancing future neuroprosthetic control.

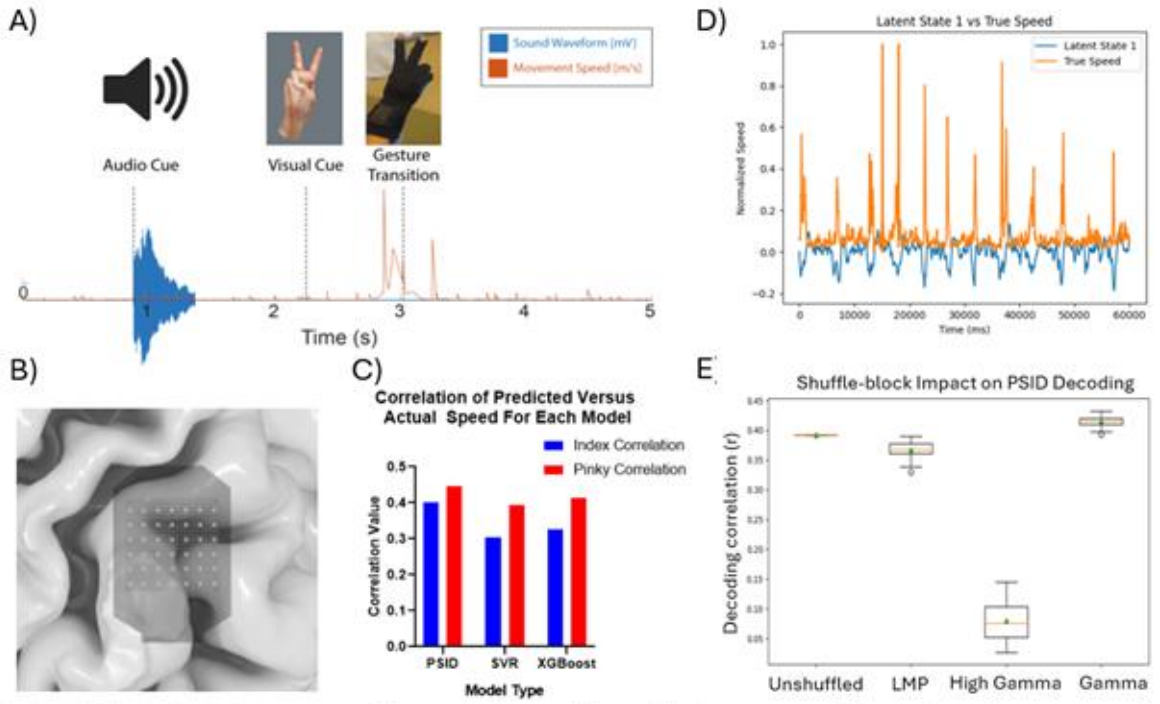


Fig 1. A) Single trial of gesture transition task, the participant first hears an audio cue, then the movement is prompted visually on a screen followed by actual movement. B) Array localization on M1 surface. C) Correlation values of index and pinky predicted vs actual speed for each model. D) Trace of first PSID latent state (blue) and true pinky speed (orange). E) Box plot of feature shuffling impact on average correlation over 50 trials

Disclosures: K. Sargur: None. **Q. Qureshi:** None. **P. Borges:** None. **T.J. Pisano:** None. **B. Wang:** None. **B.I. Rapoport:** A. Employment/Salary (full or part-time): Precision Neuroscience. **B. Pesaran:** None. **I. Cajigas:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Precision Neuroscience.

Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.19/R13

Topic: F.05. Brain-Machine Interface

Support: ”la Caixa” Foundation LCF/BQ/EU23/12010057
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NIH R01-NS129584
NSF NCS DRL 2124066
NSF NCS DRL 2123911

NIH R01-NS129098
NIH R01 NS105318

Title: Remembering a reach goal shapes neural population dynamics in motor cortex

Authors: *J. COURAS[1], E. R. OBY[3], A. MOTIWALA[4], B. M. YU[6], S. M. CHASE[5], A. P. BATISTA[2];
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Abstract: Neural population dynamics, i.e., the rules that govern the time evolution of neural activity, are a signature of neural computations. A key question is if storing the memory of a reach goal shapes the dynamical landscape of neural activity in the motor cortex or if neural activity time courses are simply a readout of upstream regions. In this study, we leverage a Brain-Computer Interface (BCI) to instruct a monkey to produce neural trajectories through the state space and interrogate the dynamical landscape set by the memory of a reach goal. While the monkey is remembering a reach goal, neural activity settles in a particular region in state space appropriate for the upcoming reach. By having the monkey acquiring BCI targets during the memory period of a memory-guided task, neural activity is traversing the state space while the monkey is holding a memory of a reach. We hypothesize that if the memory shapes dynamics, then neural activity time courses during BCI control should show a signature of that.
We implanted a rhesus monkey with 64-channel "Utah" multielectrode arrays (Blackrock, Inc) in the primary motor and dorsal premotor cortices. We trained the monkey to modulate the activity of ~50 neural units to control the cursor's velocity to acquire BCI targets during the memory period of a memory-guided task. Each trial starts with the instruction of a reach target, followed by a memory period in which the reach target is not present on the screen. Next, we present the monkey with a BCI cursor to acquire a BCI target. After BCI target acquisition the monkey either receives the go cue to execute the remembered reach or is presented with another BCI target. The monkey acquired up to 3 BCI targets before being cued to reach.
We extracted 10-dimensional neural states that capture the shared activity among neurons. We saw that the time-evolution of neural states under different memories converged to acquire a BCI target and then diverged to acquire the subsequent BCI target. We reasoned that this effect could be due to either different initial conditions set by the memories prior to BCI control or different dynamical landscapes. We subsampled neural states across memories that simultaneously satisfy two constraints: they correspond to similar cursor positions and they occupy a similar region in state space. After matching neural states across memories at a particular time, we interpret future differences in neural time courses to be due to differences in the dynamical landscape across memories. We observed a significant increase in decoding accuracy of the memory in future neural states, relative to current states. This suggests that motor memories shape the dynamical landscape in motor cortex.

Disclosures: J. Couras: None. **E.R. Oby:** None. **A. Motiwala:** None. **B.M. Yu:** None. **S.M. Chase:** None. **A.P. Batista:** None.

Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.20/R14

Topic: F.05. Brain-Machine Interface

Title: Motor cortex encoding of target specific and invariant information during brain-computer interface control

Authors: *C. M. TROMBLEY[1], J. E. DOWNEY[2], N. G. HATSOPOULOS[2];
[1]Committee on Computat. Neurosci., [2]Dept. of Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: Developing effective neural decoders for brain computer interface (BCI) applications has the potential to improve function in people with paralysis. However, traditional BCI decoding algorithms utilize neural activity that is both condition dependent and condition independent. It is relatively unknown the role condition independent neural activity plays in movement-related computations and therefore how it can be used during decoding for BCI applications. To this end, we investigate the role of condition independent and dependent neural activity in two partially paralyzed subjects with Utah microelectrode arrays chronically implanted in motor cortex. The two subjects (Subject C1 and Subject C2) performed a cursor control center-out task with 24 targets spanning 8 angles and 3 distance levels per direction. Demixed principal component analysis (dPCA) was used to separate the neural activity into condition independent, angle, distance, and angle-distance interaction components. We found that the condition independent component played a distinct role across subjects. For subject C1, the condition independent component accounted for 18% of the variance which suggests that a relatively large proportion of their motor cortical activity was invariant to task parameters. This subject had 22% of variance accounted for by distance, interaction at 33%, and angle at 27%. For Subject C2, the condition independent component accounted for 10% of the variance suggesting that most population activity was modulated by task specific information. For this subject, distance related variance was 54% of total variance, accounting for the largest proportion of variance followed by interaction at 13%, and angle at 23%,. Qualitatively, the condition independent component showed a peak during the preparatory period before reaching across both subjects. The distance component showed clear clustering for the three distances with maximal separation during the movement. Whereas the angle component shows more graded response that show maximal separation during the preparatory period that slowly converges during the movement. These results provide insight into how condition independent and dependent components play a role in movement related computation in motor cortex and their potential use in decoding.

Disclosures: C.M. Trombley: None. **J.E. Downey:** None. **N.G. Hatsopoulos:** F. Consulting Fees (e.g., advisory boards); Blackrock Microsystems.

Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.22/R16

Topic: F.05. Brain-Machine Interface

Support: Freunde der TUM
Cybathlon

Title: Real-time eeg-based motor imagery bci using structured state space models for a tetraplegic pilot

Authors: *I. TSCHERNIAK, N. THIEMANN, A. MCWHINNIE, D. PAVLOV, I. CURCEAN, L. JOKINEN, S. HODZIC, S. GORRIZ, P. MARCOLONGO, K. CZOPF, T. HUBER, N. VON MALLINCKRODT, B. AYAZ, L. FRIM, D. TASKIN-ESPINOZA; neuroTUM, Munich, Germany

Abstract: Brain-computer interfaces (BCIs) hold considerable promise for restoring communication and control to individuals with severe motor impairments. However, current systems often lack the robustness, portability, and usability required for real-world deployment. Inspired by the Cybathlon 2024 competition, we developed a modular, mobile, and user-centered EEG-based BCI system aimed at improving accessibility for individuals with tetraplegia. Our system uses two motor imagery (MI) tasks and rest to generate up to five control signals. EEG data is recorded using a 24-channel mobile eeg with a custom layout. The processing pipeline consists of four parallel modules: (1) data acquisition, (2) preprocessing, (3) classification, and (4) a transfer function that maps classification output to control commands. Real-time latency is minimized through parallel execution. Preprocessing includes bandpass filtering (4-40 Hz), artifact removal, and epoching with a 1.5s sliding window. Features are extracted using Morlet wavelets and Common Spatial Patterns. Classification is performed using a deep neural network with three stacked S4D layers achieving up to 88% accuracy across three classes.We designed a gamified data collection and real-time accuracy testing tool based on the T-Rex Dinosaur game, where MI tasks control in-game actions during quick-time events. A mobile feedback app, accessible via any internet-connected device, was co-developed with a tetraplegic user to ensure usability. Preliminary real-time testing using the game-based interface showed minimal accuracy loss compared to offline evaluations.We present a modular, portable BCI framework designed for real-world use, integrating low-cost hardware, real-time processing, user-centered design, and online feedback. While our system builds on existing methods, it demonstrates practical feasibility and paves the way for more accessible BCI applications outside the lab. Future work will focus on improving robustness by detecting real-time error-related potentials to mitigate misclassifications, enhancing adaptability through transfer learning, and incorporating richer feedback modalities tailored to user preferences. We also plan to open-source the platform to support broader community engagement and development.

Disclosures: I. Tscherniak: None. **N. Thiemann:** None. **A. McWhinnie:** None. **D. Pavlov:** None. **I. Curcean:** None. **L. Jokinen:** None. **S. Hodzic:** None. **S. Gorriz:** None. **P. Marcolongo:** None. **K. Czopf:** None. **T. Huber:** None. **N. von Mallinckrodt:** None. **B. Ayaz:**

None. **L. Frim:** None. **D. Taskin-Espinoza:** A. Employment/Salary (full or part-time): Technical University of Munich.

Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.23/S1

Topic: F.05. Brain-Machine Interface

Support: NIH

Title: Utility Information in Local Field Potentials from PMd, M1, and S1.

Authors: *J. T. FRANCIS;
Univ. of Houston, Sugar Land, TX

Abstract: Reward and physical effort expectations are crucial in motor control and decision-making. While previous studies have demonstrated that subcortical regions encode expected reward and effort costs, little is known about how sensorimotor cortices (S1, M1, PMd) integrate these factors before movement planning. This study investigates how local field potentials (LFPs) in these cortical areas are modulated by expected reward and effort levels, with a focus on Phase-Amplitude Coupling (PAC) and Granger Causality (GC) as indicators of intra- and inter-cortical connectivity. A rhesus macaque was trained to perform a center-out reaching task in three conditions: (1) reward-only, (2) effort-only, and (3) combined reward-effort, where visual cues indicated future reward magnitude (R1-R3) and effort level (E0-E3), before any reaching target was present. LFPs were recorded from 96-electrode Utah arrays implanted in the sensorimotor cortices. Spectral analyses were conducted to examine changes in alpha (8-13 Hz) and beta (14-30 Hz) band amplitudes, PAC between low-frequency (alpha, beta) phase and gamma (60-100 Hz) amplitude, and GC to assess causal interactions between cortical regions.We found significant reward-dependent alpha and beta amplitude suppression in S1, M1, and PMd following reward cue presentation, with more substantial suppression for higher reward levels (R3 < R2 < R1). In contrast, significant effort-related modulation was observed primarily in PMd beta activity, suggesting a distinct role for the premotor cortex in effort representation. The combined reward-effort condition revealed a non-linear interaction where beta amplitude tracked subjective reward value, including effort costs, in all regions. Connectivity analyses revealed PAC was strongest between S1 and M1 for reward cues and within PMd for effort cues, indicating functionally distinct cortical networks. In general, GC was strongest in Alpha and Beta between regions for reward > reward effort > effort. These findings demonstrate that sensorimotor cortices, with distinct spatial and spectral signatures, encode expected reward and effort costs before movement initiation, or planning. Our results suggest that cortical oscillations represent movement-relevant information and contribute to pre-movement decision-making by integrating reward and effort expectations before a movement can be planned and executed.

These insights have implications for brain-machine interfaces, where contextual encoding of movement intent could enhance neural decoding strategies.

Disclosures: J.T. Francis: None.

Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.24/S2

Topic: F.05. Brain-Machine Interface

Title: Precision-edited induced human neurons for biohybrid neural interfaces

Authors: K. SMITH, A. NAVA, M. ELTAEB, R. CHOWDHURY, Y. LEWIS ISRAELI, B. RAKELA, J. BROWN, E. B. KNUDSEN, G. BALAKRISHNAN, N. IBE, K. SANGALANG, S. THOMPSON, Y. HUMRICH, M. J. HODAK, ***A. R. MARDINLY**;
Sci. Corp., Alameda, CA

Abstract: Brain-computer interfaces (BCIs) hold exciting therapeutic potential, but tissue damage caused by probe insertion limits channel count. Biohybrid devices, in which the cell-device interface is crafted in the laboratory, could dramatically expand the number of available channels for BCIs. Recently, we demonstrated that stimulation of a simple biohybrid neural interface could be used for goal directed behavior, but the translational potential of these interfaces has been critically limited by the use of mouse primary neonatal neurons. To overcome this limitation, we derived a new human iPSC line and employed several rounds of precision genetic editing and clonal selection to introduce numerous genetic features that facilitate its use with biohybrid neural interfaces. Our biohybrid iPSCs include several edits that serve to mask the cells from the immune system, express a small-molecule kill switch, express an ultra-sensitive excitatory opsin, and inducibly express a matrix metalloproteinase. We tested our iPSC master cell bank and verified that it was high quality and free of genetic abnormalities. We observed expected protein and functional behavior in our cell line, including resistance to cell death mediated by primary human immune cells. We differentiated biohybrid iPSCs into excitatory forebrain neural progenitor cells (NPCs) and screened for quality via FACS. RNA sequencing, immunohistochemistry, and functional recordings demonstrated that Biohybrid NPCs matured to functional neurons both in vitro and in vivo upon transplantation over the course of several weeks. NPCs transplanted onto the cortical surface of mice on a biohybrid device scaffold exhibited spontaneous firing, and once mature, their activity reflected the arousal state of the mouse, allowing us to reliably decode locomotion. Optical stimulation of engrafted neurons evoked reliable activity in the mouse brain. Histological examination showed that grafts matured into deep layer excitatory neurons in vivo with minimal immune response. Dendrites were observed in the superficial cortex, and axons infiltrated most of the brain, including hippocampus and other subcortical structures. These results show that precision-edited induced human neurons allow full functional integration in a biohybrid neural interface.

Disclosures: **K. Smith:** A. Employment/Salary (full or part-time): Science Corporation. **A. Nava:** A. Employment/Salary (full or part-time): Science Corporation. **M. Eltaeb:** A. Employment/Salary (full or part-time): Science Corporation. **R. Chowdhury:** A. Employment/Salary (full or part-time): Science Corporation. **Y. Lewis Israeli:** A. Employment/Salary (full or part-time): Science Corporation. **B. Rakela:** A. Employment/Salary (full or part-time): Science Corporation. **J. Brown:** A. Employment/Salary (full or part-time): Science Corporation. **E.B. Knudsen:** A. Employment/Salary (full or part-time): Science Corporation. **G. Balakrishnan:** A. Employment/Salary (full or part-time): Science Corporation. **N. Ibe:** A. Employment/Salary (full or part-time): Science Corporation. **K. Sangalang:** A. Employment/Salary (full or part-time): Science Corporation. **S. Thompson:** A. Employment/Salary (full or part-time): Science Corporation. **Y. Humrich:** A. Employment/Salary (full or part-time): Science Corporation. **M.J. Hodak:** A. Employment/Salary (full or part-time): Science Corporation. **A.R. Mardinly:** A. Employment/Salary (full or part-time): Science Corporation.

Poster

PSTR125: BMI Movement, Cognition, and Perception

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.25/S3

Topic: F.05. Brain-Machine Interface

Support: R01 NS121079

Title: Identification of a neural engagement signal in human motor cortex activity

Authors: ***N. G. KUNIGK**[1,2,5], W. HOCKEIMER[2,3], A. ALREJA[4], S. M. CHASE[6,5,7], M. L. BONINGER[3,1,2], B. M. DEKLEVA[3,2,5], J. L. COLLINGER[3,1,2,5,7];
[1]Bioengineering, [2]Rehab Neural Engin. Labs, [3]Physical Med. and Rehabil., [4]Dept. of Neurolog. Surgery, Univ. of Pittsburgh, Pittsburgh, PA; [5]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [6]Neurosci. Inst., [7]Biomed. Engin., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Despite advances in decoding algorithms, intracortical brain-computer interface (iBCI) systems can experience large fluctuations in daily performance even when calibration is performed at the beginning of each use session. While the mechanical micromotion of electrodes may explain some of these performance inconsistencies, it cannot fully account for changes in decoder training success within the same experimental session. Furthermore, a significant amount of research has established the impact of various mental states - such as fatigue and task engagement - on cortical activity. One of these states, dubbed “neural engagement”, was found to aid or hamper motor learning based on reach direction during a 2D cursor control task using an iBCI in nonhuman primates (NHPs) (Hennig et al., 2021). However, the presence and impact of neural engagement in human motor cortex activity has yet to be explored. Here, we sought to identify a neural correlate of engagement in human motor cortex during iBCI calibration and online use. Data were collected from one participant with tetraplegia enrolled in an ongoing

clinical trial of an iBCI conducted under an Investigational Device Exemption from the Food and Drug Administration. The participant had two intracortical microelectrode arrays (Blackrock Microsystems, 100 electrodes each) implanted in motor cortex and wore a pair of eye tracking glasses which recorded pupil diameter (Tobii). Neural and pupillary data were recorded while the participant performed an 8-target 2D cursor task. Experimental sessions included an open-loop calibration set and a fully participant-controlled set. Firing rates for each channel were reduced to the top 10 factors via factor analysis; factor data was trial averaged and mean-centered target-by-target. In this mean-centered data, the axis of greatest variance (identified via principal components analysis and labeled as neural engagement) was found to correlate significantly with pupil diameter (mean Pearson correlation across sessions = 0.213, $p < 0.0005$), which agrees with previous NHP results. Furthermore, the amount of neural engagement was found to abruptly increase with changes in context (e.g., switching between experimental sets) and subsequently decrease as a set went on. Lastly, sets that required more effort from the participants (direct control vs open loop) displayed higher values of engagement (Last 50% of set, open loop mean value -1.034, closed loop mean value 0.543, z-scored by session. Paired t-test, $p < 0.0001$). These results indicate that activity related to overall mental state is present in human motor cortex and may influence iBCI control under different task contexts.

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Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.01/S4

Topic: F.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N2864C,A4820R, A2295R)
NIH NIDCD (U01DC017844, U01DC019430, K23DC021297,1DP2DC021055)
AHA (23SCEFIA1156586)

Title: Decoding intended speech with an intracortical brain computer interface in a person with locked-in syndrome

Authors: *J. JUDE[1,4,6], S. HARO[6], H. LEVI-AHARONI[2,4,6], A. ACOSTA[2], S. ALLCROFT[6,8], N. CARD[9], M. WAIRAGKAR[9], D. BRANDMAN[9], S. D. STAVISKY[9], Z. WILLIAMS[3,10,5], J. D. SIMERAL[8,6,7], L. R. HOCHBERG[8,6,2,4,7], D. B. RUBIN[2,4];
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Syst., Providence, RI; [9]Dept. of Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [10]Harvard-MIT Div. of Hlth. Sci. and Technol., Boston, MA

Abstract: For people who are losing or have lost their ability to communicate due to amyotrophic lateral sclerosis (ALS) and other neurologic conditions that cause paralysis, brain-computer interfaces have been developed to restore and maintain communication by decoding intended movement directly from the motor cortex.Intracortical brain-computer interfaces (iBCIs) for decoding intended speech have recently been shown to provide individuals with ALS and severe dysarthria an intuitive method of high-throughput communication.These advances have been demonstrated in individuals who, although dysarthric, are still able to vocalize and move speech articulators. In this work, we decode intended speech from an individual with anarthria, quadriplegia, and ventilator dependence due to advanced ALS. This individual has locked-in syndrome, his only remaining volitional motor control being over his extraocular muscles.Using neural signals acquired from six 64-channel microelectrode arrays placed in left precentral gyrus, we decode intended articulatory movements during attempted speech to decode spoken sentences based on neural activity in two speech related areas of the motor cortex. Decoding from ventral precentral gyrus, we found promising performance on a standardized 50-word vocabulary, resulting in a 22% word error rate. When extended to a conversational 125,000-word vocabulary, this resulted in a phoneme error rate of 42% and a subsequent word error rate of 50%, with a speaking rate of 45 words per minute. Phoneme decoding using an RNN trained on neural data recorded during closed-loop speech trials resulted in an outsized improvement in speech decoding when compared to performance when trained on open-loop data. We hypothesize that feedback during real-time speech decoding improves separation between phoneme representations in neural space. Moreover, we find that ventral precentral gyrus (area 6v) encodes attempted articulator movement, as electrodes in this area have strong tuning to phoneme generation. In contrast, electrodes in mid precentral gyrus (area 55b) are more strongly tuned to larger units of language, such as phrases and sentences. We find that activity from area 55b carries information about the semantics of intended speech. We outline an approach to use this semantic representation to inform suitable sentence selection from candidates inferred by the phoneme predicting RNN.These results demonstrate that ensemble model speech decoding is feasible in people with anarthria and ventilator-dependence, with possible contributions to decoding at varying hierarchies of language unit from multiple areas of motor cortex.

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property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp.. F. Consulting Fees (e.g., advisory boards); Advisor to Sonera. **Z. Williams:** None. **J.D. Simeral:** None. **L.R. Hochberg:** 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.; LRH is a co-investigator on an NIH SBIR grant with Paradromics. F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement (CRSA) with Ability Neuro, Axoft, Neuralink, Neurobionics, Paradromics, Precision Neuro, Synchron, and Reach Neuro, for which LRH provides consultative input. Other; Non-compensated member of the Board of Directors of a nonprofit assistive communication device technology foundation (Speak Your Mind Foundation), Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC);, Charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **D.B. Rubin:** Other; The MGH Translational Research Center has a clinical research support agreement (CRSA) with Paradromics, for which DBR provides consultative input.

Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

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Program #/Poster #: PSTR126.02/S5

Topic: F.05. Brain-Machine Interface

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NIH NIDCD (U01DC017844, K23DCO21297)
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Title: Reanimating the paralyzed upper extremity using an intracortical brain-computer interface and a soft wearable robot

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RI; [4]Ctr. for Neurotechnology and Neurorecovery, Massachusetts Gen. Hosp., Boston, MA; [5]VA Ctr. for Neurorestoration and Neurotechnology, VA Providence Healthcare Syst., Providence, RI; [6]John A. Paulson Sch. of Engin. and Applied Sci., Harvard Univ., Cambridge, MA; [7]Worcester Polytechnic Inst., Worcester, MA; [8]Dept. of Neurol., Harvard Med. Sch., Boston, MA

Abstract: Restoring voluntary upper limb movement in individuals with tetraplegia is a major goal in neurorehabilitation. Here we demonstrate restoration of shoulder abduction and adduction in this population using an intracortical brain-computer interface (iBCI) and a soft wearable robot (SWR), a pneumatically actuated, garment-like assistive device. Neural activity was recorded from the precentral gyrus during attempted shoulder movements and was decoded using a rapidly calibrating Kalman filter. The decoded signal is then passed to a high-level kinematic controller composed of a feedforward Preisach hysteresis model and a proportional-integral (PI) feedback controller. Real-time shoulder angle estimates from inertial measurement units (IMUs) embedded in the SWR enable closed-loop physical control of the limb.
Two participants with cervical spinal cord injury in the BrainGate2 clinical trial used the BCI-SWR system to perform a virtual "PostureTrack" task, which required manipulating a virtual avatar's shoulder to track a target traversing five discrete joint angles. Participants first completed two blocks of the task under a virtual-only condition, followed by several blocks with the SWR engaged under neural control. In the virtual condition, average root mean squared error (RMSE) between the avatar and target angle was 5.94 ± 0.33 degrees for participant T11 and $2.41 \pm 0.01°$ for T18. When controlling the SWR, RMSE increased to $11.76 \pm 2.67°$ for T11 and $7.66 \pm 0.66°$ for T18, reflecting the added complexity of pneumatic actuation and system dynamics. Cross-correlation showed a lag between IMU-measured shoulder angle and target movement, consistent with delay times associated with pneumatic actuators. Variation in performance between participants could not be attributed solely to decoder accuracy. Differences in seating posture and wheelchair configuration likely influenced shoulder alignment and SWR effectiveness, as upper body orientation and trunk support affected actuator placement and forces generated about the upper limb. Additionally, participant-specific residual movement played a role: T11, who retained partial shoulder abduction, showed greater tracking error—potentially due to interaction between voluntary motor output and BCI-driven actuation. These results demonstrate that an intracortical BCI paired with a pneumatically actuated soft wearable robot can enable intuitive, embodied control of paralyzed limbs. They also highlight the critical need to account for user-specific biomechanical factors, such as posture and residual motion, when designing and evaluating assistive neurotechnologies for real-world use.

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Poster

PSTR126: BMI Speech

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.03/S6

Topic: F.05. Brain-Machine Interface

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CAUTION: Investigational Device. Limited by Federal Law to Investigational Use

Title: Bimanual neural control of two cursors by person with tetraplegia with microelectrode arrays in bilateral precentral gyri.

Authors: *M. C. OTTENHOFF[1,2], R. LI[3,2], T. PUN[4,2], S. ALLCROFT[4,6], A. DEMPSEY[4], A. ACOSTA[7], B. E. LACAYO[7], L. PANAGOS[7], C. E. VARGAS-IRWIN[5,2,6], L. HOCHBERG[6,4,7,8,2];
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Abstract: Restoring upper limb functionality has been rated as top priority to improve life satisfaction by people with tetraplegia. Emerging intracortical brain-computer technology (iBCI) has the potential to restore motor function when no voluntary muscle activation is present, by decoding neural signals recorded from the motor cortical surface directly into a control signal. Although many tasks of daily living require bimanual coordination, the iBCI field has targeted restoration of mostly unimanual motor function. iBCI studies have demonstrated that bimanual

control can be achieved using neural ensemble activity from unilaterally placed arrays. However, nonlinear tuning differences of neurons required recurrent neural networks trained on multiple days of data to gain bimanual control. Here, we demonstrate independent neural control of two cursors by a person with tetraplegia with MEAs placed in the bilateral precentral gyri. A rapid-calibration paradigm enabled our participant to gain control of both cursors within minutes of the session day, without the need for any prior training data. We recorded neural data from a single human participant (T18) enrolled in the ongoing BrainGate pilot clinical trial (www.ClinicalTrials.gov; Identifier: NCT00912041). T18 is a 48 y/o male with tetraplegia from a cervical spinal cord injury (C4 ASIA A). T18 has four 64-channel intracortical microelectrode arrays placed in the hand knob area of the left precentral gyrus and two in the right precentral gyrus. T18 was asked to perform a bimanual target acquisition task, by moving two cursors simultaneously to their corresponding targets and holding both in place for 300ms. T18 moved each cursor by attempting to control an imagined gaming joystick with each hand. A single 4D Kalman filter with additional magnitude adjustments was used to decode 2D directional vectors for both cursors simultaneously. In bimanual tasks, T18 was able to reach a mean angle error of 16.8 and 25.5 degrees for left and right respectively, and a time-to-targets of 9.1 seconds. These results demonstrate that neuronal ensemble activity from bilateral precentral gyri enables an iBCI user to rapidly gain 4D independent simultaneous control of two effectors, without the need for an open loop calibration block.

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Poster

PSTR126: BMI Speech

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Topic: F.05. Brain-Machine Interface

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Title: Neural representations are separable with altered geometric context

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Abstract: Cursor control has long served as a benchmark task for evaluating the performance of intracortical brain-computer interfaces (iBCIs) which support assistive technologies for individuals with impaired motor or communication capabilities. Over the past two decades, reliable closed loop cursor control has been consistently achieved by linear decoders such as linear regression and Kalman filters. However, nearly all known cursor control tasks involve cursor movement confined to a 2D plane. This conventional design might conflate neural representations of the intrinsic movement of the cursor together with the background geometric context — an important consideration for future applications in non-Euclidean environments. In this study, we investigated whether dissociating intrinsic cursor movements from the ambient geometric context reveals distinct neural encoding patterns. To do so, we designed a novel cursor control paradigm in which both the cursor and eight targets were constrained to the surface of a hidden 3D sphere. The visual display remained similar to that of a standard radial-8 cursor task, and participants were unaware of the altered geometric context. The task required participants to move the cursor along geodesics connecting sequential targets, which—due to the designed positions of targets—coincided with cardinal directions (up, down) rather than oblique ones. Neural data were recorded from two participants (T11 and T18) enrolled in the BrainGate2 pilot clinical trial (NCT00912041). A Kalman filter was calibrated using data from the standard radial-8 task and then directly applied for closed-loop control in the cursor-on-the-sphere task. To assess changes in neural representation, we trained a support vector machine (SVM) classifier on neural activities corresponding to “direct” movements in both task types. The classifier achieved an average accuracy of 94.89% across task types, and 94.54% when evaluated separately for each of the two cardinal directions. These results suggest that the altered game visual and underlying geometric context—despite being visually hidden—elicits a measurable shift in neural encoding. This points to the presence of a motor component modulated by the spatial structure. Future work will examine how making the sphere explicitly visible further influences the neural encoding of ambient geometry and its interaction with intrinsic movement representations.

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Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

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Program #/Poster #: PSTR126.05/S8

Topic: F.05. Brain-Machine Interface

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Brown University Provost's STEM Postdoctoral Fellowship to S. Haro
AHA (23SCEFIA1156586)

Title: Sentence-level neural dynamics in speech motor cortex

Authors: *H. LEVI-AHARONI[1,4], J. JUDE[1,4], S. ALLCROFT[6], A. ACOSTA[2], S. HARO[6], N. CARD[9], M. WAIRAGKAR[9], A. PRITCHARD[10], C. IACOBACCI[9], B. RICHARDS[11], D. BRANDMAN[9], S. D. STAVISKY[9], N. AU YONG[12], C. PANDARINATH[13,12], Z. WILLIAMS[3,5], S. S. CASH[2,4], J. D. SIMERAL[7,14,8], L. HOCHBERG[2,4,7,14,8], D. B. RUBIN[2,4]; [2]Ctr. for Neurotechnology and Neurorecovery, Dept. of Neurol., [3]Dept. of Neurosurg., [1]Massachusetts Gen. Hosp., Boston, MA; [5]Program in Neurosci., [4]Harvard Med. Sch., Boston, MA; [7]Sch. of Engin., [8]Robert J. and Nancy D. Carney Inst. for Brain Sci., [6]Brown Univ., Providence, RI; [9]Dept. of Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [10]Biomed. Engin., [11]Dept. Neurosci. and Behavioral Biol., [12]Dept. of Neurosurg., Emory Univ., Atlanta, GA; [13]Biomed. Engin., Emory Univ. and GA Tech., Atlanta, GA; [14]Ctr. for Neurorestoration and Neurotechnology (CfNN), Dept. of VA Med. Ctr., Providence, RI

Abstract: Recent investigation into the representation of language production at the single-neuron level has revealed both phonemic and syllabic encoding within language-processing areas of the dominant prefrontal cortex [Khanna 2024, Silva 2022]. These representations contain sufficient information to control a phoneme-based intracortical brain-computer interface (iBCI) for decoding intended speech [Willett 2023, Metzger 2023, Card 2024]. However, it is unknown how higher-level representations of language structure influence neural activity in downstream motor areas and the unique computations performed across these brain regions. Here we report on research sessions that were conducted with three participants enrolled in the BrainGate2

clinical trial (ClinicalTrials.gov ID: NCT00912041) who have microelectrode arrays chronically implanted in left precentral gyrus, including in Brodmann areas 6v and 55b. Participants T15 and T17 both have tetraparesis and dysarthria (T15) or anarthria (T17) due to ALS; T16 has tetraparesis and dysarthria caused by brainstem stroke. Using an instructed delay paradigm, neural activity was recorded as participants attempted to read aloud four different types of visually presented texts: English sentences, word lists, grammatically structured sentences with gibberish content words, or gibberish word lists [Fedorenko 2010]. Within area 6v, we observed low firing rates during the delay (preparatory) period, higher firing rates during the task execution (go) period, and minimal modulation in mean firing rate by stimulus class in all three participants. However, for all participants we found well above chance level (= 25%) Gaussian Naïve Bayes decoding for the text category (73% for T15, 53% for T16, 44% for T17). Within area 55b we found higher decoding accuracy for two of the three participants (58% for T15, 72% for T16, 61% for T17), in addition to task modulation in the mean activity that was not observed in area 6v. We then looked into the population dynamics in these cortical areas. Using PCA and jPCA we extracted the population trajectories during the prep and go periods. We found qualitatively different firing rate dynamics for the text categories in the different areas across participants that leads us to propose a dynamical model of interaction between the two areas. As previously described by Churchland et al., we hypothesize that these trajectories represent output null and output potent spaces of neural activity for speech preparation and production. This expands our understanding of the neural processing underlying this uniquely human behavior and will make possible improved decoding for speech neuroprostheses.

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Poster

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Wu Tsai Neurosciences Institute at Stanford
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Title: Ventral Motor Cortex Reveals Contextual and Rotatory Encoding of Phoneme Sequences

Authors: *C. FAN[1], B. MESCHEDE-KRASA[4], E. KUNZ[2], F. KAMDAR[5], N. CARD[6], M. WAIRAGKAR[7], C. IACOBACCI[8], L. R. HOCHBERG[10,11,12,13], D. BRANDMAN[14], S. D. STAVISKY[9], S. DRUCKMANN[1], J. M. HENDERSON[3], F. WILLETT[15];
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Abstract: Psycholinguistic and neuroscience models of speech production commonly adopt parallel sequence representations, notably the competitive queue (CQ) model. However, supporting evidence for CQ has largely relied on behavioral observations such as speech errors.Here, for the first time, we record single-neuron activity from the ventral motor cortex

(VMC) during attempted speech in two BrainGate2 clinical trial participants to directly investigate neural sequence encoding. We show that VMC simultaneously encodes all phonemes in a word via linear superposition. Activations form a gradient: the current (onset) phoneme shows the highest magnitude, with future phonemes progressively decreasing . This directly supports CQ's predictions.However, we also uncover features not predicted by the CQ model. First, phoneme activations persist beyond onset, leading to co-activation of past and future phonemes. Second, we find that phonemes occupy distinct but correlated subspaces based on their temporal position—past, present, or future—that rotate as speech unfolds, resembling a rotating fan. Finally, vowels and consonants are encoded in separate subspaces, more accurately explained by their sequential context than by articulatory similarity.We observe similar contextual and rotary encodings in recurrent neural networks (RNNs) trained to recall phoneme sequences. By manipulating the RNN, we find the rotary encodings emerge from position-independent encoding of inputs and outputs, which may cause networks to rotate inputs away from a singular space into memory, and from memory into a singular output space. When trained on natural sequences, RNNs also show consonant-vowel subspace separation; this disappears with random input, further supporting a context-driven encoding structure.In sum, we provide the first direct neural evidence for core CQ features and propose additions —rotary subspaces and contextual encoding. These insights provide a unique opportunity to update current speech production models and may offer broader implications for understanding how the brain encodes and generates sequential behaviors.

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intellectual property rights/patent holder, excluding diversified mutual funds); inventors of intellectual property related to speech neuroprostheses owned by the University of California, Davis, including some IP that has been licensed to a neurotechnology startup. F. Consulting Fees (e.g., advisory boards); advisor to Sonera. **S. Druckmann:** None. **J.M. Henderson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); a shareholder in Maplight Therapeutics, co-founder of Re-EmergeDBS.. F. Consulting Fees (e.g., advisory boards); consultant for Paradromics, serves on the Medical Advisory Board of Enspire DBS. **F. Willett:** None.

Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.07/S10

Topic: F.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N2864C, A4820R, A2295R, A3803R)
NIH NIDCD (K23DC021297)
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AHA (23SCEFIA1156586)
CDMRP (HT94252310153)
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, or the Department of Veterans Affairs or the United States Government.

Title: Spatiotemporal dynamics of speech preparation and execution in human motor cortex

Authors: *H. HASHIMOTO[1], A. ACOSTA[1], S. HARO[3], H. LEVI-AHARONI[1], J. JUDE[1], A. DEMPSEY[3], S. ALLCROFT[3,5], Z. WILLIAMS[2,6], J. D. SIMERAL[3,5,4], L. R. HOCHBERG[1,3,5,4,7], D. B. RUBIN[1];
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Abstract: Recent studies have identified Brodmann area 55b, located in the middle precentral gyrus, as a key region in language processing. However, how this region contributes to the preparation and execution of speech-related motor tasks remains unclear. To address this, we examined the spatiotemporal dynamics of speech-related neural activity across multiple Brodmann areas within the precentral gyrus. We hypothesized that preparatory activity would show region-specific differences in temporal stability and spatial localization. A 34-year-old

male with ALS enrolled in the BrainGate clinical trial (NCT00912041), with six 64-channel Utah arrays (two each in areas 6v, 55b, and 6d) chronically implanted in the left precentral gyrus, performed a “phoneme sweep” task. In an instructed delay paradigm, he attempted to produce one of the 39 English phonemes (or “Do Nothing”). Each trial began with a visual and auditory Presentation Cue, followed by a Go Cue after a delay ranging from 2.50 to 3.00 s. The participant was anarthric and unable to produce any volitional movements of the mouth, tongue, or vocal tract; thus, responses consisted of attempted but not overt speech. Task-discriminative channels were identified using a Kruskal-Wallis test ($p < 0.05$) during the Presentation and Go Cue periods. For each array, the evolution of task-related activity across periods was assessed by (1) the Jaccard index of active channels and (2) permutation testing of the spatial centroid of task-specific channels. The centroid was computed using electrode positions; significance was determined by comparing centroid distances to a null distribution of randomly selected channel sets. Distances below the 5th percentile were considered significantly close, indicating spatial reactivation. In 55b, transient reactivation was observed, with Jaccard values > 0.7 between 0.75-1.35 s post-Presentation and 0.35-0.45 s post-Go. Permutation tests showed significant spatial overlap ($p < 0.05$) between 0.85-1.05 s post-Presentation and 0.45-0.55 s post-Go. In contrast, 6v showed more sustained activation, with some channels remaining active for up to 2 s after the Go Cue. Permutation tests also confirmed high spatial overlap between the two phases. No consistent task-related activity was observed in 6d. In both 55b and 6v, channels activated after the Go Cue had already been active during the Presentation Cue period, suggesting the presence of preparatory activity. However, this activity was spatially and temporally transient in 55b, whereas it was broader and more sustained in 6v, suggesting that 55b may support higher-level planning, while 6v is involved in sustained articulatory control.

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Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.08/S11

Topic: F.05. Brain-Machine Interface

Support: NeuralStorm NRT Award #2152260
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NIH-NIDCD (U01DC017844)
VA RR&D (A2295-R)
DP2 from the NIH Office of the Director and managed by NIDCD (1DP2DC021055)
DOD CDMRP ALS Pilot Clinical Trial Award (AL220043)

Title: Speech and non-speech articulator movements occupy shared neural dimensions in speech motor cortex

Authors: *T. SINGER-CLARK[1], M. WAIRAGKAR[2], E. OKOROKOVA[6], N. CARD[3], X. HOU[1], C. IACOBACCI[4], L. R. HOCHBERG[7], S. D. STAVISKY[5], D. BRANDMAN[8]; [2]Dept. of Neurolog. Surgery, [1]Univ. of California, Davis, Davis, CA; [3]Bioengineering, Univ. of California, Davis, SACRAMENTO, CA; [4]Univ. of California, Davis, Pacifica, CA; [5]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [6]Univ. of California Davis, Davis, CA; [7]Neurol. / Engin., Brown Univ., Boston, MA; [8]Neurolog. Surgery, UC Davis Hlth., Sacramento, CA

Abstract: To what extent can we view a compound movement's underlying neural activity as the modular combination of simpler movements versus to what extent does a compound movement correspond to its own new neural computation? Such topics have been studied extensively for upper limb movements, but analogous questions can also be asked in the context of speech, which involves skilled coordination and sequencing of articulator movements. Does the brain utilize the same neural circuitry to produce a simple articulator movement (e.g., pressing lips together) as it does to produce speech sounds that involve that same movement (e.g., the phoneme /m/ as in "me")? To address this question, we collected action potential resolution neural recordings from four 64-microelectrode arrays implanted in the ventral precentral gyrus of one BrainGate2 clinical trial participant (T15) while he performed an instructed delay task. Each prompt was either (1) a word to speak, such as "mall", or (2) a non-speech lip or tongue movement to perform, such as "[press lips together]". The prompts included 4 lip movements, 3 tongue movements, 6 words chosen to evoke different lip movements, and 8 words chosen to evoke different tongue movements. Both the words and non-speech movements were highly decodable from neural data, with classification accuracies between 0.85 and 0.95. Sparse component analysis (SCA) applied to only the non-speech movement trials' neural activity revealed neural dimensions which were occupied during only one type of non-speech movement (e.g., a "press-lips-together dimension", an "open-lips dimension", etc.). Projecting word trials' neural activity onto each of these non-speech dimensions displayed modulation consistent with articulatory phonetics. For example, neural activity during "mall" and "me" modulated along the "press-lips-together dimension" more than words without /m/ did. Finally, principal components (PCs) calculated from non-speech movement trials explained more variance during word trials than PCs calculated from baseline activity or random data did. These results reveal neural overlap between speech movements and their corresponding simple articulator movements, supporting the idea that speech motor cortex employs a kinematic neural encoding that is at least partially preserved across speech and non-speech movement contexts.

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funds); Patent applications related to speech BCI owned by the Regents of the University of California. **E. Okorokova:** None. **N. Card:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent applications related to speech BCI owned by the Regents of the University of California. **X. Hou:** None. **C. Iacobacci:** None. **L.R. Hochberg:** F. Consulting Fees (e.g., advisory boards); CRSA with Ability Neuro, Axoft, Neuralink, Neurobionics, Paradromics, Precision Neuro, Synchron, and Reach Neuro. Other; non-compensated member of the Board of Directors of a nonprofit assistive communication device technology foundation (Speak Your Mind Foundation), convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC), Charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech support the iBCI-CC. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp, Patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); Advisor to Sonera. **D. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); Brandman was a surgical consultant to Paradromics Inc. at the time of data collection, and is currently an advisor to Globus Medical.

Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.09/S12

Topic: F.05. Brain-Machine Interface

Support: Ketterer-Vorwald Neurosciences Interdisciplinary Graduate Fellowship
Simons Institute
NIH
Larry and Pamela Garlick

Title: Decoding the mosaic of Broca's area: Single-neuron insights into language and multiple-demand networks in inferior frontal gyrus

Authors: *E. M. KUNZ[1], S. MADUGULA[2], D. AVANSINO[3], F. KAMDAR[4], A. SINGH[5], N. HAHN[6], L. R. HOCHBERG[9], S. DRUCKMANN[7], F. WILLETT[10], J. M. HENDERSON[8]; [1]Stanford Univ., San Francisco, CA; [2]Neurosurg., Stanford Univ., Hoffman Estates, IL; [3]Electrical Engineering, Neurosurg., Stanford Univ., San Mateo, CA; [4]Stanford Univ., Moutnain View, CA; [5]Stanford Univ., San Ramon, CA; [6]Neurosurg., Stanford Univ., Mountain View, CA; [8]Dept Neurosurgy, R 227, [7]Stanford Univ., Stanford, CA; [9]Neurol. / Engin., Brown Univ., Boston, MA; [10]Neurosurg., Stanford Univ. / HHMI, Stanford, CA

Abstract: Broca's area, first implicated in speech production, has been shown by functional neuroimaging to correlate to a vast array of variables including language, working memory, autobiographical recall, and spatial processing. However, its function at a single neuron level has not yet been elucidated. Here, we show that recordings from microelectrode arrays placed in Broca's area of a Braingate2 clinical trial participant were not tuned to speech production, but instead appeared to relate mostly to cognitive operations used to compute an answer word, while only weakly representing the answer word itself. For example, the neural representation when computing an answer word based on a semantic relationship was consistently distinct from that of a phonological (i.e. rhyming) relationship, even if the answer word was the same. Additionally, while recording microelectrode data we asked our participant to perform a comprehensive set of tasks that are traditionally performed during task-based fMRI experiments to localize voxels to particular networks. We identified sub-regions whose response profiles across the two arrays match the language, multiple-demand, and default-mode networks. These results reinforce recent fMRI work showing that Broca's area is a functional mosaic and provide the first single-neuron view of what each tile in that mosaic does—revealing, for example, that even language-network channels encode the cognitive rules guiding a response rather than the phonetic form of speech itself.

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Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.10/T1

Topic: F.05. Brain-Machine Interface

Support: NS Card: A.P. Giannini Postdoctoral Fellowship
T Singer-Clark: NeuralStorm NRT Award #2152260, ARCS Foundation Scholar Award
LR Hochberg: NIH-NIDCD (U01DC017844), VA RR&D (A2295-R)
DM Brandman: ALS Association Assistive Technology Grant (24-AT-732)
SD Stavisky: DP2 from the NIH Office of the Director and managed by NIDCD (1DP2DC021055), DOD CDMRP ALS Pilot Clinical Trial Award (AL220043), Searle Scholars Program, Career Award at the Scientific Interface from the Burroughs Wellcome Fund

Title: Decoding face and hand gestures from intracortical activity for emotional expression

Authors: *E. OKOROKOVA[1], N. CARD[2], T. SINGER-CLARK[2], C. IACOBACCI[2], H. PERACHA[2], L. R. HOCHBERG[4], D. BRANDMAN[5], S. D. STAVISKY[3];

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Abstract: Expressing oneself - not only through speech but also through hand and facial gestures - is a fundamental aspect of human communication that shapes meaning, engagement, and social connection. However, individuals with motor impairments—such as people with amyotrophic lateral sclerosis (ALS), stroke, or spinal cord injury—are often deprived of this critical mode of self-expression. While recent advances in intracortical brain-computer interfaces (iBCIs) have enabled highly accurate speech decoding from neural activity, these systems still lack the emotional nuances of natural human communication. To reduce this limitation, we developed a multimodal approach to enrich iBCI-decoded speech with gesture expression. One participant with paralysis due to ALS (T15, BrainGate2 clinical trial NCT00912041) was instructed to attempt up to 20 facial and hand gestures that convey emotional/communicative intent (e.g., smile, frown, wink, thumbs up/down), presented as emoji cues in an open-loop instructed delay task. We recorded neural activity from chronically implanted microelectrode arrays in the ventral precentral gyrus, and found that neural activity from most electrodes showed significant and separable modulation to instructed gestures. Next, we trained a convolutional-recurrent neural network (CNN-RNN) decoder to classify the attempted gestures from neural activity and achieved an average closed-loop decoding accuracy of 92%. Finally, we integrated gesture decoding with a previously developed speech iBCI framework (Card et al., 2024). The participant was cued to attempt to speak nuanced sentences, with an embedded emoji indicating the intended emotional emphasis, and was instructed to attempt the corresponding facial or hand gesture at the point in the sentence where the emoji cue appeared. Speech and gestures were decoded simultaneously in real time. These results demonstrate the feasibility of decoding emotional gestures alongside speech from intracortical signals, offering a path toward more expressive and naturalistic communication for iBCI users.

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Poster

PSTR126: BMI Speech

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.11/T2

Topic: F.05. Brain-Machine Interface

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ALS Association Assistive Technology Grant (24-AT-732)
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DP2 from the NIH Office of the Director and managed by NIDCD (1DP2DC021055)
DOD CDMRP ALS Pilot Clinical Trial Award (AL220043)
Searle Scholars Program

Title: 99% accurate intracortical speech decoding without prior same-day calibration

Authors: *Z. FOGG[1], N. CARD[2], X. HOU[2], T. SINGER-CLARK[2], H. PERACHA[2], M. WAIRAGKAR[2], C. IACOBACCI[2], L. R. HOCHBERG[3], D. BRANDMAN[2], S. D. STAVISKY[2]; [1]Computer Sci. Grad. Group, [2]Dept. of Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [3]Neurol. / Engin., Brown Univ., Boston, MA

Abstract: Intracortical brain-computer interfaces (BCIs) show promise for restoring communication to individuals with paralysis by decoding neural activity during attempted speech. Recent "brain-to-text" speech BCIs have achieved word prediction accuracy of up to 97.5% in prompted speech tasks, but accuracy is lower during unstructured conversations. Additionally, these speech BCIs required extensive same-day calibration to achieve optimal accuracy. These challenges limit the practicality of speech BCIs for daily use and motivate new decoding methods that provide better accuracy and robustness to neural nonstationarity.
To meet this need, we developed a causal transformer-based neural decoder trained with Connectionist Temporal Classification (CTC) loss on 595 hours of intracortical neural data from BrainGate2 clinical trial participant 'T15'. T15 is a 46-year-old man with severe dysarthria due to amyotrophic lateral sclerosis (ALS). He has four chronic microelectrode arrays (each with 64 electrodes) implanted in the speech motor cortex. Our transformer decoder generates phoneme predictions in real-time with a latency of 160 ms, which are then converted to the most likely sequence of words by a language model.
In real-time online evaluation sessions, the transformer decoder achieved a phoneme error rate (PER) of 4.74% (pre-language model) and a word error rate (WER) of 0.82% (post-language model, 125,000-word vocabulary) without prior same-day calibration. This is a substantial improvement over the current state-of-the-art (SOTA) recurrent neural network (RNN) decoder, which obtained a PER of 9.24% and WER of 2.25% in online sessions and benefited from same-day calibration immediately prior to evaluation. Additional offline analyses spanning several months demonstrated stable decoding performance despite neural signal drift, with minimal performance degradation (ΔWER/week = 0.18%). Furthermore, we showed that our transformer decoder leverages larger datasets more effectively than the SOTA RNN and consistently outperformed the RNN model across multiple electrode (subset) counts.
Our findings highlight the transformer decoder's superior ability to utilize extensive intracortical datasets, significantly improving decoding accuracy, robustness, and thus usability. These results represent progress towards clinical deployment of practical assistive communication devices for people with severe speech and motor impairments.

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speech BCI owned by the Regents of the University of California. **C. Iacobacci:** None. **L.R. Hochberg:** Other; The MGH Translational Research Center has a clinical research support agreement with Neuralink, Synchron, Axoft, Precision Neuro, and Reach Neuro, for which LRH provides consultative input, Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC); charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **D. Brandman:** Other; Brandman was a surgical consultant to Paradromics Inc. at the time of data collection, and is currently an advisor to Globus Medical, Brandman has patent applications related to speech BCI owned by the Regents of the University of California. **S.D. Stavisky:** Other; Stavisky is an inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp., Stavisky has patent applications related to speech BCI owned by the Regents of the University of California, Stavisky is an advisor to Sonera.

Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

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DOD CDMRP Department of Defence CDMRP ALS Pilot Clinical Trial Award (AL220043)
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Searle Scholars Program
Career Award at the Scientific Interface from the Burroughs Wellcome Fund to Stavisky
A. P. Giannini Postdoctoral Fellowship to Card

Title: A voice synthesis neuroprosthesis with prosody decoding

Authors: *M. WAIRAGKAR[1], N. S. CARD[1], T. SINGER-CLARK[1], X. HOU[1], C. IACOBACCI[1], L. M. MILLER[1], L. R. HOCHBERG[2], D. M. BRANDMAN[1], S. D. STAVISKY[1];
[1]Univ. of California, Davis, Davis, CA; [2]Massachusetts Gen. Hospital/ Brown University/ Harvard Med. School/ Providence VAMC, Boston, MA

Abstract: The prosodic nuances of human speech help in communicating efficiently and emotively - not just what words are said but also how those words are spoken determines their meaning. A brain-computer interface (BCI) that can decode both phonemic and

prosodic elements of speech has the potential to fully replace voice lost due to a neurologic injury.

We built a "brain-to-voice" neuroprosthesis that directly synthesized voice from intracortical neural activity in real-time. The brain-to-voice framework comprised of a Transformer-based decoder that translated spike-band power and threshold crossings into low-dimensional speech features which were vocoded into synthesized voice. The entire neural processing, from signal acquisition to synthesis of speech samples, occurred within 10 ms, enabling nearly-instantaneous speech synthesis. We demonstrated this neuroprosthesis in BrainGate2 clinical trial participant 'T15', a man with amyotrophic lateral sclerosis (ALS) and severe dysarthria (unintelligible speech) with four 64-electrode Utah arrays placed in his ventral precentral gyrus (vPCG). As T15 tried to speak, his intended voice was synthesized by the BCI and played aloud. We decoded paralinguistic features from neural activity to modulate BCI-voice prosody, enabling him to ask a question, emphasize words and sing short melodies. Naïve human listeners could understand the BCI-synthesized voice with a 43.7% word error rate, as opposed to 96.4% word error rate for T15's residual dysarthric speech without using the BCI.

We decoded a variety of prosodic features from T15's neural activity. A causal online binary decoder yielded 90.5% accuracy for statement vs. question intonation modulation and 95.7% accuracy for word emphasis. A three-class combined decoder classified statement, question and emphasis offline with 80.0% accuracy. We also causally decoded three pitch levels where human listeners could distinguish between pairs of BCI-synthesized melody notes with 73.0% accuracy. In an offline analysis, we predicted continuous pitch contours of T15's intended question and emphasis intonation using a neural decoder which matched the time-aligned target pitch contours with the Pearson correlation coefficient of 0.80±0.07. These results point a path towards continuous prosody decoding.

Together, these findings suggest that there is a robust encoding of prosody in vPCG that can be leveraged to make a BCI-enabled voice more expressive.

Disclosures: M. Wairagkar: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); licensed University of California, Davis IP related to intracortical speech BCIs. **N.S. Card:** None. **T. Singer-Clark:** None. **X. Hou:** None. **C. Iacobacci:** None. **L.M. Miller:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); IP from University of California, Davis related to speech evaluation. **L.R. Hochberg:** Other; Research support agreements with Ability Neuro, Axoft, Neuralink, Neurobionics, Paradromics, Precision Neuro, Synchron, and Reach Neuro. **D.M. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); licensed University of California, Davis IP related to intracortical speech BCIs. F. Consulting Fees (e.g., advisory boards); Globus Medical. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); licensed University of California, Davis IP related to intracortical speech BCIs, licensed Stanford IP related to intracortical BCIs. F. Consulting Fees (e.g., advisory boards); Scientific advisor to Sonera.

Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.13/T4

Topic: F.05. Brain-Machine Interface

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NIH NIDCD (DP2DC021055)
AHA (23SCEFIA1156586)
CDMRP (HT94252310153)

Title: Neural Dynamics Underlying Phoneme Encoding in Individuals with Severe Speech and Motor Impairment due to Amyotrophic Lateral Sclerosis

Authors: *S. HARO[1], J. JUDE[3], A. ACOSTA[4], H. LEVI-AHARONI[5], S. ALLCROFT[1], N. CARD[7], M. WAIRAGKAR[8], D. BRANDMAN[10], S. D. STAVISKY[9], Z. WILLIAMS[11], J. D. SIMERAL[12], L. R. HOCHBERG[2], D. B. RUBIN[6];
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Abstract: Individuals with severe speech and motor impairments (SSMI) may lose the ability to communicate due to loss of volitional control over muscles needed to control their hands and voice. Intracortical brain-computer interfaces (iBCIs) using microelectrode arrays (MEAs) have demonstrated the ability to decode attempted speech from motor cortex in individuals with impaired speech (Willett 2023, Card 2024). However, decoding performance varies across individuals, possibly due to differences in the impaired speech phenotype. Here, we investigated how motor cortex encodes attempted speech in individuals with distinct speech impairment phenotypes. We analyzed neural activity from two participants with ALS implanted with MEAs in Brodmann area 6v, a region previously shown to encode phonemic features of attempted speech. These participants differ in their speech phenotypes: T12 has dysarthric speech with residual phonation, and T17 has anarthric speech characterized by an inability to phonate or control articulatory muscles. Participants performed an instructed-delay task involving attempting phonemes in isolation. Neural spike threshold crossing events were computed in 20

ms bins. Phoneme-selective channels were identified using a Kruskal-Wallis test; T12 had more tuned channels than T17 (95% vs. 55% of channels in area 6v). Vowel decoding accuracy was higher for T12 than T17 (87.1%±11.1% and 49.0%±15.6%, respectively with Bonferroni-corrected t-test $p<1e-7$). In contrast, consonant decoding accuracy was not different across the two participants (48.2%±16.3% and 47.3%±18.3%, respectively). To characterize population-level dynamics, we projected trial-averaged firing rates into a low-dimensional space using principal component analysis. We quantified trial-to-trial variability of phoneme-specific neural trajectories. Both participants showed similar temporal structure in the variability throughout the trial's preparatory and execution phases. T12's vowel trajectories were significantly more coordinated than consonant trajectories (Bonferroni-corrected t-test $p<1e-5$) while this was not true for T17 trajectories. This work suggests that further research, with additional participants, should explore the degree to which residual phonation reflected in motor cortex affects quality of decoding during attempted phoneme production. These findings offer insight into the neural dynamics underlying attempted speech production and provide a path to improving the performance of speech neuroprostheses for people with SSMI.

Disclosures: S. Haro: None. **J. Jude:** None. **A. Acosta:** None. **H. Levi-Aharoni:** None. **S. Allcroft:** None. **N. Card:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. **D. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California.. F. Consulting Fees (e.g., advisory boards); ad-hoc consultant for Paradromics Inc. at the time of data collection and an ad-hoc consultant for Globus Medical. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California,, inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp.. F. Consulting Fees (e.g., advisory boards); advisor to Sonera and received equity.. **Z. Williams:** None. **J.D. Simeral:** None. **L.R. Hochberg:** Other; The MGH Translational Research Center has a clinical research support agreement (CRSA) with Axoft, Neuralink, Neurobionics, Precision Neuro, Synchron, and Reach Neuro, for which LRH provides consultative input., and is a non-compensated member of the Board of Directors of a nonprofit assistive communication device technology foundation (Speak Your Mind Foundation), Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC); charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort.. **D.B. Rubin:** None.

Poster

PSTR126: BMI Speech

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Program #/Poster #: PSTR126.14/T5

Topic: F.05. Brain-Machine Interface

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Veterans Affairs RR&D A2295-R

Title: Hierarchical state decoding for seamless selection between multiple iBCI functions

Authors: *A. L. PRITCHARD[1], S. R. NASON-TOMASZEWSKI[1], B. JACQUES[1], Y. ALI[1], M. RIGOTTI-THOMPSON[1], K. TUNG[2,3], P. H. BECHEFSKY[1], B. A. RICHARDS[4], L. R. HOCHBERG[7,9,10,11,8], N. AU YONG[5,1,6], C. PANDARINATH[1,5];
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Abstract: Intracortical brain-computer interfaces (iBCIs) have demonstrated significant potential for restoring control of movement and speech for people with tetraplegia and dysarthria. In previous demonstrations, iBCI users had arrays placed in brain areas canonically associated with a single control *modality* (either hand or speech). Recently, we placed 4 microelectrode arrays in the precentral gyrus of BrainGate2 Clinical Trial participant T16 targeting hand (Brodmann's area 6d) and speech (6v & 55b/PEF) modalities. Recording from multiple brain areas enables multi-modality control, but usability is severely limited without the ability to switch between *functions* (controllable outputs within a modality), as alternatives require constant activation of all functions or manual switching. Here, we investigate the potential for a hierarchical state decoder to infer the iBCI user's intended functional output. First, we designed a multifunctional iBCI task where T16 was instructed to sequentially read a sentence, type the sentence with a brain-to-text decoder, and select incorrect text predictions with an iBCI-controlled cursor. Transitions between functions caused distinct changes in neural firing rates: reading and speaking modulation was most evident in 55b/PEF & 6v arrays and cursoring modulation was primarily in 55b/PEF & 6d. We modeled the data with Hidden Markov Models (HMMs) to classify read, speak, and cursor phases (83/92/79% acc.). Then, we demonstrated the feasibility of these HMMs to decode T16's functional intent in an online iBCI setting. T16 performed a similar multifunctional task as before, but cursor and speech decoders were de/activated according to the decoded user intention. Speech (91% acc.) and cursor (72%) classification reflect offline results with minimal latencies for decoded speech onset/offset (mean +/- SD: 0.069+/-0.53s on., 0.48+/-0.36s off.). Finally, we investigated differences in neural activity when T16 controlled two functions within the hand modality - a virtual robotic hand or a cursor - both

controlled via flexing/extending her small finger. We used demixed principal component analysis (dPCA) to identify a 'function' dimension in the neural data that accounted for 7% of the neural variance, suggesting this signal may be sufficient to train state decoders for function switching. Next, we will develop state decoders for switching between robot and cursor functions. These decoders enable iBCI users to independently switch control between multiple modalities, may enable control of multiple functions within a modality, and can be extended to facilitate multifunctional iBCI control across a multitude of applications.

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Poster

PSTR126: BMI Speech

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Title: Preparatory activity in the human motor cortex richly encodes features of upcoming movement

Authors: *M. RIGOTTI-THOMPSON[1], S. R. NASON-TOMASZEWSKI[2], P. BECHEFSKY[2], A. ACOSTA[3], N. HAHN[4], D. AVANSINO[4,5], B. RICHARDS[2], C. NICOLAS[3,7], J. M. HENDERSON[4,6], L. R. HOCHBERG[3,7,8,9], N. AU YONG[10,2,11], C. PANDARINATH[2,10];
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Gen. Hospital, Harvard Med. Sch., Boston, MA; [4]Dept. of Neurosurg., [5]Howard Hughes Med. Inst., [6]Wu Tsai Neurosciences Inst., Stanford Univ., Stanford, CA; [7]Sch. of Engin., [8]Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [9]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of Veterans Affairs Med. Ctr., Providence, RI; [10]Dept. of Neurosurg., [11]Dept. of Cell Biol., Emory Univ., Atlanta, GA

Abstract: Preparatory activity that precedes movement execution is an inherent property of neural spiking activity within the motor cortex. Non-human primate studies have demonstrated that preparatory activity encodes several properties of upcoming movements, such as direction, distance, and speed. In the context of intracortical brain-computer interfaces (iBCIs), this activity might be leveraged to generate better and earlier predictions of movement intention to improve the control of assistive devices. However, it is unclear to what extent diverse features of upcoming movements are encoded by preparatory activity in humans. In this work, we studied preparatory spiking activity within the human motor cortex through intracortical recordings from the hand-knob area of three participants (T16, T11, T5) enrolled in the BrainGate2 clinical trial. To isolate activity tied to movement preparation, participants were instructed to perform instructed-delay tasks using attempted movements of their wrist to match cursor movements on a screen. During a first task which required participants to prepare and execute movements to 8 radially distributed targets, we identified preparatory activity that was tuned to the direction of upcoming movement (SVM class. acc.: 62-88%). We further probed this directional tuning through a second instructed-delay task that required participants to attempt movements following curved trajectories, where the initial and end target directions could be up to 90° apart. We found that preparatory activity was predominantly tuned to the initial direction of movement, with some additional tuning to movement curvature. Next, to characterize the dependence of preparatory activity on a richer set of upcoming movement features, we designed a third task where participants had to attempt movements with independently cued distances and speeds (2 directions x 3 distances x 3 speeds = 18 conditions). With this, we found that in addition to direction, preparatory activity in the human motor cortex also encodes both the distance and speed of upcoming movement (SVM class. acc.: 45-52% for distance, 45-47% for speed). Finally, as a proof of concept for practical iBCI use, we designed a control paradigm where both movement initiation and intended direction were decoded online from preparatory activity. This allowed participants to achieve rapid (400-600 ms), self-paced control of an on-screen cursor to fixed-distance targets (median err. < 19.5°). Altogether, these results demonstrate that preparatory activity in the human motor cortex richly encodes features of upcoming movement, highlighting its potential use for high performance iBCI applications.

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Synchron, Precision Neuro, Neuralink, Blackrock Neurotech, Speak Your Mind Foundation. **N. Au Yong:** None. **C. Pandarinath:** A. Employment/Salary (full or part-time): Meta (Reality Labs).

Poster

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Program #/Poster #: PSTR126.16/T7

Topic: F.05. Brain-Machine Interface

Support: McNair Medical Scholar (NPS)

Title: Adaptive Sampling for Efficient iBCI Decoder Calibration

Authors: *S. TAO[1], N. P. SHAH[2];
[2]Electrical and Comptuer Engin., [1]Rice Univ., Houston, TX

Abstract: Intracortical brain-computer interfaces (iBCIs) have shown impressive capabilities in enabling individuals with paralysis to perform experimental tasks such as 2D cursor control or robotic arm manipulation. However, their practical deployment remains constrained by the substantial time users must spend on cued movements to collect data for decoder calibration. In this work, we propose a method to accelerate iBCI decoder calibration by adaptively optimizing the distribution of movement cues presented to the user across multiple training blocks in a typical experimental session. After each training block, our approach iteratively updates decoder parameters and selects cues for the subsequent block based on the estimated variance of loss gradient associated with each cue. Crucially, this variance is estimated using synthetic neural activity generated by a surrogate model trained on previously collected data. We evaluated our approach on a two-dimensional closed-loop control task, comparing its performance against a baseline that samples movement cues uniformly. Using a synthetic pseudo-linear neural response generator with anisotropic signal-to-noise ratios (SNR) across two degrees of freedom (DOFs), our method improved both the calibration speed and the asymptotic performance of a logistic regression decoder. For example, training time required to reach 80% success rate decreased by 40% when SNR of one DOF is 1.41 times higher than the other. These benefits also extended to a nonlinear neural generator fit from neural recordings of non-human primate primary motor cortex during two-finger-group movements. These results demonstrate that our method accelerates iBCI decoder calibration compared to uniform sampling. Notably, the method's use of variance of loss gradient makes it inherently compatible with any parameterized decoder architecture, and our experimental findings align with this generality, highlighting its broad potential for future applications.

Disclosures: S. Tao: None. **N.P. Shah:** None.

Poster

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Searle Scholars Program

Title: Assessing the long-term usability of a multimodal BCI for a person with ALS

Authors: *C. IACOBACCI[1], H. PERACHA[1], N. CARD[1], M. WAIRAGKAR[1], X. HOU[1,2], T. SINGER-CLARK[1,3], L. R. HOCHBERG[4,5,6], S. D. STAVISKY[1], D. BRANDMAN[1];
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Abstract: Agency is paramount to one's sense of self. Unfortunately, for thousands of people living with dysarthria and paralysis due to neurological diseases and disorders such as stroke and amyotrophic lateral sclerosis (ALS), achieving a desired level of agency can range from difficult to impossible. This leads to increased rates of isolation, depression, and decreased quality of life. Brain-computer interfaces (BCIs) offer a promising path toward restoring some agency in the form of communication and computer control to people with dysarthria and paralysis. As part of the BrainGate2 clinical trial, we have previously demonstrated accurate and intuitive multimodal speech and cursor decoding from neural activity using an intracortical BCI. Here we assess the usability of this BCI for independently directed tasks. We recruited a 45 year old man with ALS (participant 'T15') to the BrainGate2 clinical trial and placed 4 microelectrode arrays into his ventral precentral gyrus (vPCG). These arrays record his neural activity from 256 total intracortical electrodes and allow him to speak through the BCI and control his own computer's cursor. With participant permission we captured meta-data such as decoder performance in different situations. We also solicited participant feedback through a series of surveys (an assistive technology assessment, a personal use task evaluation assessment, and a user-centered design questionnaire). We found that the BCI performed consistently well across different types of noisy and calm environments. Over the first 9 months, T15 recorded over 250 hours of personally directed use, which was limited by the system requiring a researcher present to initiate it. Since adding the capability for the system to be initiated by a care partner, T15's use hours increased rapidly. Now at over 2 years in the study, he consistently uses the BCI for full days at a

time. We also integrated the BCI into T15's standard consumer software by creating an application that can run on his personal computer and allow for tasks such as sending a text message using the integrated speech decoding or browsing the web - allowing T15 to sustain full time employment. We demonstrate that the neuroprosthesis provided T15 with a stable, long-term means to not only communicate accurately, quickly, and naturalistically, but also the ability to interface with his own devices. This work suggests that BCIs may be a viable alternative to current state of the art assistive devices.

Disclosures: C. Iacobacci: None. **H. Peracha:** None. **N. Card:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regents of the University of California. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regents of the University of California. **X. Hou:** None. **T. Singer-Clark:** None. **L.R. Hochberg:** F. Consulting Fees (e.g., advisory boards); Neuralink, Synchron, Axoft, Precision Neuro, Reach Neuro. Other; Paradromics, Synchron, Precision Neuro, Neuralink, Blackrock Neurotech. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stanford University, Blackrock Neurotech, Neuralink Corp., Regents of the University of California. F. Consulting Fees (e.g., advisory boards); Sonera. **D. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regents of the University of California. F. Consulting Fees (e.g., advisory boards); (former) Paradromics Inc., Globus Medical.

Poster

PSTR126: BMI Speech

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Program #/Poster #: PSTR126.18/T9

Topic: F.05. Brain-Machine Interface

Support: Shenoy Undergraduate Research Fellowship in Neuroscience awarded by Simons Foundation

Title: Advancing Speech BCIs Towards Conversational Speeds in People with Paralysis

Authors: *K. HUSSAIN[1,6], E. KUNZ[2], N. HAHN[3], A. SINGH[4], M. RIGOTTI-THOMPSON[7], D. E. BROWN, Jr.[8], S. YOON[9], B. RICHARDS[10,11], C. IACOBACCI[13], P. H. BECHEFSKY[12], L. R. HOCHBERG[14], D. BRANDMAN[15], S. D. STAVISKY[16], N. AU YONG[12], C. PANDARINATH[17], F. WILLETT[18], J. M. HENDERSON[5];
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Abstract: Intracortical speech Brain-Computer Interfaces (BCIs) have shown promise for restoring rapid communication for individuals with paralysis by decoding the neural representation of speech into text. However, current speech BCI systems still operate at rates below that of conversational rate speech. It remains unknown whether people with dysarthria can comfortably increase their speech rate when instructed to do so, and if so, whether decoding accuracy is affected by this change in preferred speech behavior. To answer these questions, we tested the maximum speech rates achievable by BrainGate2 clinical trial participant T12, who has two 64-channel microelectrode arrays in ventral motor cortex, using various verbal behaviors. Imagined speech reached conversational speeds (120-160 words per minute), while even attempted speech at higher instructed rates surpassed T12s typical pace (100 words per minute compared to her usual 60). We then tested how decoding performance varied across four attempted speaking rates using non-vocalized, mimed speech (attempted mouthed behavior) at 15, 30, 60, and 120 words per minute, using an open-loop karaoke-style task to control the speech rate. In offline evaluations with a limited 50-word vocabulary, we found that decoding accuracy decreased with increasing speech rate, with the optimal decoding accuracy occurring at 30 words per minute. Finally, we examined the neural correlates of speech rate and found sentences repeated at different speech rates were largely stretched or compressed versions of a consistent neural activity template, suggesting linear time scaling describes the neural correlates of speech. Encouragingly, these results suggest that speaking rates can be increased substantially when instructed, and the resulting neural activity remains decodable (although accuracy declines). Additionally, the maximum speech rate for each verbal behavior indicates imagined behaviors can achieve typical conversational speeds while potentially being less tiring and uncomfortable, though trade-offs with decoding accuracy will need to be addressed.

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Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.19/T10

Topic: F.05. Brain-Machine Interface

Title: Intraoperative detection and classification of speech-related neural signals using the Layer 7 Cortical Interface

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Abstract: Brain-computer interfaces (BCIs) based on electrocorticography (ECoG) have shown promise for restoring communication in severely paralyzed individuals, with higher electrode density contributing to improved decoding accuracy. However, optimal placement of high-density grids requires real-time assessment during implantation to ensure adequate signal quality and to guide potential repositioning. Until now, it remained unclear whether speech detection and classification could be performed in real time during awake surgery using high-density µECoG arrays in the data-limited surgical environment. Here, the Layer 7 Cortical Interface was temporarily placed over ~1.5 cm² of ventral sensorimotor cortex in a participant with intact speech during awake craniotomy for tumor resection. The participant performed a word repetition task while an online speech detection algorithm identified high-gamma energy increases (70-170 Hz). A simulated online classification pipeline segmented trials, trained neural network models with the growing dataset, and made classification decisions using the best available model at each timepoint. These results demonstrate that real-time speech detection and classification is feasible using high-density µECoG during awake neurosurgical procedures, supporting the potential clinical viability of intraoperative BCI assessment to optimize electrode placement for long-term implantation success.

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Poster

PSTR126: BMI Speech

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Program #/Poster #: PSTR126.20/T11

Topic: F.05. Brain-Machine Interface

Support: NIH Grant R01-DC019498

Title: Automated speech annotation achieves manual-level accuracy for neural speech decoding

Authors: *Z. SPALDING[1], A. HADWAN[7], S. DURAIVEL[1], K. BARTH[2], S. LAD[3], J. VIVENTI[2], G. B. COGAN[4,2,5,6];
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Abstract: Advances in speech neuroscience have yielded key insights into how neural activity enables speech production, paving the way for translational devices like speech brain-computer interfaces (BCIs) that restore communication to patients with impaired speech function. Accurately assessing the link between speech information and neural activity requires annotations of when participants spoke during experimental tasks to align speech features to windows of neural activity. Manual annotation of participant speech features (e.g. phonemes) is time-consuming and prone to inaccuracies and inconsistencies across different annotators. While automated speech annotation tools that improve speed and reduce annotator bias exist, their performance with respect to paired neural-speech analyses remains untested. Here, we demonstrate that automated speech annotation can achieve comparable neural decoding performance to manual annotation while significantly reducing the required time and effort. We used the Montreal Forced Aligner (MFA), a widely used speech annotation tool, to automatically annotate timing information for spoken phonemes uttered by patients performing an overt, non-word speech repetition task. We compared these automated speech labels to manually generated ones. For associated neural data, we used high-density micro-electrocorticography (μECoG) to collect neural signals from the sensorimotor cortex of five intraoperative patients and extracted the time-varying high-gamma power (70-150 Hz) in one-second windows around MFA- and manually-annotated phoneme labels. Phoneme-level annotations from the MFA were generated ~36 times faster than manual annotations (MFA: 5 min, manual: ~3 hours). We found little difference between the timing of the MFA and manual labels (phoneme start: 17 ms difference between MFA and manual, phoneme end: 39 ms difference, phoneme duration: 22 ms difference; average phoneme duration: 160 ms). Using a linear-discriminant analysis classifier to decode phoneme identity (9-way phoneme classification) from windows of neural activity, we found no significant difference in phoneme decoding accuracy from neural features extracted with the MFA (35.5 ± 2.9%) vs manual annotation (34.6 ± 3.2%). These findings indicate that automated speech annotation using the MFA offers a time-efficient, reliable alternative to manual labeling for neural speech decoding applications. Future speech neurosciences studies

can use this automated system to improve speech annotation pipelines that are essential for advancing the next generation of speech BCIs.

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Poster

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Topic: F.05. Brain-Machine Interface

Support: NIH Grant NINDS 5U01DC018671
JST Moonshot R&D Grant JPMJMS2012

Title: Towards a neuroprosthetic system for restoring both speech and non-verbal gestures in people with paralysis and anarthria

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Abstract: Both speech and non-verbal gestures are fundamental to natural communication and self-expression. However, these abilities can be lost due to paralysis. Brain-computer interfaces (BCIs) offer a promising route to restore the ability to convey both speech and gestures by translating intact neural signals from the sensorimotor cortex into commands to control external devices. While prior BCI research has primarily focused on decoding either the orofacial movements underlying speech or the body movements underlying gestures separately, natural communication often involves the simultaneous use of both modalities. Here, we demonstrate progress toward a BCI that translates neural activity into speech and non-verbal gestures to drive a full-body virtual avatar customized to the user's likeness, enabling more expressive and embodied communication than previous approaches have offered. To show that a single electrocorticography (ECoG) array spanning the sensorimotor cortex captures relevant neural signals for both orofacial and body movements in a chronically implanted participant with paralysis, we first analyzed the somatotopic organization of evoked high-gamma (70-150 Hz) responses during attempted movements. We show robust activity for a range of discriminable effectors. Next, we recorded neural activity as the participant attempted (i) spoken words, (ii) everyday communicative gestures involving discriminable effectors (e.g. waving, nodding, handshakes), and (iii) combinations of words and gestures (e.g. "Hello" while waving). We trained two recurrent neural networks (one for speech, one for gestures) to enable parallel decoding of speech and gestures. We show that speech and gestures can be decoded and used to animate the virtual avatar whether attempted in isolation or simultaneously. Offline analyses show that the electrodes contributing most to speech and gesture decoding are generally distinct

and somatotopically organized. To further demonstrate the versatility of a single implant, we trained models to decode 26 code words representing letters of the English alphabet, as well as the 26 handshapes of the American Sign Language (ASL) alphabet. We show the same ECoG array can decode either speech or fine-grained handshapes for spelling. Together, this work represents a significant step toward a unified neuroprosthetic system capable of supporting multiple forms of communication—spoken language and body movements—thus expanding the possibilities for naturalistic interaction in people with paralysis.

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Poster

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Program #/Poster #: PSTR126.22/T13

Topic: F.05. Brain-Machine Interface

Support: NSF EFRI BRAID 2223822
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Title: The Hidden Limitations of CTC in SOTA Brain-to-Text BCI Systems

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Abstract: State-of-the-art (SOTA) brain-to-text brain-computer interface (BTT-BCI) systems have shown promise in supporting daily communication across various control modes (attempted speech, handwriting, and typing) and recording modalities, with intracortical electrodes offering the highest performance, followed by ECoG and MEG. Despite recent advances, significant error rate disparities persist across words in decoded test sentences. In our previous work, we found that infrequent words with less than 10% probability in a sentence exhibit error rates three times greater than frequent words, leading to semantically significant decoding failures.
BTT-BCIs translate continuous neural activity into discrete behavioral states with variable, and typically unobserved, timing across trials. A key component of SOTA BTT-BCIs is Connectionist Temporal Classification (CTC) loss, which addresses classification and alignment uncertainty by marginalizing over all valid alignments and introducing a blank token. While blank tokens stabilize learning by absorbing uncertain timepoints, they also induce peaky alignments where non-blank predictions occur at a single time point. In this condition, the gradient for surrounding blank frames approaches zero, preventing the model from extending predictions across the full span and causing premature learning plateaus.

We found that in intracortical BCI datasets for both handwriting (Willet et al. 2021) and speech (Willet et al. 2023, Card et al. 2024), the predicted state spans only a fraction of the true movement production time. For instance, phonemes are predicted over a single time bin (40 or 80 ms), while typical speech phonemes last ~100 ms for speakers at 120 words per minute (wpm), compared to 32~62 wpm for the BCI users. This discrepancy strongly suggests a temporal misalignment between model predictions and the full extent of neural population response that unfolds throughout movement production.
Our comparisons across model architectures further confirm that learning halts prematurely. Both MLPs (timepoint-independent) and RNNs (with temporal context) exhibit similar alignment patterns. RNNs demonstrate 5.17% and 7.26% gains over MLPs for speech and handwriting primarily from improved decoding of frequent words. Consistent with recent benchmark results, increased model capacity yields limited gains in raw behavioral state decoding as models remain constrained by CTC's reliance on localized alignments. Consequently, future modeling strategies that account for the full temporal extent of neural activity are likely to learn more robust classifiers to improve generalizability of the BTT-BCIs decoders.

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Poster

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Topic: F.05. Brain-Machine Interface

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Title: Data-driven ECoG Filters for Speech and Hand Motor Decoding in an ALS Patient

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Abstract: Advances in brain-computer interface (BCI) technology have made chronic neural recording in clinical populations both feasible and informative for long-term decoding studies. The present study examines data from one such clinical trial with approximately 2.5 years of neural data from an individual with progressive ALS, during the performance of an established

speech and hand grasp task. The patient was implanted with two electrocorticographic (ECoG) arrays over the sensorimotor cortex, positioned for speech and upper-limb motor decoding. Such rare longitudinal ECoG data from an ALS patient provides the unique opportunity to train data-hungry deep-learning models for data-driven feature characterization and decoding performance analysis. For these purposes, the well-established EEGNet deep-learning architecture for neural signals is employed. Individual EEGNet models are trained to effectively decode action versus idle states using raw grasp and speech data, independently and jointly. The learned convolutional filters are examined to identify interpretable spectral and spatial features associated with each modality. The resulting filters revealed some expected spatio-temporal patterns including activity resembling local motor potentials over hand areas for the hand movements and broadband gamma over more diffuse regions for speech production. Additionally, unexpected patterns were observed that warrant further investigation, such as low-frequency ventral motor activations for hand movements and distinct gamma-range spectral peaks for the combined models. The results elucidate the common neural activations and substrates across speech and grasp tasks, which can be used to inform speech BCI development.

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Poster

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Topic: F.05. Brain-Machine Interface

Support: NIH-NIDCD Grant U01DC19430

Title: Improving brain-to-text decoding via late-fusion ensembling and test-time augmentation

Authors: *S. YOON[1], D. AVANSINO[1], S. MADUGULA[1], B. MESCHEDE-KRASA[2], C. FAN[3], A. D. LEVIN[3], N. S. CARD[6], N. HAHN[1], H. LEE[3], A. SINGH[1], S. R. NASON-TOMASZEWSKI[7], B. JACQUES[7], P. H. BECHEFSKY[7], L. R. HOCHBERG[8,9,10], N. AU YONG[7,11,4], C. PANDARINATH[7], D. BRANDMAN[6], S. D. STAVISKY[6], J. M. HENDERSON[1,5], F. R. WILLETT[1];
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Abstract: Brain-computer interfaces (BCIs) can restore communication in people with paralysis. However, general clinical usage is hindered by limited accuracy, as even modest decoding errors can disrupt naturalistic communication.
To address this problem, we benchmarked an ensemble of neural decoders in an offline setting, achieving considerable improvements over the previous state-of-the-art (SOTA). We then deployed a cloud-based ensemble for online evaluation. However, full ensembling may be impractical for everyday use due to the computational cost of training and continuously recalibrating multiple models. Therefore, we present an equally effective, but significantly more computationally efficient "pseudoensembling" variant via test-time augmentation (TTA). Unlike a full ensemble, TTA generates multiple predictions from just a single model by perturbing input data or model weights.
Our study involved three BrainGate2 clinical trial research participants (T12, T15, and T16) with dysarthria secondary to amyotrophic lateral sclerosis (ALS, 2 participants) or brainstem stroke (1 participant). Recordings were obtained from silicon "Utah" microelectrode arrays placed along precentral gyrus targeting speech production. Participants were instructed to attempt to vocalize a sentence displayed on a screen following a delay period. Sentence cues were drawn from two standard corpora used in automatic speech recognition and language model training, selected to cover both conversational and syntactically complex English.
We find that ensembling substantially reduced offline word error rate (WER) compared to the previous SOTA baseline, from 9.74 to 6.31% (T12), 5.94 to 2.99% (T15), and 40.07 to 33.61% (T16). Notably, TTA, coupled with further regularization, was able to achieve comparable performance. These results demonstrate that our method generalizes across various linguistic and neural signal-to-noise domains.
As decoder complexity grows in parallel with hardware capabilities, full ensembling may remain computationally expensive, despite its reliable performance gains. Our approach highlights a scalable and model-agnostic method to improving decoding accuracy, offering a promising direction toward future clinical translation.

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Poster

PSTR126: BMI Speech

Location: SDCC Halls B-H

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Program #/Poster #: PSTR126.25/T16

Topic: F.05. Brain-Machine Interface

Title: Foundation Models for Reconstructing Speech and Meaning During Naturalistic Story Reading

Authors: *A. SINGH[1], N. TANDON[2];
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Abstract: Neural decoding of speech from intracranial recordings is rapidly evolving into a clinically viable pathway for both functional language mapping and restorative communication in patients with severe speech impairments. While phoneme-based models provide temporally precise articulation mapping, semantic decoders offer generalized communication access for patients unable to produce speech. However, integration of both approaches during continuous, naturalistic language tasks remains underexplored in clinical settings. In this work, we evaluate the feasibility and accuracy of decoding both phonemic and semantic content from high-gamma activity during naturalistic story reading, and to assess their complementary roles in mapping speech networks and supporting communication prosthetics. Nine patients undergoing stereo-EEG implantation for seizure localization completed an active story reading task using excerpts from commonly available storybooks *[e.g., Alice in Wonderland, Hitchhiker's Guide, etc]*. High-gamma (70-150 Hz) neural activity was extracted time-locked to 2s epochs of articulated phrases with a jitter of 500ms to account for word onset and offset effects. We trained a transformer-like model to predict phoneme sequences and diffusion-like architecture to predict contextual embeddings from open-source large language models. These models achieved 40% word-level classification accuracy across 61 unique words, with an average phoneme error rate of [47% ± 11 S.E.], as well as the ability to generalize on unseen vocabulary through phonemic assembly of the articulated words. Vector quantized based decoding of compressed semantic information yielded a mean cosine similarity of [0.67 ± 0.14], accurately reconstructing concept-level meaning even for novel phrasings. Decoding accuracy varied by region and target (semantic versus phonemic), allowing us to isolate shared and unique areas of both processes. We were able to improve performance by creating group-level latent manifolds for both semantic and phonemic decoding models and move towards generalizable, foundation models for language prediction. This study decodes phonemes and meaning from intracranial recordings during naturalistic story reading, revealing distinct yet overlapping circuits for articulation and semantic

intent. By integrating deep sequence models and compressed LLM embeddings, we demonstrate a scalable, interpretable framework for communication BCIs.

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Poster

PSTR127: Upper Limb Neuroprosthetics

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Topic: F.05. Brain-Machine Interface

Support: National Council for Science and Technological Development of Brazil (CNPq) for the doc- toral scholarship (Process n. 142113/2017-4) Coordination for the Improvement of Higher Education Per- sonnel (CAPES) for the mobility scholarship (PSDE Pro- cess 88881.187410/2018-01

Title: Motor Pattern Recognition a Comparative Study for HDsEMG Signal Classification in Transradial Neuroprosthesis Control

Authors: *R. T. XAVIER[1], F. ARTONI[2], E. R. MACHADO[3], M. SANCHES[4], A. CARVALHO[4], S. MICERA[5];
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Abstract: The loss of an upper limb has a profound impact on an individual's personal development, limiting their ability to perform daily tasks and reducing overall quality of life. The use of upper limb prosthetic devices aims to restore lost functions and support rehabilitation, yet this remains a complex challenge for researchers worldwide. Despite technological advancements and improved functionality of these systems, initiating and maintaining effective control remains a significant challenge. Neuroprosthetic devices enable both motor control and artificial sensory feedback, enhancing user interaction and embodiment. Achieving this realistically and safely requires advanced artificial intelligence techniques to ensure autonomy and reliability. The objective of this work was to compare the classification between two deep convolutional neural network models, the deep learning using the transfer learning method for the recognition of muscle contractions in the activation of transradial neuroprostheses. The chosen models were the deep learning GoogLeNet and the 19-layer Visual Geometry Group (VGG19). The database used in this work is the result of the implementation of a multichannel neural interface with high-density surface electromyographic signals (HDsEMG). It contains 64 acquisition channels with monopolar electrodes and a wearable modular structure for the forearm. These signals were processed and converted into scalograms, time and frequency

domain representations using continuous and discrete wavelet transforms, as well as features for feature extraction, pattern recognition, overlapping and an algorithm for extracting classes from signals, labeling. In the classifications, nine classes for training originated from eight movements of the hand and wrist, plus a rest class was applied. The models received the application of four validation metrics to ensure training efficiency. These are the accuracy, sensitivity, specificity, selectivity, and the F1 Score. A database with scalogram images was generated for the training of the investigated models. The GoogLeNet model presented a maximum accuracy of 79.46%, and the VGG19 model presented a maximum accuracy of 85.66%. This work provides evidence on the efficiency of deep learning classifiers with the GoogLeNet and VGG19 models, where they demonstrated their potential to increase the functional capacity of upper limb neuroprostheses. The strategy of using the HDsEMG neural interface with the proposed models effectively improved the results. These discoveries open promising prospects for applications in transradial neuroprostheses.

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Poster

PSTR127: Upper Limb Neuroprosthetics

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Program #/Poster #: PSTR127.02/U2

Topic: F.05. Brain-Machine Interface

Support: University of Arkansas Women's Giving Circle Grant

Title: Grasping real-world and virtual objects with neuro-haptic feedback: a comparison of cognitive load

Authors: *A. K. SHELL, J. ASBEE, A. PENA, J. J. ABBAS, R. JUNG;
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Abstract: Touch is an intuitive sense that naturally guides human movement. Integrating touch into extended reality (XR) systems or prosthetic devices presents challenges, as the tactile feedback produced by these systems often lacks fidelity and fails to replicate the intuitive nature of real-world touch. This could increase cognitive demands on the user. We aim to understand differences in cognitive load related to the interpretation of object characteristics with natural touch and non-invasive neurostimulation based haptic feedback (neuroHF). Participants (n = 12 able-bodied, n = 2 upper-limb loss) were blindfolded and grasped six virtual objects with neuroHF and six physical objects with their hand (sound limb for participants with limb loss) in a randomized order for 36 and 18 total presentations, respectively. Referred sensations to the hand were induced using neuroHF at the wrist to emulate the tactile experience of grasping virtual objects of varied sizes (small, large) and compliances (soft, medium, hard). Functional near-infrared spectroscopy (fNIRS) measuring activity of the left (L-PFC) and right (R-PFC)

prefrontal cortex (PFC), a region known to be taxed during cognitively demanding tasks, was used to assess cognitive load during virtual and physical object grasping. Group-level activation within the L-PFC and R-PFC was determined using a mixed-effect model. For each level of the size and compliance characteristics, estimated marginal means were computed and used to assess effect size and pairwise contrasts with significance correction $q<0.05$. Preliminary results with able-bodied participants reveal that there were differences in PFC activation between virtual and physical object grasping for two object properties. Pairwise contrasts indicated significant differences in HbO in the L-PFC for Soft ($d = 0.72$, $p = 0.01$) compliant objects and in the R-PFC for Small ($d = -0.47$, $p < 0.05$) sized objects. No differences in HbR deactivation were observed. These findings suggest that cortical activation with natural touch and neuro-haptics may vary based on some properties of the object. Ideally, sensory feedback should enhance the user experience rather than introduce added cognitive load. By examining how emulated tactile feedback affects cognitive load, we may find strategies to reduce cognitive demands when implementing sensory feedback in XR and during use of prosthetic systems. Additionally, understanding differences in cognitive load when using emulated and natural touch could guide the development of sensory feedback approaches that are more intuitive for users.

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Poster

PSTR127: Upper Limb Neuroprosthetics

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Topic: F.05. Brain-Machine Interface

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Title: Evaluating proportional force and position regression in children with congenital upper limb deficiencies

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Abstract: In prior work, we have shown that when children born without a hand attempt to move their missing hand, their residual muscles retain a consistent and high level of control. Children are able to achieve up to ten unique hand movements distinguishable through machine learning algorithms, as well as intermediate positional states between rest and a full grasp—otherwise known as proportional control. However, we still do not know what other information may be encoded in the muscle activity, such as level of intended force, and the parameters used to extract relevant proportional data from sensor signals have yet to be optimized in pediatric users. Because this information may be highly relevant to intuitive control of assistive devices such as prostheses, we sought to more deeply examine proportional force and position information in children. Therefore, in order to better understand the muscular control of children born with congenital limb absence and to more effectively translate advanced control techniques to pediatric users, we collected data from 7 participants with unilateral, congenital, below-elbow deficiencies (ages 10-20 years) as they slowly modulated their missing hand position or force level during five different grasp movements. A Delsys Trigno Research System and Terason uSmart clinical ultrasound system were used simultaneously to capture the muscle activity of the children's forearms with 6 sEMG electrodes and one linear array transducer each adhered around the participant's affected and typical limb. By implementing a bilateral mirroring paradigm, we were able to use the typical hand's force and position information as the ground truth intent for the missing limb. Using machine learning regression techniques with conventional signal analysis features (Hudgins set, Efficient set, etc.), we found that for each grasp, the model was able to predict the participants' positional state or force level with above-chance R^2 values of model fit. These results varied depending on the limb, grasp, features, and task, but all participants showed a level of proportional control over their missing hand. The work presented here adds to the growing body of knowledge of how much control children born with upper-limb deficiencies have over their residual muscles, and starts to prioritize some parameters which may work best to optimize algorithmic predictions of proportional state, with the end goal of incorporating proportional control into pediatric prostheses.

Disclosures: E.J. Winslow: None. **H.E. Williams:** None. **W.M. Joiner:** None. **A. Bagley:** None. **M. James:** None. **E. Scheme:** None. **J. Schofield:** None.

Poster

PSTR127: Upper Limb Neuroprosthetics

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.04/U4

Topic: F.05. Brain-Machine Interface

Support: Department of Defense CDMRP OR230164
NSF 128621

Title: A Virtual Hand Platform for Target Achievement Control Task to Evaluate Prosthetic Control Interfaces

Authors: *P. H. D. TRIEU[1], J. D. MCGINNIS[2], J. S. SCHOFIELD[3];
[1]Biomed. Engin., [2]Univ. of California, Davis, Davis, CA; [3]Mechanical and Aerospace Engin., UC Davis, Davis, CA

Abstract: Most children that use an upper limb prosthesis are born with a limb absence. Despite recent technological advancements and sophisticated prostheses that resemble the form and function of an intact hand becoming available, abandonment rate remains alarmingly high with 35-45% of children abandoning their device. Controlling the newly available dexterity remains a significant driving factor for these populations. Our previous work has shown that despite never having actuated an intact hand on the affected side, children with congenital limb absence still retain significant motor control over the muscle that would have controlled the hand. Using ultrasound imaging, we showed that when they attempt to move their missing hand into different positions, distinct patterns of muscle activity emerge that can be used to predict their intended movements. This offers exciting possibilities for intuitive and dexterous control of modern advanced prostheses. However, tools to evaluate this muscle control and potentially train new skills in the context of using prosthetic control remain limited. Thus, we developed a virtual prosthetic platform to evaluate the performance of our sonomyographic control interface. Built in Unity software, this upper limb prosthetic simulator is controlled in real-time by sonomyographic data that is collected and processed by our portable Terason ultrasound equipment, data acquisition system, and MATLAB software. The platform is programmed for the Target Achievement Control (TAC) test, in which participants are prompted to match a target hand by moving the virtual hand to hand grasps at specific levels of closure and maintain this grasps for a period of time. During the task, this task is displayed on a monitor lying flat on a table positioned over the subject's real arm. Variables such as time to grasp and success rate will be measured to evaluate one's performance in the proportional control of a prosthetic hand using sonomyography. In order to properly validate our virtual platform and determine the best parameter settings for our protocol, we beta tested our system in a cohort of able-bodied adults demonstrating its feasibility to accept control commands from our ultrasound control system and to track real time task performance and machine learning metrics. Future work will include the use of the virtual platform and TAC task in testing with children with ULDs to evaluate the performance and translatability of sonomyography-based control interfaces for pediatric prosthetics.

Disclosures: P.H.D. Trieu: None. **J.D. McGinnis:** None. **J.S. Schofield:** None.

Poster

PSTR127: Upper Limb Neuroprosthetics

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.05/U5

Topic: F.05. Brain-Machine Interface

Support: R01 NS130302

Title: Does Motor Cortex Preferentially represent velocity or position during brain-computer interface control of the hand and the wrist?

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Abstract: Motor Cortex (MC) activity reflects a complex interaction between muscle-level dynamics, kinematic/kinetic parameters, and movement goals during voluntary movement. While MC shows preferential tuning to the velocity of arm movements, a study of grasping movements in non-human primates indicated stronger tuning to the position of fingers than to velocity. Studies of tuning to wrist movement have primarily focused on force production and not free orientation in space. To make a controlled comparison of types of tuning to movements of these different sections of the upper limb, we analyzed neural activity from the MC of human brain-computer interface (BCI) participants during center-out-back tasks for the hand, wrist and arm spearately. Here, we show that the strength and timing of neural tuning vary systematically across limb segments, with wrist- and hand-related activity demonstrating greater position sensitivity than previously reported. These findings suggest that finer control over endpoint spatial goals may be supported by position-dominant representations in MC. In contrast, arm-related activity more closely aligned with traditional velocity-based tuning profiles. At the single neuron level, encoding strength fluctuated dynamically across time and movement phase. An improved understanding of the representation of different types of upper-limb movement will contribute to improved ability to decode desired movements of a BCI-controlled upper-limb prosthesis for people with paralysis or amputation.

Disclosures: Y. Won: None. **A.M. Emonds:** None. **M. Iskarous:** None. **C.M. Greenspon:** None. **J.E. Downey:** None.

Poster

PSTR127: Upper Limb Neuroprosthetics

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.06/U6

Topic: F.05. Brain-Machine Interface

Support: MUR PRIN 2022 G53D23004500006

Title: Action enhancement drives embodiment of supernumerary robotic digits

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Abstract: Wearable robotics (WR) combines engineering and neuroscience principles to enhance or rehabilitate motor capabilities (Wu & Asada, 2014; Prattichizzo et al., 2021; Eden et al., 2022). Despite extensive research in behavioral psychology (Hussain et al., 2017; Segura Meraz et al., 2018; Shafti et al., 2021) and cognitive neuroscience (Kieliba et al., 2021; Rossi et al., 2021; Liu et al., 2024), how WR devices can be embodied and how their embodiment relates to enhanced action possibilities remains largely unexplored. This study aimed to address this gap by investigating the potential embodiment of a Sixth Soft Finger (SSF) and its relationship to expanding users' action possibilities. This has significant implications for SSF development and implementation, as embodiment likely promotes device acceptance and daily use. We adapted a proprioceptive drift paradigm from rubber hand illusion research (Tosi et al., 2023) to measure SSF embodiment. Participants (n=32; 16 women, aged 19-53) performed two tasks: grasping and lifting objects using the SSF (Real task) versus raising their hands while activating the SSF without object interaction (Control task). The SSF was mounted on either the palm or the back of the hand. The Palm condition involved actions achievable without the SSF, while the Dorsal condition enabled otherwise anatomically impossible actions, thereby extending users' action capabilities. Proprioceptive drift was measured before and after each task (ten points per measurement). The drift index was calculated as post-task minus baseline means for each condition. To assess the impact of action enhancement on SSF embodiment as measured by proprioceptive drift, we performed a two-way repeated-measures 2×2 ANOVA with CONDITION (Palm vs. Dorsal) and TASK (Real vs. Control) as within-subject factors. The results showed significant main effects of CONDITION ($F_{1,31}=9.18$, $p=0.005$, partial-$\eta^2=0.229$) and CONDITION×TASK interaction ($F_{1,31}=10.93$, $p=0.002$, partial-$\eta^2=0.261$). Post-hoc t-tests showed significantly greater proprioceptive drift in Dorsal versus Palm conditions during the Real task ($t_{31}=4.071$, $p<0.001$, Cohen's $d=0.72$), but not the Control task ($t_{31}=1.293$, $p=0.206$, Cohen's $d=0.229$). Within-condition comparisons revealed significant differences between Real and Control tasks for the Dorsal condition ($t_{31}=3.276$, $p=0.003$, Cohen's $d=0.579$) but not the Palm condition. This study provides the first evidence that SSF embodiment depends on extending the range of users' action possibilities. Future research should investigate SSF embodiment during learning phases in patients and explore underlying neural mechanisms.

Disclosures: F. Genovese: None. **E. Mussini:** None. **M. Fanghella:** None. **G. Barchiesi:** None. **C. Sinigaglia:** None.

Poster

PSTR127: Upper Limb Neuroprosthetics

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.07/U7

Topic: F.05. Brain-Machine Interface

Support: Federal Ministry of Education and Research of the Federal Republic of Germany (BMBF) by funding the project AI.D under the Project Number 16ME0539K

Title: Deep convolutional decoding of complete arm-hand kinematics from intercortical recordings

Authors: *A. CRAIK[1], A. AGUDELO-TORO[2], M. ZAVAGLIA[1], H. SCHERBERGER[2,3], S. HADDADIN[4];
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Abstract: Advancements with invasive Brain computer interfaces have opened up life-altering technologies to the paraplegic population. Brain-controlled robotic limbs can help provide a means for this patient population to interact with their environment, significantly increasing their quality of life. Restoring natural hand use to people with paralysis through robotics will require brain-computer interfaces (BCIs) that decode the entire arm-hand configuration, not just endpoint trajectories. Towards that goal, we present a deep convolutional neural-network (CNN) framework that reconstructs 32-joint kinematics from primate intracortical activity with near-real-time fidelity. Through this work, two adult rhesus monkeys performed a reach-and-grasp task with 50 objects spanning a broad range of shapes and sizes. Spiking activity was recorded from six 32-channel micro-electrode arrays (192 channels total) implanted in anterior intraparietal (AIP), ventral premotor (F5) and primary motor (M1) cortices, while joint angles were extracted with the use of an instrumented glove with electromagnetic sensors (Schaffelhofer et al., 2015). We first benchmarked preprocessing choices—exponential spike-rate smoothing (time constants 5-20 ms), kinematic filtering (low-pass vs. Kalman) and neural history windows (50-400 ms)—using an empirically designed CNN base model. Next, we conducted a grid search over architecture variables (number/width of convolutional blocks, residual vs. dense connections, pooling strategy), regularization methods, training hyperparameters and loss functions. The trials, stratified by object category, were split 80/10/10 % for train/validation/test. Spike-rate smoothing with a 10 ms kernel increased mean R^2 by 0.05. Decoding accuracy rose with window length up to 300 ms and then plateaued; kinematic filter choice had minimal impact. The optimal four-block CNN trained with Huber loss achieved mean $R^2 = 0.83 \pm 0.12$ across all joints. Performance generalized to a second subject ($R^2 = 0.81$), and predicting 150 ms into the future incurred only a modest decline ($\Delta R^2 = -0.08$). A rigorously optimized CNN can decode full arm-hand motion from motor-cortical populations while tolerating latencies compatible with robotic control. This advance narrows the gap toward dexterous, whole-limb prostheses; ongoing work will test transfer to intended-movement decoding in virtual environments.

Disclosures: A. Craik: None. **A. Agudelo-Toro:** None. **M. Zavaglia:** None. **H. Scherberger:** None. **S. Haddadin:** None.

Poster

PSTR127: Upper Limb Neuroprosthetics

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.08/U8

Topic: F.05. Brain-Machine Interface

Title: Soft, wearable sensors for measuring contact forces at the fingertips during unrestrained grasping

Authors: *D. KUDUG[1], L. BORDA[2], D. K. PATEL[2], J. SHULGACH[2], C. MAJIDI[2], D. J. WEBER[3];
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Abstract: The ability to generate and modulate fingertip forces is fundamental for hand function and object manipulation in daily life. Restoring functional hand use after motor impairments requires patient-specific therapy and assistive technologies that can precisely measure user intent from available bio-signals. Additionally, accurate monitoring of finger forces throughout the rehabilitation program can provide information on the patient's progress and the effectiveness of the therapy. The use of high-density electromyography (HD-EMG) to measure muscle activity involved in object manipulation tasks has recently caught much attention. However, while HD-EMG signals can provide spatially rich data for inferring muscle activation patterns, it lacks direct information on fingertip forces. In this work, we introduce a sensing platform that combines HD-EMG with soft, capacitive, high-sensitivity pressure sensors to capture digit-specific contact force profiles during object manipulation tasks.
Our sensors utilize conformable SIS/Ag/EGaIn (Styrene Isoprene Styrene/Silver/Eutectic Gallium-Indium) conductive ink encapsulated in PDMS matrix, enabling robust and repeatable capacitive measurements in the picofarad range. The thin sensor design allows easy integration into the digits of customized gloves to directly capture the contact forces during object manipulation tasks.
This dual-modality setup, combining conformable fingertip sensors with HD-EMG, enables us to easily relate muscle activity to finger force production during tasks. Initial validations, focusing on characterizing the pressure sensors across a range of physiologically relevant forces (5-20 N), have been conducted to evaluate their response characteristics. Future work will include the recruitment of able-bodied participants for in-human validation, aiming to evaluate how the system captures both coordinated muscle recruitment and corresponding fingertip force profiles. This will open up the possibility to better understand inter-digit coordination and grip force modulation patterns used during object manipulation, laying the groundwork for more intuitive feedback systems and adaptive assistive devices.

Disclosures: D. Kudug: None. **L. Borda:** None. **D.K. Patel:** None. **J. Shulgach:** None. **C. Majidi:** None. **D.J. Weber:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock options from NeuroOne, NeuronOff,, cofounder and shareholder of Bionic Power, Inc. and Reach Neuro, Inc..

Poster

PSTR127: Upper Limb Neuroprosthetics

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.09/U9

Topic: F.05. Brain-Machine Interface

Support: NSF Grant CMMI-2128465

Title: Does user performance in high-dimensional control of assistive robot arms depend on the control mode (task space/joint space, position/velocity)?

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Abstract: Advanced robotic arms now have the capacity, in principle, to perform a wide range of activities of daily living, but their use as an assistive technology is limited because controlling complex, high-DOF (degrees of freedom) robots accurately and quickly remains a challenge. Though the type and number of DOFs are a property of the physical robot itself, the schema by which they are issued instructions are numerous (called the **Control Mode**). For example, requesting a specific position in space of the robot's gripper versus the velocities of each of the robot's joints. Here we investigate how (or if) the choice of control mode affects a user's ability to operate a robot arm and gripper. Previous studies investigating joystick-based robot control have found that the robot control mode significantly affects user performance. However, few studies have examined this effect in the context of high-dimensional user inputs, which are common in assistive technologies where the activity of many muscles or neurons is harnessed to generate the user's commands. As a testbed for optimizing high-dimensional input control schemes for robotic manipulators, we link an able-bodied person's finger movements (19-D) into robot commands (6-D), providing the user with simultaneous control of all the robot DOFs. In this within-participants study, we compare participants' performance as they pilot an assistive robot arm to pick up and move objects across four 1.5-hour sessions. In each session, participants use a different robot control mode (joint angle, joint angular velocity, end effector position/orientation, or end effector velocity/rotation). To account for practice effects the sequence of robot control mode used in each session is organized into a balanced Latin square design. Participant performance is evaluated during each session based on the time taken to complete each stage of the task (where stages are object-gripper contact, object grasp, object lift, and object place). Preliminary data from our ongoing study reveal differences in individual participants' performance across the robot control modes. This finding suggests that identifying the preferred robot control mode may be a critical step for maximizing performance in high-dimensional control of assistive robot arms.

Disclosures: S. Khan: None. **Z.C. Danziger:** None.

Poster

PSTR127: Upper Limb Neuroprosthetics

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.10/U10

Topic: F.05. Brain-Machine Interface

Support: NINDS U44NS123301
HAPTIX W911NF-15-2-0016

Title: Training across multiple wrist postures improves EMG-based finger decoding performance

Authors: *S. POTHURAJU[1], B. DEKLEVA[2], J. L. COLLINGER[1], L. E. FISHER[2], R. A. GAUNT[2];
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Abstract: Over one-third of upper-limb prostheses are rejected by people living with an amputation, partly due to limited functionality and lack of independent finger. A major challenge in independent finger control is understanding its complexity, particularly the influence of wrist posture on individual finger movements. Wrist posture affects the biomechanics of the extrinsic finger muscles, with electromyographic (EMG) activity varying up to 70% for the same finger movement across different wrist postures. This variability poses a challenge, as decoders are often trained using EMG data from a single wrist posture. We hypothesize that EMG patterns for individual finger movements vary with wrist posture, as reflected in non-overlapping manifolds, and that decoders trained on one posture will show reduced accuracy on others. Our dataset consists of intramuscular EMG signals from the forearm muscles of 11 able-bodied people and 3 people with transradial amputations. Participants performed 10 repetitions of individual finger flexion-extension movements across five wrist postures: neutral, flexed, extended, pronated, and supinated. To quantify EMG activity similarity between any two postures, the Cross Projection Similarity Index (CPSI) was used. CPSI employs Principal Component Analysis (PCA) to define manifold spaces and measures variance preservation when projecting between configurations. Bidirectional variance ratios were averaged, ranging from 0 (dissimilar) to 1 (identical), and repeated across all wrist configurations. To assess decodability, we trained four classifiers—Linear Discriminant Analysis (LDA), Naïve Bayes (NB), Support Vector Machine (SVM), and Long Short-term Memory (LSTM)—to predict finger identity using EMG data (70:30 training-testing split, 10-fold Monte Carlo validation) across all participants. The EMG data from one posture did not fully capture the variance present in another posture, reducing the CPSI ($p < 0.0125$, Wilcoxon rank-sum test with Bonferroni correction). All classifiers achieved ~88% accuracy when trained and tested on a single posture data. However, accuracy dropped to 34-37% when tested on data from other wrist postures. Training decoders on all postures improved accuracy to ~68%, outperforming cross-posture models but below within-posture performance. Wrist posture significantly impacts EMG activity patterns, as reflected in the reduced CPSI values and training on diverse postures enhances generalization. Future work should explore advanced machine learning techniques to model non-linear and temporal dependencies to further improve accuracy.

Disclosures: S. Pothuraju: None. **B. Dekleva:** None. **J.L. Collinger:** None. **L.E. Fisher:** None. **R.A. Gaunt:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Blackrock Neurotech. F. Consulting Fees (e.g., advisory boards); Blackrock Neurotech.

Poster

PSTR127: Upper Limb Neuroprosthetics

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.11/U11

Topic: F.05. Brain-Machine Interface

Title: Rehabilitation of limbless patients by acquiring EMG signals for the construction of a prosthesis using 3D scanning technology.

Authors: *J.-D.-J. NAVARRO-JR, Jr.[1], I. VALADEZ-ORTEGA[1], A. A. GONZALEZ-GUERRERO[1], R. LOPEZ-CEJA[1], C. A. DEL REAL-HERNANDEZ[1], G. GARCIA-GIL[1], S. G. SANDOVAL-LOPEZ[2];
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Abstract: Introduction: Amputations due to an accident or disease strongly affect people's lives, from the personnel to the work environment, preventing them from performing their activities in the way they used to. Nowadays, more and more technological advances have been developed in the design and implementation of prostheses, however, this technology is not yet available to everyone. In Mexico, about 75 people receive amputations daily, and only 10% of those affected can receive a prosthesis, and the percentage of patients who receive rehabilitation therapy to adapt and use the prosthesis is even lower. Because of that, we propose a portable and economic system, to support the patient's rehabilitation and prosthesis customization. Methodology: Implement a 3D scanning system through the creation of a point cloud to obtain the 3D mesh of the affected patient's limb, as well as the implementation of a sEMG system that helps us to compare the electrical signals of the affected and unaffected limb when performing certain actions. Results: It has been possible to obtain the point cloud and through external software to obtain the 3D mesh to obtain a model of the limb that can be worked on. The correct implementation of the sEMG in non-amputated limbs has been successfully tested. Conclusions: With the implementation of a portable and inexpensive system that supports the rehabilitation of patients who have suffered from amputations, it can change their lives in a great way, returning them the functioning of said lost limb with a customized prosthesis thanks to the sEMG study and the scanning of their limb.

Disclosures: J. Navarro-jr: None. **I. Valadez-Ortega:** None. **A.A. Gonzalez-Guerrero:** None. **R. Lopez-Ceja:** None. **C.A. Del Real-Hernandez:** None. **G. Garcia-Gil:** None. **S.G. Sandoval-lopez:** None.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.01/U12

Topic: F.05. Brain-Machine Interface

Support: I01 RX003699

Title: The effect of perceived simultaneity on the perception of tactile motion evoked by peripheral nerve stimulation

Authors: *J. WRIGHT[1], L. ROLDAN[1], D. J. TYLER[1,2], H. CHARKHKAR[1,3], E. L. GRACZYK[1,2];
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Abstract: Humans can quickly identify the speed, direction, and probable path of an object moving across the skin using information encoded in the first hundred milliseconds of object contact. Restoring this ability in individuals with limb loss is crucial for object manipulation, grasp maintenance, and stereognosis. Previous sensory restoration research with peripheral nerve stimulation (PNS) has focused mainly on static touch properties, such as intensity or location, but much less is known about the spatio-temporal properties of dynamic stimuli. Towards that end, we examined the ability of three subjects with upper extremity limb loss to determine the perceived simultaneity and temporal order of two tactile sensations delivered via PNS. All participants were implanted with Composite Flat Interface Nerve Electrodes (C-FINE) around the median and/or ulnar nerves within the residuum, and two contacts were selected that elicited sensations in distinct locations on the hand. In each experiment, the duration of stimulation through each contact and the temporal offset between the beginning of stimulation on the first and second contacts (inter-stimulus onset interval, ISOI) was varied. For some experiments the intensity of the stimuli was also changed by adjusting the pulse width (PW). All experiments were performed with a forced choice paradigm. In separate sessions, participants identified either 1) whether the sensations at the two locations were delivered simultaneously, or 2) the direction of movement between the two sensations. From experiment 1, we determined the point of subjective simultaneity (PSS) by fitting a logistic function to the data as a function of ISOI and determining the point at which accuracy was 75%. We repeated this experiment for two PW conditions (low and high) and found that there was no significant difference in PSS between PW conditions (grand mean=88 ±44 ms, Mann-Whitney U, $p>0.3$). Experiment 2 showed that the direction of movement between the sensations could not be determined for delays below the PSS (Test of two proportions, $p < 0.02$) but were detectable at 100% accuracy for a large delays. Our data demonstrates that for sensations with an ISOI greater than PSS, participants can reliably detect the order of successive stimuli and therefore the direction of sensations of movement across the skin. These findings allow us to further develop stimulation strategies to evoke sensations of movement across the skin to convey salient time-varying information to neuroprosthesis users. We are further investigating how ISOI and stimulus duration affect the qualitative experience of movement and the experience of continuity in moving touch percepts.

Disclosures: J. Wright: None. **L. Roldan:** None. **D.J. Tyler:** None. **H. Charkhkar:** None. **E.L. Graczyk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patents on Stimulation Algorithms.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.02/U13

Topic: F.05. Brain-Machine Interface

Support: DoD SCIRP SC180308
VAMR I01 RX003699
DARPA INI HR00111990044

Title: Perceptual and cortical representation of frequency modulation of peripheral nerve stimulation

Authors: *P. R. BHAT[1,2,3], B. SPILKER[1,2,3], W. MEMBERG[1,3], J. SWEET[2,4], B. AJIBOYE[1,2,3], E. L. GRACZYK[1,2,3];
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Abstract: Modulating the pulse frequency (PF) of peripheral nerve stimulation (PNS) has been shown to elicit sensations of varying quality for individuals with upper-limb loss, but the neural basis of these perceptual changes has not been explored. Improving our understanding of PF effects could lead to more robust sensory encoders to improve the stability and efficacy of PNS-evoked sensation for people with sensory impairments. In this study, we examined both the perceptual and cortical responses to varying PNS PF in an individual with a C3/C4 sensory-incomplete spinal cord injury. As part of the Reconnecting the Hand and Arm to the Brain (ReHAB) clinical trial, suprathreshold PNS was delivered to selected contacts of an extraneural cuff electrode placed around the median nerve and threshold crossings were recorded from two 64-channel microelectrode arrays in the primary somatosensory cortex (S1). Six PF conditions - 5, 20, 50, 100, 200, 500 Hz - and a control condition of no stimulation were presented for two seconds pseudorandomly. After each stimulation trial, the participant was instructed to rate the perceived intensity and perceived naturalness on a self-selected, open-ended numeric scale. Additionally, the participant selected quality descriptors from a bank of words related to all classes of somatosensation. Intensity ratings at the lowest PF conditions of 5 and 20 Hz were significantly lower than those for PF conditions at 50 Hz and above (Kruskal-Wallis test, $p < 0.0001$, with Dunn-Sidak post-hoc comparisons $p < 0.04$). PFs of 5 and 20 Hz were also associated with the highest naturalness ratings, which were significantly different than all the other conditions (Kruskal-Wallis test, $p < 0.0001$, with Dunn-Sidak post-hoc comparisons $p <$

0.003). Interestingly, naturalness ratings were significantly lower at intermediate frequencies of 50 Hz and 100 Hz than at the highest PF conditions of 200 and 500 Hz (Dunn-Sidak post-hoc comparisons $p < 0.004$). All PNS stimuli were described as 'buzzing', 'electrical', and 'sudden'. The word 'vibrating' was reported more frequently for the 50 and 100 Hz conditions, but the word 'pulsing' was given to all conditions except the 50 and 100 Hz. Intracortical activity in S1 electrodes displayed a peak in normalized firing rate during stimulation onset, and peak amplitude increased with increases in PF (slope-line test, $p < 0.01$). These results help us understand the correspondence of cortical activity to the perceptual experience of modulating PNS frequency, which has implications for designing better stimulation paradigms. This study also explores the effects of PNS in a new population who can benefit from sensory feedback.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

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Title: Evaluating direct motor point targeted functional electrical stimulation in a non-human primate for specific and fatigue resistant control

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Abstract: Functional electrical stimulation (FES) is used to restore movement of a patient's own hand after spinal cord injury, a top priority for many patients (Anderson, 2004). Success has been achieved with simple grasp control, but fully dexterous movements likely require fatigue resistant, coordinated control of multiple degrees of freedom. Many implantation targets (spinal, nerve, muscle, etc.) and electrodes (transcutaneous, cuff, intraneural, etc.) have been developed for this purpose. Each comes with tradeoffs. While some targets are thought to reduce fatigue by leveraging natural recruitment, they risk less specific activation. Some electrodes also carry additional risk as they compress or damage the nerve.

Here, we evaluate our novel approach direct motor point FES (dmpFES) in a Rhesus Macaque using custom PermaLoc electrodes (Synapse Biomedical) implanted on the muscle surface at each motor point (the nerve entry point into the muscle belly). Motor points have been described as the site of lowest threshold (Grandjean and Mortimer 1986) and should have the same benefits as targeting upstream peripheral nerves while being less likely to activate off-target nerve branches. Monkey R had 16 electrodes implanted into motor points of the extrinsic hand muscles while monkey N had 8 intramuscular electrodes in the same muscles. Stimulation data was collected with the monkey under nerve block and bipolar pulses were delivered at 32 ms intervals with either increasing pulse width (PW, 0-255 μs) or amplitude (0-20 mA). Fatigue was studied at a set PW and amplitude pulse train which was repeated for up to 20 minutes in 4 second increments with equal rest periods in between. Joint angle measurements were performed with ImageJ (Schneider 2012) or DeepLabCut (Mathis 2018).
Preliminary results show that joint angle deflections have a sigmoid-like response to increasing PW or amplitude, experiencing threshold, rising phases, and eventual saturation. For example, one wrist extensor in Monkey R had a logistic fit with a slope of .39 degrees/μs, a 52.2 μs midpoint, and a 5.56° maximum deflection from rest. Day-to-day variability in response was observed (both increasing and decreasing the angle). When evaluating fatigue in the same muscle, Monkey R reached 14.6% reduction in absolute angle by the 100th pulse train while Monkey N reached 20% reduction by the 30th. Monkey N never reached 180° at any point, while Monkey R reached 200° before fatigue onset.
Our early observations suggest that dmpFES has potential for specific control that mitigates fatigue. Ongoing characterization to define the output space of all of the electrodes will provide valuable guidance for future use and design.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Topic: F.05. Brain-Machine Interface

Support: DoD CDMRP SCIRP SC180308
VAMR 5I01RX002654

Title: Reconnecting the hand and arm to the brain: targeting optimal grasp-related cortical areas for intracortical brain-computer interfaces in spinal cord injury

Authors: *T. JOHNSON[1,2,3], C. FOLI[1,2], R. BOSE[1,2], R. F. KIRSCH[1,2], W. MEMBERG[1,2], D. M. TAYLOR[3,2,1], E. L. GRACZYK[1,2], B. AJIBOYE[1,2];

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Abstract: Restoration of arm and hand function remains a paramount challenge for individuals with cervical spinal cord injury (SCI). Intracortical brain-computer interfaces (iBCIs) integrated with functional electrical stimulation (FES) offer a promising method for movement restoration; however, their efficacy depends on precise array placement within functionally relevant cortical areas. This study details a multi-modal strategy to identify optimal implantation sites for reach/grasp motor decoding and sensory encoding, extending beyond traditional motor cortex targets. Our approach combines anatomical mapping, task-based functional MRI (fMRI), advanced neuroimaging, vascular imaging, preoperative 3D surgical modeling, intraoperative stimulation, and a post-implantation whole-body mapping paradigm to confirm functional array engagement.

A participant with C3-C5 tetraplegia underwent extensive preoperative neuroimaging (anatomical MRI, diffusion-weighted imaging, task-based fMRI with imagined grasp, reach, and auditory paradigms) to delineate motor targets while avoiding eloquent areas and vasculature. Computational analysis using Quicktome software, integrating Human Connectome Project data, provided refined cortical parcellation and connectivity. Anatomically accurate 3D-printed skull and cortex models supported surgical simulation. Functional imaging identified grasp-related activation in motor cortex (M1), anterior intraparietal area (AIP), ventral premotor cortex (PMv), and inferior frontal gyrus (IFG), clearly dissociable from auditory regions. Quicktome analyses corroborated these results, revealing strong connectivity with motor cortex. Implant sites in M1, AIP, and PMv subregions (6v, 6r) were selected based on functional activation, connectivity, accessibility, and vascular safety. Sensory implant locations were identified using awake intraoperative cortical stimulation, anatomical scans, and fMRI.

Post-implant analysis revealed robust hand/arm-specific tuning across all arrays, validating our targeting strategy. Additionally, we observed tuning to imagined whole-body movements across the sensorimotor network (discrimination rate of 71% across 30 attempted movements), expanding upon prior studies demonstrating whole-body representations in the precentral gyrus. Our findings extend this by revealing novel intermixed motor representations within premotor and sensory regions. This comprehensive, validated strategy represents a significant advancement toward more efficacious and reliable iBCI-FES systems for restoring upper limb function in individuals with severe paralysis.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Program #/Poster #: PSTR128.05/U16

Topic: F.05. Brain-Machine Interface

Support: NIH Grant R01 NS134834-01A1
NIH SPARC HORNET Award 1U41NS129436-01

Title: High-performance, stable decoding of continuous, multi-finger movements from intramuscular electromyography

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Abstract: Full restoration of hand function after upper limb loss will require continuous control of multiple degrees of freedom (DOF). While high-performance classification of discrete grips using intramuscular electromyography (EMG) is well established, continuous, multi-DOF decoding remains a more difficult problem. Current control strategies for prosthetic hands also require frequent recalibration, which can be burdensome for the user. Here we evaluate continuous, multi-DOF EMG decoding with and without same-day calibration. One male rhesus macaque, Monkey N, previously implanted with eight bipolar electrodes in his extrinsic finger and wrist muscles was trained to perform a 2-DOF task to move his index and middle/ring/small (MRS) finger groups to random targets presented on a screen while his EMG and finger kinematics were simultaneously recorded. As a part of a multi-year clinical study, one person suffering from transradial limb loss (P2) was also previously implanted with bipolar electrodes in their residual hand muscles and existing regenerative peripheral nerve interfaces. Their EMG was simultaneously recorded with the finger movements of a virtual hand while they followed along with their phantom limb. EMG from both subjects was used to predict corresponding finger movements for several experimental sessions across nine months. In real-time experiments, only the subjects' decoded muscle activity controlled the virtual hand during the 2-DOF task. Subjects used the controller to move the index and MRS finger groups to targets and hold for half a second. Mean offline correlations of 0.81 +/- 0.04 (45 sessions) and 0.79 +/- 0.06 (7 sessions) between the true and predicted finger positions were achieved using a Kalman Filter (KF) for Monkey N and P2, respectively. During online control, Monkey N and P2 achieved mean trial success rates of 98% and 90%, and mean trial completion times of 1.5 and 2.7 seconds, respectively. To evaluate decoder performance over time, we trained a KF during an initial experimental session and reused those decoder parameters for subsequent sessions over nine months. We found that for both Monkey N and P2, there was no significant slope in online task performance over time ($p > 0.05$). While there were some small but significant differences in task performance within days between the initially trained KF and a same-day trained KF ($p < 0.05$), differences occurred in both directions Variability in online performance within days is expected, given that the offline prediction errors changed day to day, consistent with our previous evaluation of EMG variability (*Vu et al*, 2023).

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

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Topic: F.05. Brain-Machine Interface

Support: NIH Grant R21NS128685
NIH Grant R01NS119160

Title: Predicting and Optimizing Network Effects of Area 3a Intracortical Microstimulation for Restoration of Proprioception

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Abstract: Intracortical Brain-Machine Interfaces (BMIs) are being developed to restore arm and hand function after spinal cord injury by using neuromuscular stimulation to reanimate paralyzed limbs. BMIs can also control robotic or prosthetic limbs for those who may not be candidates for neuromuscular stimulation.
IntraCortical MicroStimulation (ICMS) is often combined with BMIs for restoration of touch in these closed-loop systems as a sense of touch is key to successfully grasping and holding objects. lCMS can also be used to replace lost proprioception and provide real time information about how the limb is moving in space. Although ICMS is most often applied to S1 to restore touch sensation, sensory area 3a, located deep within the central sulcus, is likely a better target for restoring proprioception.
In this study, two Rhesus macaques were chronically implanted with microelectrode arrays in area 3a as well as PMd and M1. Neural recordings from all arrays showed a range of limb-movement-related encoding properties useful for neuroprosthetic control. Importantly, we were able to identify 3a electrode channels that were good candidates for ICMS to restore muscle force sensation--the first step in using ICMS to convey co-contraction or 'limb stiffness'. We are focusing on restoration of muscle force sensation over other proprioceptive sensations because, unlike muscle length or change-in-length, muscle force cannot be deduced visually.
Various heuristics are being explored for picking channel(s) and stimulus parameters to have better specificity of the percepts generated via ICMS.
Additionally, we are exploring the evoked response of different motor network nodes to 3a ICMS (and vice versa) to better understand connectivity within this sensorimotor network. This process will help us identify groups of channels that act in unison for stronger percept generation at lower current densities. Characterizing these evoked responses may also help us better account

for how proprioceptive ICMS could be positively or negatively altering the motor recordings used to drive a BMI-controlled device. By looking at the evoked response to both positive-first and negative-first rapid biphasic stimulation, we can separate out stimulation artifact from the true evoked network responses. The timing, polarity, and spread of the true evoked responses can then be used to make educated guesses regarding how ICMS will affect a network via both ortho- and antidromic neuronal activation as well as mono- and multisynaptic propagation effects.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Program #/Poster #: PSTR128.07/V2

Topic: F.05. Brain-Machine Interface

Title: Representation of high-frequency electrical stimulation in human somatosensory cortex

Authors: *E. ROGERS[1], M. CATTABRIGA[3], B. DEKLEVA[2], C. M. GREENSPON[5], L. E. FISHER[2], G. VALLE[4], R. A. GAUNT[2], M. CAPOGROSSO[1];
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Abstract: Understanding the neural basis of somatosensation is a fundamental neuroscience question with critical translational implications for neuroprosthetics. To address this question, it is crucial to how the cortex responds to both natural and electrical stimuli, as well as the relationship between this behavior and perceived sensation. Recently, there has been particular interest in high frequency stimulation of somatosensory afferents (i.e., at least several hundred pulses per second) due to . Chronic pain patients are now implanted with kilohertz-frequency spinal cord stimulators that are marketed as providing “paresthesia-free” pain relief, in stark contrast to conventional (50 Hz) stimulators that necessarily generate constant buzzing or tingling due to activating mechanosensory afferents, yet it is not known how this is possible. A notable leading hypothesis is that high-frequency stimulation asynchronously activates mechanoreceptors which then produces inhibition in the brainstem, thereby blocking the transmission to supraspinal regions. However, we hypothesize that the unique properties of high-frequency stimulation are not due to blocked transmission but rather due to driving different cortical behavior. To test this hypothesis, we applied both low and high frequency transcutaneous electrical stimulation to a participant (with cervical spinal cord injury but well-preserved sensation) with multi-channel microelectrode arrays implanted in primary somatosensory cortex, as well as various mechanical stimuli. In line with our hypothesis, we found that high frequency stimulation drove robust activity in S1 (rather than be blocked subcortically). Furthermore, we found differences between the stimuli in both trial-averaged

responses on individual channels as well as when using dimensionality reduction techniques to perform population analysis. Altogether, our results provide important context for interpreting current experimental and clinical observations as well as important implications for the design of future neuroprosthetics.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Title: Long-term microelectrode impedances and evoked sensory percepts from intracortical microstimulation

Authors: *R. BOSE[1], M. ABATE[2], B. HUTCHISON[1], K. ALFARO[3], W. MEMBERG[2], T. JOHNSON[1], D. M. TAYLOR[4], J. SWEET[5], B. AJIBOYE[1], E. L. GRACZYK[1];
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Abstract: Tactile feedback is crucial to perform activities of daily living. People with spinal cord injury (SCI) have significant deficits in their tactile feedback, which affects their function and causes negative psychological outcomes. Intracortical microstimulation (ICMS) of the primary somatosensory cortex (S1) using implanted microelectrode arrays has been proposed as a viable option to restore the tactile sensation. To be a reliable feedback modality, ICMS-evoked percepts should be stable across time. Here, we present the initial characterization of ICMS-evoked percepts at one month (T_1) post-implant for a new participant (RP2) and investigate the stability of ICMS-evoked percepts between months 4 (T_2) and 48 (T_3) post-implant for one participant (RP1). As part of the Reconnecting the Hand and Arm to the Brain (ReHAB) clinical trial, 2-3 Utah microelectrode arrays (Blackrock, USA) were implanted in S1 in two individuals with cervical SCI. We delivered ICMS to each electrode and the participants reported the perceived locations of the resulting percepts and their perceived intensities on their own open-ended scale. At T_2 for RP1 and T1 for RP2, we observed that ~40% of the contacts evoked a sensory percept. The percepts spanned across index, middle, ring & palm for RP1, and thumb, index, middle & palm for RP2. In RP1, we observed a decline in the number of electrodes that evoked any sensation from 51 electrodes at T_2 compared to 8 electrodes at T_3. However, the percept location evoked from the remaining 8 electrodes at T_3 were consistent with the percept

location evoked by the same electrodes at T_2. The average impedance across S1 electrodes for RP1 also increased from 0.6 kΩ at T2 to 105 kΩ at T3. In addition, for RP1, there were 44 electrodes that had an impedance >211kΩ (potentially disconnected) at T_3. At T_1, the average impedance for RP2 was 112 kΩ. We observed that ICMS can evoke percepts in the hand within the first month post-implant and that the percept locations can remain stable for 4 years. This is promising for the long-term translation of ICMS. However, over time there was a decline in the number of electrodes that evoked sensation, suggesting that future design improvements are needed to increase the longevity of these microelectrode arrays.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Support: NIH UH3NS107714
NIH R35 NS122333

Title: Single-neuron encoding of corporeal and observed touch in the human somatosensory cortex

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Abstract: The sense of touch plays a crucial role in manual dexterity, object interaction, and experience of our own body. S1 is responsible for extracting and processing tactile inputs from the body, generating a conscious sensory experience. Interestingly, recent studies have shown that this cortical area is active when we observe touch-related actions on the body of others (i.e. vicarious or mirror activity). However, it remains unclear to what extent S1 integrates multisensory information and how this information is encoded. While mirror neurons have been extensively observed in motor-related cortical regions, including M1, PMd, and PMv, there is no concrete evidence of a similar system in S1. Most studies relied on non-invasive brain imaging techniques, leaving open the question of whether S1 neurons encode vicarious properties. Chronically implanted microelectrode arrays in humans allow access to actual and observed touch coding at cellular level. In this study, we simultaneously recorded S1 and M1 neural activity during corporeal and observed touch in multiple participants implanted with

microelectrode arrays. First, we characterized neural responses in S1 to mechanical stimuli on their hands, computing a detailed map of receptive fields (RFs). This map revealed a higher number of multi-digit compared to single-digit RFs, consistent with non-human primate studies and it respected the canonical somatotopic organization of S1. To investigate the dynamics of the neural responses during mechanical touch, we performed a rate coding analysis, which revealed event-locked responses with no adaptation across consecutive touches. We also compared neural responses before, during and after touch, showing significant modulation only during touch. In addition, we measured single-unit activity that allowed us to disentangle individual coding at granular level. By analyzing M1 activity during passive touch, we observed strong, somatotopically organized activity even without movements, highlighting the tight interplay of S1 and M1. Then, to explore possible mirror-like properties, we recorded neural activity during the observation of touches. Preliminary analyses didn't reveal a somatotopic organization and clear event-locked responses. Instead, it seems to induce a more widespread activation, possibly more pronounced in higher-level areas, like BA2, and S2, where visual inputs are more strongly integrated.These findings provide a detailed understanding of how actual and observed touch are processed in the human brain. In the BCI context our results might inform the design of biomimetic ICMS encoding strategy to restore touch in people with paralysis.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Title: Integration of somatosensory percepts from intracortical microstimulation and peripheral nerve stimulation

Authors: *B. SPILKER[1,4,2], P. R. BHAT[2,4], W. MEMBERG[2,4], B. AJIBOYE[2,4,3], E. L. GRACZYK[2,4,3];
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Abstract: Peripheral nerve stimulation (PNS) and intracortical microstimulation (ICMS) can restore tactile sensation to people living with sensory deficits due to spinal cord injury (SCI) or

amputation, but thus far have been characterized in separate patient populations and separate studies. However, in the Reconnecting the Hand and Arm to the Brain (ReHAB) clinical trial, PNS and ICMS can be implemented in the same system. Co-application of PNS with ICMS may allow us to probe how peripheral inputs interact with neural activity in cortical circuits, and could result in more complex or nuanced sensory percepts than either approach individually. The goal of this study was to investigate how percepts evoked from ICMS and PNS integrate, and what effects the relative stimulation onset timing will have on the sensory experience.
A participant living with SCI (AIS-B, C3/C4) was implanted with two 64-channel microelectrode arrays in S1 and composite flat interface nerve electrodes (C-FINE) around the contralateral median and ulnar peripheral nerves. For each experiment, we selected one PNS contact and one ICMS electrode, each with a percept location on the hand. In experiment 1, we conducted a temporal order judgment (TOJ) task for PNS and ICMS stimuli applied at varying onset delays. We calculated the conduction delay for PNS signals to reach the cortex (Td = 52 ms), and selected ten stimulation onset delay values between -2000 and 2000 ms so that PNS inputs would reach the cortex relative to ICMS application at the given delay. The participant was asked to make a TOJ and rate the perceived intensity of both the ICMS and PNS stimuli. In experiment 2, we applied either spatially overlapping or non-overlapping ICMS and PNS and asked the participant to rate the intensity and naturalness of the overall percept.
In experiment 1, the point of subjective simultaneity was -113 ms, indicating that ICMS should be applied 165 ms before PNS to be perceived as maximally simultaneous. The perceived intensity of the ICMS was higher when it was preceded by PNS than when it was applied individually (ANOVA with Tukey post-hoc $p < 0.05$). In experiment 2, the perceived naturalness ratings were significantly greater for conditions when percepts were spatially overlapped than conditions when they were not overlapped (ANOVA with Tukey post-hoc $p < 0.01$).
This study provides new knowledge about how stimulation applied simultaneously at different levels of the somatosensory pathway interact and modulate the evoked sensory experience. These findings lay the foundation for the development of novel neurostimulation strategies for sensory restoration.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Topic: F.05. Brain-Machine Interface

Support: NIH Grant 1R01NS134834-01A1

Title: Improving individuated finger movement decoding from electromyography using intention based recalibration

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Abstract: Brain machine interfaces (BMIs) are a promising technology for restoring mobility to individuals with spinal cord injuries, using machine learning algorithms to decode neural signals into desired actions. There are many approaches to decoding neural signals, including Kalman Filters (KFs). However, KFs are limited in generalizability, speed, and accuracy (Vidal et al, 2016). There have been many advancements in BMIs, such as Recalibrated Feedback Intention Training (ReFIT), which modifies KFs by adding a second calibration step. ReFIT has enabled higher performance (Gilja et al, 2012), and remains useful today. To date, the most independent degrees of freedom (DOF) achieved by a BMI is four, using a ReFIT neural network (Willsey et al, 2025). However, ReFIT's underlying mechanism is not fully understood. It has been suggested that ReFIT improves decoding by interpreting goal-related information in brain signals, which is often referred to as the "intention" to move towards a target. Another hypothesis for ReFIT's success is that it could be more robust to changes in user strategy between effectors (e.g. native hand vs cursor). To examine ReFIT's functionality, we decoded electromyograph (EMG) signals using ReFIT, to our knowledge, for the first time. EMG signals may represent the output of intention rather than intention itself. Therefore, if ReFIT improves BMI decoding purely by better intention estimation, we might expect ReFIT recalibration to show little to no improvement for EMG decoding.
To test this, an adult male rhesus macaque implanted with 8 intramuscular electrodes in his forearm was trained to do a 2-DOF finger movement task. On 5 days, we compared the performance of KF and ReFIT KF (RFKF) decoders using trial time and orbit rate across n=2162 and 2007 trials for each decoder respectively. Orbit rate is the percent of successful trials in which the monkey's fingers oscillated around the targets on screen before settling into place. RFKF exhibited a small but significant improvement in performance compared to the KF. The improvement was dominated by reduction in orbiting rate, which dropped by 26.71% (chi-sq., $p<0.001$) from the KF to RFKF. Trial times also improved by 16.1% (t-test; $p<0.001$). ReFIT's positive effect on EMG decoding suggests that intention estimation alone may not account for ReFIT's decoding improvements, adding nuance to prior understanding of its underlying mechanisms. One possible explanation is that ReFIT reduces noise in the training data. These data also validate ReFIT's ability to decode EMG signals. Future studies will examine ReFIT's functionality further by analyzing its pronounced effect on decoding orbiting behavior.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

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Program #/Poster #: PSTR128.12/V7

Topic: F.05. Brain-Machine Interface

Support: NIH UH3NS107714
NIH R35 NS122333

Title: Cortical and perceptual hand representations explored using intracortical microstimulation of the human somatosensory cortex

Authors: *C. RAZZUOLI[1], G. RISSO[3], N. SHELCHKOVA[4], M. CATTABRIGA[1], T. HOBBS[6], R. A. GAUNT[7], C. M. GREENSPON[5], G. VALLE[2];
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Abstract: Human somatosensation is shaped by principles of somatotopic and hierarchical organization of the primary somatosensory cortex (S1). By measuring tactile perception, we learn not only about the organization of the somatic sensory system, but also about the formation and maintenance of coherent mental body representations. Extensive evidence proved large and systematic perceptual distortions of the tactile space. However, emerging psychophysical phenomena have been studied mostly with natural touch, which undergoes extensive processing along the tactile system, and it is unclear at which stages these distortions arise. Intracortical microstimulation (ICMS) of S1 directly evokes focal and salient touch sensations on the body, which can be modulated by varying stimulation parameters. In this work, we use ICMS of human S1 in participants implanted with microelectrode arrays to define cortical-body maps of the human hand and link them to mental-body maps. First, we identified the spatial acuity of ICMS-based artificial touch, and its reliability compared to natural touch. This technique enables exploration of the cortical hand representations with unprecedented level of granularity. Thus, we used ICMS of S1 to evoke percepts on the contralateral hand by directly activating cortical neurons projecting on specific patches of skin, which we also stimulated mechanically. We found that the detection threshold to distinguish two ICMS-evoked points in S1 (7.02±4.55 mm) was slightly lower than fingertip spatial acuity with natural touch, but comparable to the mechanical acuity thresholds of other parts of the body (e.g., the palm). Then, we compared distances of these points on skin and cortex (via inter-electrode distances) creating fine cortical-body maps, observing somatotopic and magnification factors typical of the somatosensory homunculus. Collecting both physical and perceived distances between two points, we defined the relationship between cortical-body and mental-body spaces. We found perceptual biases in both skin and cortical stimulation, rejecting the hypothesis of effects of peripheral processing on mental-body representation. These biases showed significant correlations with cortical representations, suggesting that S1's spatial layout contributes to perceptual distortions. Hence, by modeling perceived distances based on anatomical and activation brain and skin parameters, we confirmed that mental-body representations are shaped by multiple spatial factors. Finally, in the context of bionics, our study sheds light on the needs of current neurotechnology, guiding implant design for somatosensory restoration.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

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Program #/Poster #: PSTR128.13/V8

Topic: F.05. Brain-Machine Interface

Support: National Cancer Institute of the NIH R01CA281301

Title: Restoring sensation post-mastectomy: First implementation of peripheral nerve stimulation to restore sensation and reduce pain post-mastectomy

Authors: *L. ROLDAN[1], N. SHELCHKOVA[4], R. BOSE[2], T. A. MENDOZA[4], D. ROMANCHICK[4,6], S. HANSON[6], N. JASKOWIAK[6], S. SHUBECK[6], D. J. TYLER[3], C. M. GREENSPON[5], S. LINDAU[6], E. L. GRACZYK[3];
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Abstract: In a mastectomy, one or both breasts are removed for the treatment or prevention of breast cancer. This operation includes cutting many of the nerves to the breast, which often results in loss of sensation or chronic pain. Restoring sensation has the potential to improve embodiment of the chest, reestablish affective and erogenous touch, reduce pain, and improve quality of life. Prior work has successfully used Composite Flat Interface Nerve Electrodes (C-FINEs) to stimulate peripheral nerves and restore touch sensation to the hands and feet. The Bionic Breast Project aims to restore breast sensation and mitigate pain by electrically stimulating the intercostal nerves via implanted C-FINEs. Here, we report the results from the first participant who received C-FINEs and will complete 8 weeks of peripheral nerve stimulation (PNS). Tactile sensitivity of the breasts pre-surgery was evaluated with the monofilament detection and 2-point discrimination tests. During this baseline testing the finger had lower detection thresholds than the breast and nipple-areolar complex, and the medial side of each breast had lower thresholds than the lateral side. The patient underwent bilateral skin-sparing mastectomies with 4-contact C-FINEs implanted around intercostal nerves T3 and T4 on the non-cancer side. The target nerves were 1.5-2 mm in diameter and 1-2 cm of nerve length was preserved. The nerve ends were sutured by their epineurium to the chest wall to secure their position, and the C-FINE leads were tunneled through the skin above and lateral to the incision. There were no surgical or immediate post-operative complications related to C-FINE implantation. Following 4-6 weeks of recovery, PNS will be delivered to the C-FINEs weekly to characterize the evoked percepts. Adaptive psychophysical methods, including detection, estimation, and discrimination tasks, will be used to characterize the percepts' location, intensity, quality, and naturalness. Surveys and questionnaires will also be used to track pain, sexual

function, and other quality of life metrics over the course of the study. To evaluate changes to residual sensation, pain post-mastectomy, and changes due to PNS, the implanted side will be compared to the non-implanted side. The C-FINEs will be removed during the second phase of the reconstructive surgery (4-6 months post-implant). The Bionic Breast Project is the first of its kind to evaluate the application of PNS to the intercostal nerves post-mastectomy to restore touch sensation and mitigate pain. Success of this study will lead to further development of this innovative neuroprosthetic technology to improve the lives of people undergoing mastectomy.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.14/V9

Topic: F.05. Brain-Machine Interface

Support: DoD SCIRP SC180308
VAMR I01RX002654

Title: Reconnecting the Hand and Arm to the Brain (ReHAB): Using multi-contact nerve cuffs for motor and sensory restoration

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Abstract: Spinal cord injury (SCI) can result in motor and sensory deficits below the injury. The Reconnecting the Hand and Arm to the Brain (ReHAB) clinical trial restores motor and sensory function by using neural interfaces to bridge the gap between the brain and the body. Motor intent is decoded from the brain and translated into functional electrical stimulation (FES) to activate the shoulder, arm, and hand. Sensory percepts can be evoked using peripheral nerve stimulation or intracortical microstimulation. Two research participants with tetraplegia due to SCI (RP1: AIS B C3/C4, and RP2: AIS C C3-C5) were implanted with multi-contact composite flat-interface-nerve-electrode (C-FINE) cuffs around various nerves serving proximal and distal arm and hand movements for functional restoration. Prior to implantation, ultrasound was used

to measure the cross sectional area of the nerves, including median, radial, and ulnar nerves at varying locations along the arm. Custom fit C-FINES were implanted in the upper arm around the suprascapular, median, radial, and ulnar nerves. In RP2, additional median and ulnar cuffs were placed in the forearm around the with the goal of providing more selective control of individual fingers. IM electrodes were placed in various muscles including the anterior deltoid, triceps, and pectoralis major muscles to supplement the C-FINEs and help stabilize reaching movements. Each electrode was briefly tested intrasurgically to ensure that the expected muscle activation was evoked.Characterization of responses to cuff stimulation in RP1 (up to four years post-implant) and RP2 (currently four months post-implant) showed strong and expected motor responses, including functional reaching movements as well as individuated finger movements, both independently and synergistically. In RP2, preliminary comparison of motor responses to median and ulnar cuff stimulation showed greater selectivity of muscle activation for hand movement using cuffs located below vs above the elbow. Cuff stimulation also produced sensory afferents due to the participant's injury being sensory incomplete, evoking somatosensory percepts in the hand and arm for the median, radial and ulnar nerve cuffs. Further work will characterize the evoked motor and sensory activations more fully and compare the selectivity between the proximal and distal electrodes on the same nerves using standard recruitment curve approaches.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Program #/Poster #: PSTR128.15/V10

Topic: F.05. Brain-Machine Interface

Support: NIH 5T32DC000023
NIH R01DC018300

Title: Histological analysis of chinchilla inner ears following two weeks of continuous vestibular ionic direct current stimulation

Authors: *W. M. THOMAS[1], C. FERNANDEZ BRILLET[2], M. LEHAR[1], Y. BALHI[1], C. GRAHAM[1], C. C. DELLA SANTINA[1,2], G. Y. FRIDMAN[1,2];
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Abstract: Ionic direct current (iDC) stimulation is a neuromodulation technique for directly exciting, inhibiting, and sensitizing neurons. It has potential advantages over conventional pulsatile stimulation including improved inhibitory capacity and preservation of stochastic firing properties. To date there has not been an evaluation of the safety of iDC exposure per se in a

chronic implant, and understanding the cumulative risk of prolonged iDC stimulation is important for future translation efforts. To assess the safety of iDC, four chinchillas were bilateral implanted with iDC fluid conduits filled with agarized artificial perilymph into their superior semicircular canals. Prior to implantation, the animals received intratympanic gentamicin injections in both ears to cause vestibular hypofunction. After implantation, the left side tubes delivered iDC stimulation for 14 days from a head-mounted stimulator, while the right side remained unstimulated as a within-animal control. Following the implant period, the subjects were placed under deep anesthesia and euthanized via transcardiac perfusion using 4% paraformaldehyde fixative solution. The inner ears were dissected from the skull with the implant remaining incased in dental acrylic within the tympanic bulla. Following dissection, the specimens were placed in 0.5 M ethylenediaminetetraacetic acid to decalcify. Once decalcification was complete, the implant and remaining dental acrylic were removed, and the specimens were embedded in paraffin and sectioned along the horizontal plane at 10-micron intervals. The sections were stained with hematoxylin and eosin. Foreign body encapsulation could be observed around the conduit track in all specimens, with some observed instances of neo-ossification. Hair cells within the superior canal ampulla, horizontal canal ampulla, and utricle in both conditions (stimulated vs. unstimulated) showed signs of gentamicin-induced damage, but there was no clear indication of any additional damage due to delivery of iDC. Evaluations of the superior aspect of vestibular (also known as Scarpa's) ganglion could not be performed for every specimen due to loss during dissection, but there was no qualitative difference in the ganglion cells of stimulated and unstimulated inner ears when examining two good specimens in each condition. These results indicate that iDC delivery may be no more injurious than the conduit implant alone.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Topic: F.05. Brain-Machine Interface

Support: NIH BRAIN Initiative UG3NS107688
Blackrock Neurotech Contract to West Virginia University
Blackrock Neurotech Contract to University of Utah
Blackrock Neurotech Contract to University of Minnesota
Blackrock Neurotech Contract to Hannover Medical School

Title: Auditory Nerve Implant: Evaluating a new hearing prosthetic technology

Authors: *L. RIETH[1], I. SONDH[2], K.-H. DYBALLA[7], M. LEBER[8], J. CREW[8], K. HUEBNER[9], A. P. HEILLER[3], L. A. JOHNSON[10], G. M. GHOSE[4], W. M. THOMAS[11], H. A.

HOLMAN[12], R. GURGEL[13], D. J. WARREN[15], S. ZUNIGA[16], A. LOVELAND[5], R. FRANKLIN[17], A. SAMII[18], A. J. OXENHAM[6], S. B. STRAHL[19], F. SOLZBACHER[14], H. H. LIM[2];
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Abstract: Cochlear implants have now been used to treat >1 million patients [Zeng 2022], a historic achievement for this impactful neuroprosthetic technology. Advancing cochlear implants to better stimulate the auditory nerve has plateaued, putatively due to the difficulty in stimulating the nerve through the bony wall of the cochlea with intracochlear electrodes. This has limited progress in improving outcomes for real-world tasks such as understanding speech in noise. Our project has developed a penetrating microelectrode array, a Blackrock Neurotech Auditory Nerve Interface (ANI) electrode coupled to a MED-EL Synchrony 2 cochlear stimulator. The goal is to evaluate the benefits of more direct and focal microstimulation through perceptual testing, necessitating an investigational clinical study. Extensive pre-clinical and intraoperative clinical evaluations have been performed to pave the way for a clinical study of the ANI device, which we report here. A first-in-human intraoperative study with nine volunteers was performed under Ethics Committee approval at the Hannover Medical School in Hannover, Germany. This study was performed with volunteers receiving tumor resection surgeries by a translabyrinthine approach, the same surgical approach utilized for the ANI device. We evaluated the surgical approach, device handling, and electrode placement, as well as evoked auditory brainstem responses (eABRs) and electrode impedances with a wired version of the electrode array. Nerve viability was initially verified by stimulating with the Auditory Nerve Test System (ANTS) and a cochlear electrode. High-quality responses were measured with stimulation thresholds estimated between 20 and 40 μA from subjects demonstrating viability of the surgical and technology approaches. Forward masking paradigms support independence of evoked activity between electrodes. Pre-clinical studies with 3-month endpoints in cat models with periodic stimulation, evaluation eABRs, and electrode impedances measurements were also completed. These studies demonstrated sustained evoked auditory brainstem responses (eABRs) and that a majority of electrode impedances stayed below <70 kΩ. This supports the sustained health of the nerve and performance of the device over clinically relevant periods. In conclusion, these data support the ANI device is sufficiently safe and effective to support conducting critical perceptual testing as part of a clinical study.

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Neurotech. **K. Huebner:** A. Employment/Salary (full or part-time): MED-EL. **A.P. Heiller:** None. **L.A. Johnson:** None. **G.M. Ghose:** None. **W.M. Thomas:** None. **H.A. Holman:** None. **R. Gurgel:** None. **D.J. Warren:** None. **S. Zuniga:** None. **A. Loveland:** None. **R. Franklin:** None. **A. Samii:** None. **A.J. Oxenham:** None. **S.B. Strahl:** A. Employment/Salary (full or part-time): MED-EL. **F. Solzbacher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock Neurotech. **H.H. Lim:** 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.; Blackrock Neurotech.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

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Program #/Poster #: PSTR128.17/W1

Topic: F.05. Brain-Machine Interface

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Title: Effect of sensory feedback on visual attention while using a prosthetic hand

Authors: *H. DIRRIGL, S. S. KUNTAEGOWDANAHALLI, J. ASBEE, R. JUNG, J. J. ABBAS;
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Abstract: While there have been great advancements of multifunction prosthetic hands, users of myoelectrically-controlled prosthetic hands still report high demands for visual attention while performing everyday tasks. This is primarily due to the lack of sensory feedback, resulting in ongoing visual monitoring of the prosthesis during use. To address this limitation, we developed a neural-enabled prosthetic hand (NEPH) system that uses a sensorized prosthetic hand, prosthesis-mounted electronics, and a wirelessly controlled implanted neurostimulator to elicit task-relevant sensations referred to the phantom hand. We are currently conducting a first-in-human study (clinicaltrials.gov ID: NCT03432325) with the system. Here, we report on initial studies to assess the impact of sensory feedback on visual attention during everyday tasks. Eye tracking technology has advanced the study of visuomotor behaviors in upper limb prosthesis users and offers critical insights into both the acquisition of visual information during fixation and the cognitive processes underlying the use and control of multifunction prosthetic hands. We used Tobii Glasses 3 to assess fixation, gaze, saccade, and glance metrics of participants with a unilateral upper limb amputation who are currently enrolled in the NEPH study. Eye movements were monitored during two standardized assessments, the Southampton Hand Assessment Procedure (SHAP) and the Activities Measure for Upper Limb Amputation (AM-ULA), and one additional lab-developed assessment for testing hand dexterity that required participants to use a

squeeze bottle containing water to fill a graduated cylinder to a specified level. While wearing the Tobii Glasses, participants performed each assessment twice with the prosthetic hand, once with and once without sensory feedback enabled, and once with their contralateral hand. Assessment sequence was randomized across subjects. In this study fixation duration, saccade amplitude, and fixation count were calculated to quantify visual attention to the prosthesis and objects used while performing tasks under the test conditions. Preliminary results indicate that patterns of visual attention varied across test conditions, with indications that visual attention overall was higher with the prosthetic hand compared to the contralateral hand and visual attention to the prosthesis was lower with sensory feedback enabled on the prosthetic hand compared to the condition without sensory feedback. This suggests sensory feedback could help improve the quality of life of upper-limb prosthesis users by reducing demands for visual attention while performing activities of daily living.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Topic: F.05. Brain-Machine Interface

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Title: Efficacy and longevity of intracortical microstimulation of the human somatosensory cortex

Authors: *T. HOBBS[1], C. M. GREENSPON[6], C. VERBAARSCHOT[2], R. LIENKAMPER[3], N. SHELCHKOVA[7], G. VALLE[9], J. E. DOWNEY[8], N. G. HATSOPOULOS[7], J. A. GONZÁLEZ-MARTÍNEZ[4], J. L. COLLINGER[1], M. BONINGER[1], R. A. GAUNT[5];
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Abstract: Intracortical microstimulation (ICMS) of the somatosensory cortex (SC) evokes artificial tactile percepts. To evaluate its long-term efficacy, we analyzed psychophysical and functional data from five participants with spinal cord injury (SCI) implanted with microelectrode arrays in Brodmann's Area 1. After more than 150 million delivered pulses over 23 cumulative implant years, we assessed detection thresholds, projected field (PF) coverage, and percept quality. Initial detection thresholds were low for most participants (14.5-22.5 µA median) and increased gradually over time (~5.2 µA/year on average), though variance existed

across participants. At 10 years post-implant, 42% of electrodes in one participant remained below the 80 μA functional threshold. Multi-electrode stimulation enabled the recruitment of otherwise subthreshold channels, preserving percept coverage. Projected field maps remained stable in location and spatial extent relative to year-one baselines. The distributions of sensory quality reports—including mechanical (touch, pressure) and parasthetic (tingle, buzz) descriptors—were consistent across time within electrode arrays ($r = 0.81$-0.97 in 3 of 5 participants). The reported naturalness of percepts remained stable or improved, and pain reports were rare and mild. While increases in detection thresholds can occur, these data demonstrate that ICMS reliably evokes informative, high-quality tactile sensations over years of use. These findings establish a foundation for future clinical implementation of ICMS-based sensory neuroprosthetics.

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Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

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Program #/Poster #: PSTR128.19/W3

Topic: F.05. Brain-Machine Interface

Support: KU Leuven Grant IDN/19/043
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Title: Chronic performance and biocompatibility of flexible polyimide neural implants with PLGA bioresorbable coating in the visual cortex of two non-human primates

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Abstract: Chronic neural implants must maintain long-term functionality while minimizing the foreign body response to preserve neuronal health and recording quality. We evaluated the histological and electrophysiological performance of 20 μm thin, flexible polyimide-based intracortical arrays with a 150 μm bioresorbable poly(lactic-co-glycolic) acid (PLGA) coating

designed to mitigate chronic inflammation and gliosis. Two male rhesus monkeys were implanted in the primary visual cortex (V1) with these coated arrays and monitored for 3 months (Monkey A, 8 years old) and 2.5 years (Monkey B, 10 years old), respectively. The coating loses its structural integrity after a few days and completely dissolved 3-4 weeks after implantation. Throughout the implantation periods, multi-unit and single-unit activity were recorded regularly to assess neuronal yield, while impedance spectroscopy was conducted to track electrode integrity. Both remained stable over the course of the study. In addition to passive recordings, the arrays were used in the context of cortical visual prosthesis development.
Histology was performed by cutting 5-20-µm thick slices at multiple depths with a microtome and scanning them with a Nikon-Marzhauser SlideExpress 2. Histological analysis included hematoxylin and eosin (H&E) staining, complemented by immunostaining for neuronal nuclei (NeuN) and glial fibrillary acidic protein (GFAP) to assess neuronal density and astrocytic response, respectively. Implant locations were retrieved by comparing the sections with intraoperative images and analysis was therefore not blinded.
Histological analysis revealed substantial preservation of neuronal density in both subjects, with limited glial activation in the vicinity of the coated arrays relative to control tissue in the same tissue section. These results suggest that combining a soft, flexible substrate with a bioresorbable coating offers a promising strategy for mitigating chronic immune responses and maintaining signal fidelity in long-term cortical implants. This work supports the continued development of bio-integrated brain-machine interfaces for stable, high-quality recordings in translational and clinical neurotechnologies.

Disclosures: **L. Goyvaerts:** A. Employment/Salary (full or part-time): ReVision Implant. **L.M. Merken:** A. Employment/Salary (full or part-time): ReVision Implant. **M. Schelles:** A. Employment/Salary (full or part-time): ReVision Implant. **S. Ospitalieri:** None. **N. Corthout:** None. **F. Ceyssens:** A. Employment/Salary (full or part-time): ReVision Implant. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ReVision Implant. **M. Kraft:** None. **P. Janssen:** None.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.20/W4

Topic: F.05. Brain-Machine Interface

Support: NIH NINDS Grant U01NS123127
Boswell Foundation
Tianqiao & Chrissy Chen BMI Center

Title: Experiences Elicited by Intracortical Microstimulation delivered in the Human Anterior Intraparietal Area

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Abstract: Bidirectional brain-machine interfaces (BMIs) are typically controlled by decoding movement intent from primary motor cortex and delivering information to primary somatosensory cortex (S1) via intracortical microstimulation (ICMS). Compared to S1, however, parietal cortical regions like the anterior intraparietal area (AIP) encode more complex information including entire hand conformations for grasping, specific reach trajectories (e.g., reaching toward the mouth versus the chin or cheek), and even properties about objects. Therefore, BMI performance might be improved by delivering feedback directly to such higher-level encodings via ICMS compared to primary areas like S1. Here, we investigated whether ICMS in human AIP (≤100 μA, 300 Hz, 1000 ms) could reliably elicit experiences using a two-alternative forced-choice task. If the participant could repeatedly choose in which of two otherwise identical periods ICMS was delivered, we concluded the ICMS reliably elicited experiences. The participant correctly identified the period with ICMS on at least 9/10 trials involving 41/64 (64%) AIP electrodes. As a positive control, the task was then performed with ICMS delivered on each of 32 channels across two S1 arrays, all 32/32 (100%) of which enabled the participant to correctly identify the period with stimulation on at least 9/10 trials. Whereas experiences elicited by S1-ICMS were described as “pressure”, “touch”, or “tingles” on the hand, experiences elicited by AIP-ICMS were often difficult for the participant to describe. Rather, the experiences commonly manifested as “pre-sensations” or “gut feelings” about locations on the hand. The reported locations following AIP-ICMS were somatotopically organized, and AIP-ICMS could be detected at amplitudes below 20μA, similar to detection thresholds for S1-ICMS. Given that AIP neurons encode complex movements, electrodes positioned in AIP may be used to concurrently decode such movements and deliver somatosensory feedback related to those higher-level encodings. Ultimately, ICMS can be used to safely deliver information to human AIP, which may be an effective cortical territory for improving BMIs.

Disclosures: B.M. Ruszala: None. **D.A. Bjanes:** None. **K. Pejsa:** None. **B. Lee:** None. **C. Liu:** None. **R.A. Andersen:** None.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

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Program #/Poster #: PSTR128.21/W5

Topic: F.05. Brain-Machine Interface

Support: DoD SCIRP SC180308
VAMR I01RX002654
NIH T32EB004314

Title: Fast and Accurate Mapping of Peripheral Nerve Stimulation Parameters Using the Strength-Duration Curve

Authors: *B. ALEXANDER[1,4], R. ADAMS[2], W. MEMBERG[1,4], R. F. KIRSCH[1,4,2], S. BAZAREK[3,4,2], E. L. GRACZYK[1,4,2], J. SWEET[6,3], D. J. TYLER[1,5,2], B. AJIBOYE[1,4,2]; [1]Biomed. Engin., [2]Sch. of Med., [3]Neurolog. Surgery, Case Western Reserve Univ., Cleveland, OH; [4]Functional Electrical Stimulation Ctr. of Excellence, [5]Advanced Platform Technol. Ctr. of Excellence, Louis Stokes Cleveland VA Med. Ctr., Cleveland, OH; [6]Univ. Hosp., Cleveland, OH

Abstract: Functional electrical stimulation (FES) can restore motor control to people affected by spinal cord injury (SCI) or stroke through stimulation of peripheral nerves. Because every human nerve is unique, the inputs (stimulation parameters) and outputs (muscle activations) of FES systems must be characterized for each participant before functional movements can be created. Most existing systems use 2D recruitment curves (RCs), modulating either pulse amplitude (PA) or pulse width (PW), while holding the other parameter constant. This is because it has historically been too time intensive to characterize the full PA-PW space with a 3D recruitment surface (RS). However, there are many potential benefits of full RS characterization, including greater muscle selectivity, better fatigue mitigation, and higher precision of movement. This study describes and validates a fast, accurate, and automatic method of characterizing the full PA-PW stimulation space by leveraging the strength-duration curve.
Stimulation parameters were systematically tested in two participants with tetraplegia due to SCI who are enrolled in the Reconnecting the Hand and Arm to the Brain (ReHAB) clinical trial. Multi-contact nerve cuff electrodes delivered low frequency twitch stimuli while electromyography (EMG) was recorded to determine the individual muscle responses. Three RS acquisition methods were tested with all of the available nerve cuff electrodes. An equally spaced grid (ESG) method naively sampled the entire stimulation space with 200 points. A Gompertz function inspired (GFI) method algorithmically sampled the space with a median of 69 sampled points assuming a specific surface fit equation (Freeberg et al. 2011). Finally, our novel SD curve (SDC) based method used just 16 points to acquire one PW modulated RC at maximum PA and one PA modulated RC at maximum PW. SD curves were constructed between the two RCs and a surface was fit to them. R^2 values for each acquisition method were calculated by comparing the predictions of a given method to sampled test points from the middle 80% of the normalized EMG range.
The median R^2 values for ESG, GFI, and SDC methods were 0.88, 0.85, and 0.87 respectively. No significant differences were found between the predictive performance of each method. The SD curve based method was 12 times faster than the ESG method and 4 times faster than the GFI method with no significant change in accuracy. This novel method enables faster characterization of FES parameters, making it feasible to map the full parameter space and laying the groundwork for more dexterous FES stimulation patterns.

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rights/patent holder, excluding diversified mutual funds); Afference Inc., Barologics, Inc.. **B. Ajiboye:** None.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.22/W6

Topic: F.05. Brain-Machine Interface

Support: DoD Award HT9425-23-1-0623
DoD Award W81XWH-20-1-0802
NIH T32 Grant AR007505-35

Title: Elicited plantar sensation modulates residual limb muscle activity in people with lower limb loss

Authors: *L. M. HAUCK[1,2], S. LI[1,2], R. J. TRIOLO[1,2], H. CHARKHKAR[1,2];
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Abstract: Lower limb amputation disrupts sensorimotor function, leading to locomotor deficits. Individuals with lower limb loss (LLs) often have a high risk of falls, asymmetrical gait, and impaired balance. These difficulties are partly attributable to the loss of plantar sensation which provides critical input for modulating spinal excitability, regulating muscle activity throughout the gait cycle, and supporting dynamic stability. In the absence of this feedback, LLs rely on visual feedback and compensatory strategies to maintain stability. High-density peripheral nerve cuff electrodes can electrically activate afferent fibers to elicit plantar sensations perceived as originating from the missing foot, which has been shown to improve gait symmetry, locomotor adaptation, and stability. Given the abnormal residual muscle co-contraction and irregular activation patterns commonly observed in LLs, we investigated whether electrically elicited plantar sensation (EPS) alters residual muscle activity during walking. Two individuals with transtibial limb loss and one individual with a knee disarticulation walked on an instrumented treadmill at self-selected speed for two minutes with and without EPS. Electromyograms (EMG) from residual limb muscles were recorded from implanted intramuscular electrodes. Gait cycles were identified using heel strike and segmented into four equal phases. EMG activity across phases and EPS conditions were compared by repeated measures ANOVA. Notably, significant decreases in medial gastrocnemius and biceps femoris activity ($P < 0.001$) were observed for one participant (Fig. 1) during the swing phase, indicating decreased co-contraction corresponding to the inhibition expected during unimpaired walking. These findings suggest that EPS can influence residual limb motor output, potentially through modulation of spinal circuits that inhibit muscle activity. This work supports the role of EPS in sensorimotor integration and holds promise to improve metabolic cost of ambulation and myoelectric control in lower limb prostheses.

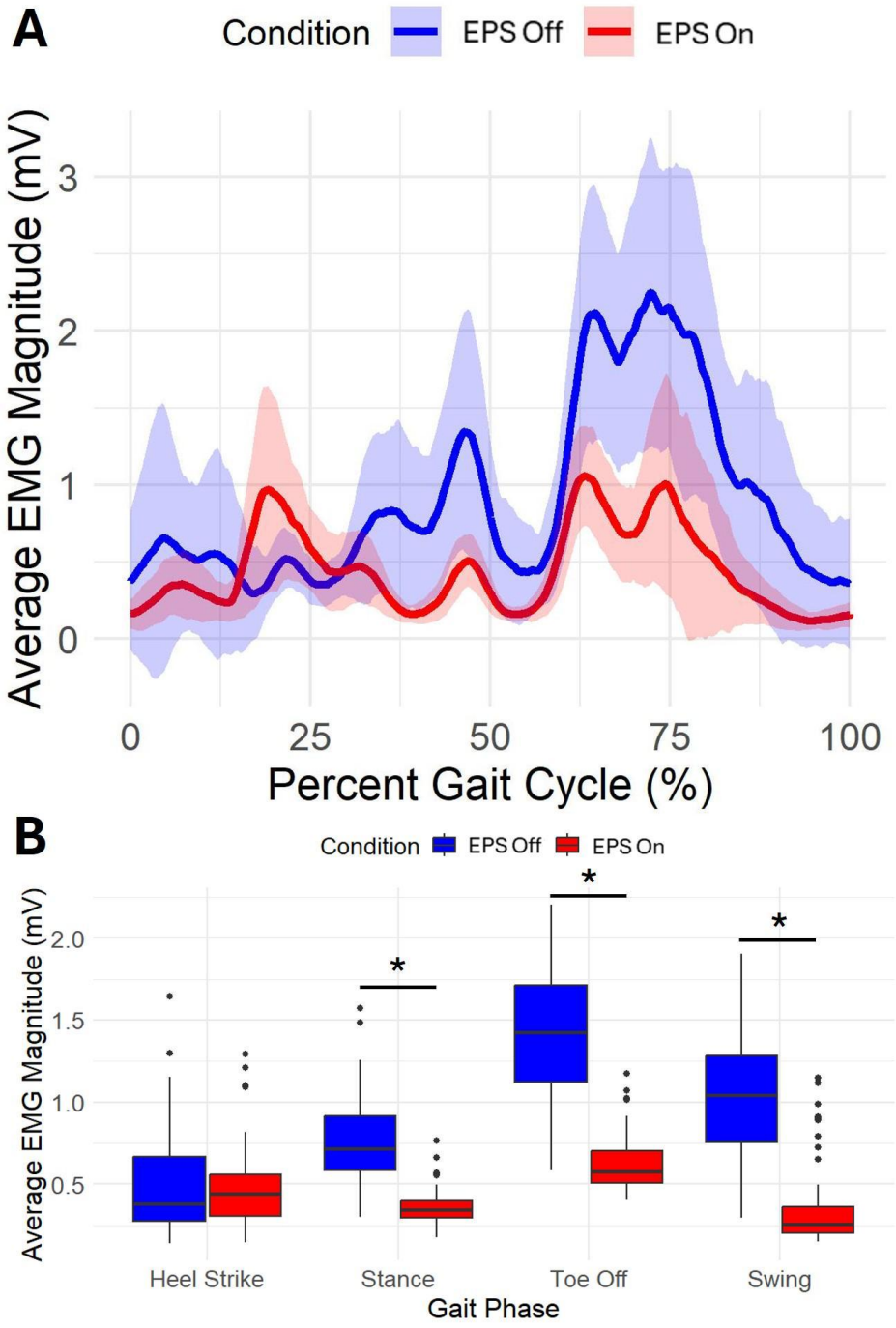


Figure 1: Activity of medial gastrocnemius from one participant with transtibial limb loss significantly decreases with EPS during stance, toe off and swing

Disclosures: L.M. Hauck: None. **S. Li:** None. **R.J. Triolo:** None. **H. Charkhkar:** None.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

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Program #/Poster #: PSTR128.23/W7

Topic: F.05. Brain-Machine Interface

Support: VA Grant I01 RX003699
ONR Grant N00014-23-1-2842

Title: Perceived Joint Position and Force Sensation from Proprioceptive Peripheral Nerve Stimulation

Authors: *J. D. MUDGE, R. BOSE, E. L. GRACZYK;
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Abstract: Proprioception is the body's sense of limb position, movement, and force. In people with amputation, prostheses can help with performing tasks of daily living, but commercial prostheses lack proprioceptive feedback. This is problematic because proprioception is important for accurate control of our limbs, and thus prosthesis control may never be fully intuitive without it. While prior studies have observed that nerve stimulation in people with limb loss can generate distally referred sensations of proprioception, these studies have not systematically characterized how different electrical stimulation parameters can modulate perceived muscle force and joint position. In this study, we investigate the effects of stimulation pulse width (PW) and pulse frequency (PF) on proprioception. Two male participants (P1, age 54 and P2, age 62) implanted with Composite Flat Interface Nerve Electrodes (C-FINEs) around their median, radial, and/or ulnar nerves rated sensations evoked by peripheral nerve stimulation. In each experiment, combinations of 4 PWs and 4 PFs were delivered to a C-FINE contact. The participants rated the intensity of the resulting sensation. A multiple linear regression was conducted to assess PW and PF effects on intensity. P1 experienced muscle force in his residual brachioradialis, while P2 experienced digit 3 and digit 4 flexion. There was a significant effect of PW and PF on sensation intensity for each participant. Muscle force sensation intensity in P1 increased with PW ($P<0.01$) and PF ($P<0.01$) ($F(3,476)=340$, Adj. $R^2=0.68$). Joint position sensation in P2 increased with PW ($P<0.01$) and PF ($P<0.05$), though the fit was poorer ($F(3,316)=37.4$, Adj. $R^2=0.25$). PW and PF interaction terms for both models were significant ($P<0.05$). These results suggest that muscle force and joint position can be modulated using PW and PF. However, the significant interaction term implies that the influence of one parameter may depend on the level of the other. Future neuroprostheses could leverage these parameters to enable encoding of proprioception in the phantom hand, providing feedback on limb state and the environment. Restoring proprioceptive feedback could reduce prosthesis users' reliance on vision, minimizing cognitive burden and improving quality of life.

Disclosures: J.D. Mudge: None. **R. Bose:** None. **E.L. Graczyk:** None.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.24/W8

Topic: F.05. Brain-Machine Interface

Support: PY23-P651

Title: Micro-ct validation and acute muscle recruitment of a novel interfascicular electrode for peripheral nerve stimulation

Authors: *M. RANDOLPH[1], V. MARCU[2], C. TSIPTSIS[3], A. SHOFFSTALL[4], J. BASKIN[5], D. J. TYLER[4];
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Abstract: Background: Peripheral nerve interfaces (PNIs) are a platform technology with broad clinical potential. The therapeutic benefit of PNIs rely on the selectivity of the interface- the ability to target specific axons while avoiding off-target activation. Historically, there has been a tradeoff between interface selectivity and invasiveness. Invasiveness is characterized by membranes penetrated by the electrode and is associated with the extent of nerve damage following chronic implantation. We hypothesize that interfascicular - between the fascicles- placement can balance invasiveness and selectivity. In this work, we present micro-computed tomography analysis to examine the spatial distribution of implanted interfascicular microwires within peripheral nerves. We hypothesize that insertion angle is correlated with perineurial rupture, and present micro-CT data to quantify intraneural wire trajectories. In parallel, we evaluate how the directionality of interfascicular microwire contacts affects stimulation selectivity. Methods: Spatial Distribution: N=10 porcine nerves (N=7 median and N=3 ulnar) were acutely implanted with interfascicular microwire arrays. The nerves were collected and stained to visualize the perineurial membrane, and the relative positions of the fascicles and electrodes. Selectivity: N=6 porcine median nerves were implanted with interfascicular microwire arrays, three implants with directional contacts and three with non-directional contacts. The resulting muscle activation of 5 downstream muscles was analyzed for selectivity. Results: Spatial Distribution: Each implanted nerve sample demonstrated distributed placement of contacts in the longitudinal and transverse directions. 82% of contacts displayed interfascicular placement, while the remaining showed evidence of perineurial disruption. Steeper insertion angle was correlated with intrafascicular placement across all samples ($p = 0.003$), and within the median nerve specifically ($p= 0.0189$). Selectivity: Interfascicular electrodes induced differential downstream muscle activation in all cases. Preliminary results suggest that implants with directional contacts induced selective activation in more muscles on average than implants with non-directional contacts (2.3 and 1.5 muscles respectively). Interfascicular electrodes demonstrate the potential to maximize selectivity while reducing

invasiveness. These findings explore implantation strategies and contact design which will inform the next generation of these interfaces.

Disclosures: M. Randolph: None. **V. Marcu:** None. **C. Tsiptsis:** None. **A. Shoffstall:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuronoff Inc. **J. Baskin:** None. **D.J. Tyler:** A. Employment/Salary (full or part-time): Afference INC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Barologics, INC.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.25/W9

Topic: F.05. Brain-Machine Interface

Title: Individualized peripheral nerve stimulation: subject-specific models predict muscle responses to multipolar stimuli

Authors: *V. MARCU[1], M. RANDOLPH[2], D. J. TYLER[1];
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Abstract: Peripheral nerve stimulation (PNS) can restore motor function through functional electrical stimulation (FES), but its effectiveness depends on the selectivity of the stimulation—its ability to activate target axons while avoiding off-target activation. Multipolar stimulation (MpS) can enhance the selectivity of PNS by generating spatially confined electric fields using simultaneous cathodic and anodic currents. However, clinical adoption remains impractical due to the time constraints of testing given the vast parameter space of currents. To enable clinical MpS use, we developed an algorithm that links simulated axonal activations in subject-specific nerve models to experimentally recorded muscle responses. These models enable clinicians to predict the outcome of MpS without needing to test each pattern directly, saving time and improving stimulation outcomes. We modeled 12 histologically-derived pig median nerves in COMSOL with composite flat interface nerve electrodes (CFINE) around them and simulated 1 mA current injections through each of 16 contacts. MpS fields were generated by linear superposition of individual voltage fields, with each stimulus modeled as a 100 μs constant current to reflect common clinical parameters. In parallel, we simulated and experimentally delivered 180 MpS stimuli at 1 Hz to an implanted CFINE on a pig median nerve. Within our simulations, axonal responses from MpS stimuli were predicted by the Izad linear approximation and produced the activation matrix, **A**. Experimentally, muscle activations were recorded from five muscles innervated by the median nerve using intramuscular EMG electrodes. Stimulation with the same MpS stimuli resulted in a muscle activation matrix, **C**. Using the 180 model-experimental pairs of axonal activations to muscle activations, a least-squares method found the

solution for **x** in the system **Ax=C**. The matrix **x** estimates the contribution of each modeled axon to muscle activity in the 5 recorded muscles. Across 12 nerve models, this method achieved a mean squared error of 0.029±0.0047 with a minimum of 0.019, indicating that the simulated nerve models closely reproduce the experimental data. Train-test splits of stimulation data showed a mean squared error of 0.0675±0.0202 in predicting novel muscle activations with a minimum of 0.0549±0.0152 in the best model, indicating that these models can accurately predict muscle activity from novel stimuli. The results suggest that these individualized nerve models can accurately predict muscle responses to MpS, potentially enabling more selective clinical stimulation while using significantly less clinician time.

Disclosures: V. Marcu: None. **M. Randolph:** None. **D.J. Tyler:** A. Employment/Salary (full or part-time): Afference, INC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Barologics, INC.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.26/W10

Topic: F.05. Brain-Machine Interface

Support: N00014-23-1-2842
I01 RX003699
NSF 1937968

Title: Pulse Amplitude-Modulated, High-Frequency Peripheral Nerve Stimulation Elicits Natural Sensation in an Upper-Limb Amputee

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Abstract: Background: Restoring touch after limb loss is critical for dexterous prosthesis control and psychosocial well-being. Although peripheral nerve stimulation (PNS) has been shown to evoke sensation in the missing limb, it often elicits unnatural, paresthetic percepts. The unnaturalness of stimulation-evoked sensation is believed to arise from the synchronous response of afferents to PNS. Stimulation paradigms which leverage asynchronous recruitment may improve quality of PNS-evoked sensation. Methods: Here, we evaluate BioS - a high-frequency, pulse amplitude-modulated approach designed to promote asynchronous, biomimetic activation of afferents. A single subject with unilateral transradial amputation was implanted with 16-contact Composite Flat Interface Nerve Electrodes (C-FINEs) as part of the iSens System, a fully implanted bidirectional neuroprosthesis. BioS trains were delivered at 20 Hz with a 0.7 duty cycle, and pulse amplitude was ramped from threshold to a mid-comfortable level on two median nerve contacts. Two BioS conditions—500 Hz (BioS1) and 1 kHz (BioS2)—were compared to

conventional 20 Hz constant amplitude stimulation (CAS). All stimuli were intensity-matched and delivered in pseudorandom order. The participant rated sensation intensity and quality - naturalness, pleasantness, smoothness, vibration, tapping, and pressure - on visual analog scales. Each session included four blocks of 10 trials per condition. Ratings were normalized to block means and combined across blocks. Effects of condition, contact, and their interaction were evaluated using two-way ANOVA. Results: Pairwise comparison of the estimated marginal means models with the Bonferroni correction revealed that both BioS1 and BioS2 conditions are perceived as significantly more natural ($p<0.0001$), pleasant ($p<0.002$), smooth ($p<0.0001$), and significantly less tapping-like ($p<0.0001$), compared to 20 Hz CAS. BioS1 and BioS2 were perceived as significantly more like pressure than 20 Hz CAS for one of the tested contacts ($p<0.002$). No significant differences in intensity or vibration quality were observed. These results highlight BioS as a promising approach to improve the naturalness of PNS. Implementation of BioS during prosthesis use is needed to evaluate its effects on psychosocial wellbeing and function.

Disclosures: R.W. Peralta: None. **E.L. Graczyk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US11116977B2.

Poster

PSTR128: Neuroprosthetics: Sensory and Perceptual Encoding and Decoding

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.27/W11

Topic: F.05. Brain-Machine Interface

Support: Physical Medicine and Rehabilitation Pilot Grant

Title: A Modified Spinal Cord Stimulator Implantation Technique for Targeting the Ventrolateral Spinal Cord

Authors: *K. J. VALESTRINO[1], C. IHEDIWA[2], J. I. HERNANDEZ BELLO[2], A. FOGARTY[3], M. MAHAN[4], A. CONGER[3], Z. MCCORMICK[3], A. GLINKA PRZYBYSZ[3], P. KONRAD[5], A. DALRYMPLE[2];
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Abstract: Epidural spinal cord stimulation (SCS) has historically been used to treat chronic pain, but is increasingly used in clinical trials for motor rehabilitation in conditions such as spinal cord injury, stroke, and Parkinson's disease[1,2]. Typically, SCS involves placing leads on the dorsal side of the spinal cord (SCS_D), where the stimulation of large diameter afferent fibers in the dorsal roots indirectly activates motoneurons through reflexive pathways[3]. Although SCS_D can enhance motor rehabilitation, its efficacy has been limited due to its lack of muscle-specific activation[3]. To address this limitation, we propose targeting the ventral spinal cord (SCS_V),

closer to the motoneurons in the ventral horn. This study aims to refine the SCS implantation procedure to target the ventrolateral lumbosacral spinal cord, providing access to unilateral ventral roots and the ventral horn. Nine SCS leads were implanted in three cadaveric specimens (three leads each): a 22-year-old female and two males, aged 68 and 69. A team of physiatrists and a neurosurgeon performed the implant procedures using an epidural Tuohy needle under live fluoroscopic guidance. Leads 1-5 and 7-9 were inserted dorsally, steered laterally around the spinal cord into the ventral epidural space, and advanced rostrally to the target level. Lead 6 was inserted transforaminally, anterior to the roots, and guided rostrally within the ventral epidural space. Following each set of implants, the lead locations were determined using computed tomography (CT) and anatomical dissection. CT imaging and dissection confirmed ventrolateral placement of Lead 3 in the first cadaver, though Leads 1 and 2 were more lateral than intended. In the second cadaver, all leads were placed ventrolaterally. However, a dural puncture during Lead 5 insertion resulted in subdural placement. In the third cadaver, Lead 7 was placed laterally, while Leads 8 and 9 were successfully positioned ventrolaterally. Successful ventrolateral placement of 6/9 leads demonstrates the feasibility of this modified implantation approach. The dural puncture is a known but rare complication[4], and may be less likely in vivo due to cerebrospinal fluid-induced distension of the dura mater and less friable tissue. We plan to proceed with intraoperative testing to correlate the location of ventrolateral lead placement with muscle activation. This technique could enable more precise targeting of lower-limb muscles, potentially improving rehabilitation outcomes and quality of life for individuals with motor impairments. References: [1] Caylor et al., 2019; [2] Iversen et al., 2024; [3] Capogrosso et al., 2013; [4] Hussain et al., 2022

Disclosures: K.J. Valestrino: None. **C. Ihediwa:** None. **J.I. Hernandez Bello:** None. **A. Fogarty:** None. **M. Mahan:** None. **A. Conger:** None. **Z. McCormick:** None. **A. Glinka Przybysz:** None. **P. Konrad:** None. **A. Dalrymple:** None.

Poster

PSTR129: Neuroprosthetics: Stroke

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.01/W12

Topic: F.05. Brain-Machine Interface

Support: R01NS131428

Title: Deep Brain Stimulation of the Motor Thalamus Alleviates Post-Stroke Upper-Limb Motor Deficits in Monkeys

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Abstract: Stroke is among the leading causes of permanent disability in the United States, affecting approximately 795,000 people each year. In most cases, infarcts damage subcortical areas, thus interrupting long-range connections between cortical and spinal centers that regulate movements, i.e., the cortico-spinal tract (CST). Accordingly, humans with stroke invading the CST suffer from the most severe and permanent upper-limb motor deficits, including loss of dexterity and muscle weakness. Despite the large population size of affected individuals, intense physical therapy remains the only significant intervention with limited impact on moderate to severe paresis. Therefore, novel and effective therapeutic approaches are necessary for these patients. We previously demonstrated that Deep Brain Stimulation (DBS) targeting the motor thalamus, a subcortical region with direct excitatory projections to the motor cortex, facilitates residual CST axons and consequently increases motor output in anesthetized monkeys. Yet, whether motor thalamus stimulation achieves functional improvements for post-stroke chronic hemiparesis remain unclear. Here, we hypothesized that DBS of the motor thalamus increases the excitability of the CST also when voluntarily activated to perform a movement and thus alleviate post-stroke upper-limb motor deficits.To test this hypothesis, we trained n=1 monkey to perform a battery of tests to measure hand and arm dexterity and strength. We then performed a controlled thermocoagulation of the CST inducing chronic stroke with moderate upper-limb paresis. We also implanted a DBS electrode in the motor thalamus and assessed behavioral performances and kinematic variables with and without DBS, for up to 40 days after the stroke. Following the CST thermocoagulation, the monkey developed hallmark post-stroke motor symptoms, including mild loss of arm dexterity, and moderate loss of finger and hand control. Stimulation of the motor thalamus immediately improved 3D arm and finger control, as evidenced by higher task success rate and improvement in several kinematic variables, such as velocity, joint angles and endpoint precision.These findings demonstrate for the first time the potential of motor thalamus DBS to alleviate motor symptoms developed following stroke, and pave the way towards novel therapies for upper-limb hemiparesis. Importantly, in humans, motor thalamic stimulation is a standard clinical practice to reduce motor symptoms in other movement disorders such as essential tremor, thus probing a compelling rationale for a faster translation to post-stroke rehabilitations in humans.

Disclosures: A. Damiani: None. **N. Macellari:** None. **M. Uribe:** None. **Z. Xu:** None. **E.M. Grigsby:** None. **L. Liang:** None. **L. Tang:** None. **S. Nouduri:** None. **M. Capogrosso:** None. **J.A. González-Martínez:** None. **E. Pirondini:** None.

Poster

PSTR129: Neuroprosthetics: Stroke

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.02/W13

Topic: F.05. Brain-Machine Interface

Support: NIH Grant R01NS131428

Title: Spinal sensory modulation change after capsular stroke

Authors: *L. LIANG[1], N. MACELLARI[2], A. DAMIANI[3], L. TANG[1], Z. XU[1], J. OSTROWSKI[8], E. ROGERS[1], J. HO[4], R. DE FREITAS[1], S. BHATIA[5], J. A. GONZÁLEZ-MARTÍNEZ[5], P. GERSZTEN[6], M. CAPOGROSSO[5], E. PIRONDINI[7];
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Abstract: Sensory afferents continuously encode and convey sensory information on limb movements to the central nervous system. This information not only gives us conscious experience of movement, but also plays a major role in shaping motor output through monosynaptic afferent-motoneuronal connections. The spinal cord is the first site of sensory modulation as these inputs enter through the dorsal roots, with primary afferent depolarization (PAD) being one of the most important mechanisms of modulation, mediated by axo-axonic GABAa receptors. Previously, we found that in the non-human primate cervical spine, PAD facilitates sensory transmission to spinal interneurons, spinal motoneurons, as well as supraspinal centers. Abundant evidence has shown that injury to the central nervous system such as stroke and spinal cord injury induce symptoms of sensory dysregulation like hyperreflexia and spasticity. Studies also commonly reported changes in the GABAergic system following injury, leading us to hypothesize that injury may alter PAD and cause the emergence of some sensorimotor deficits. Here, we investigated this hypothesis specifically following internal capsule (IC) stroke in both monkeys and humans.We used an acute setup in anesthetized monkeys (n=2 intact, n=2 subacute IC stroke) and humans (n=2 chronic IC stroke) to stimulate sensory afferents and record muscle responses. We placed either a bipolar stimulation probe or an epidural stimulation lead on the dorsal aspect of C7/C8 spinal levels to activate hand and arm primary afferents. We recorded needle electromyography (EMG) from arm and hand muscles in both monkeys and humans. In monkeys, we also recorded intraspinal PAD activity from the C6/C7 spinal cord with a linear microelectrode array (32 Ch) placed dorsoventrally throughout the spinal laminae. With doublet stimulations to the afferents (10, 20, 40, 50, 100ms delays), we found that EMG response to the second pulse is facilitated in the intact monkeys as well as the intact side of the stroke monkeys. However, this second response is suppressed in the impaired side of the stroke monkeys and the humans, and the suppression is greater with more severe stroke. This indicates that capsular stroke reduces the ability of the afferents to sustain its excitability in repetitive pulses.

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Poster

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Program #/Poster #: PSTR129.03/W14

Topic: F.05. Brain-Machine Interface

Support: NIH Grant 1UG3NS123135-01A1

Title: Regaining dexterous motor control after stroke via non-monosynaptic cortico-spinal pathways with neurostimulation

Authors: *E. SORENSEN[1], L. BORDA[4], J. OSTROWSKI[5], R. DE FREITAS[2], N. VERMA[4], D. J. WEBER[6], L. E. FISHER[3], M. GORASSINI[7], J. W. KRAKAUER[8], M. CAPOGROSSO[2]; [2]Neurolog. Surgery, [3]Physical Med. and Rehabil., [1]Univ. of Pittsburgh, Pittsburgh, PA; [4]Mechanical Engin., [6]Mechanical Engin. and Neurosci. Inst., [5]Carnegie Mellon Univ., Pittsburgh, PA; [7]Neurosci., Univ. Alberta, Edmonton, AB, Canada; [8]Neurol., Johns Hopkins Univ., Baltimore, MD

Abstract: Dexterous control of the human arm is assumed to be dependent on monosynaptic connections between the motor cortex and spinal motoneurons. We report that people with post-stroke hemiparesis could regain dexterous control using non-monosynaptic cortico-spinal tract (CST) projections during epidural electrical stimulation of the cervical spinal cord (SCS). Participants in our pilot clinical study (n=7) demonstrated the ability to improve strength, arm reaching smoothness, and fine force control of the arm and hand while receiving continuous electrical stimulation. Detailed electrophysiology of cortico-spinal connectivity with transcranial magnetic stimulation, electromyography spectral analysis, and single motor unit firing rates showed that SCS did not reliably strengthen existing monosynaptic pathways. Instead, residual CST axons sculpted the strength of spinal reflexes produced by each pulse of SCS via pre-synaptic and poly-synaptic pathways to produce functionally relevant muscle activation patterns. Our findings reveal the ability of poly-synaptic CST pathways to finely tune spinal motor output.

Disclosures: E. Sorensen: None. **L. Borda:** None. **J. Ostrowski:** None. **R. de Freitas:** None. **N. Verma:** None. **D.J. Weber:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reach Neuro. **L.E. Fisher:** None. **M. Gorassini:** None. **J.W. Krakauer:** None. **M. Capogrosso:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reach Neuro.

Poster

PSTR129: Neuroprosthetics: Stroke

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.04/W15

Topic: F.05. Brain-Machine Interface

Support: Neuralink

Title: In Silico Analysis of a High-Density Spinal Interface for Restoring Hand Function Following Spinal Cord Injury

Authors: *C. RÖSE[1,3], E. ROGERS[1], J. E. O'DOHERTY[4], M. CAPOGROSSO[2]; [2]Neurolog. Surgery, [1]Univ. of Pittsburgh, Pittsburgh, PA; [3]Electrical Engin., Tech. Univ. Munich, Munich, Germany; [4]Neuralink, Fremont, CA

Abstract: Spinal cord stimulation has been used successfully to restore upper limb voluntary movements after spinal cord injury and stroke. However, conventional epidural stimulation, which directly activates afferent fibers in the dorsal rootlets, is restricted to segmental-level selectivity, and is unable to independently target individual hand muscles since their motorpools are tightly clustered in overlapping spinal segments. Intraspinal microstimulation (ISMS), a technique in which microelectrodes are implanted directly within the spinal tissue near the targeted motoneurons, could potentially activate motorpools selectively by using low stimulation currents in close proximity to the targeted cells. However, previous work using cervical-level ISMS by other groups has produced unsatisfactory results limited by non-selective activation, causing the approach to fall out of favor. We hypothesized that this is not a fundamental restriction of ISMS but rather due to the limited spatial resolution of previous investigations and arbitrary stimulation parameters. As such, we propose that a high-density interface, combined with appropriate stimulation parameters, could overcome these hurdles and produce the selectivity necessary for restoring dexterous hand control. Here, in order to efficiently explore the vast available ISMS parameter space, we used a computational model of the cervical spinal cord to assess *in silico* the capability for ISMS to selectively activate targeted motoneuron populations. Using finite element analysis, we evaluated the electric fields generated by ISMS within the macaque spinal cord, which were applied to biophysical neuron models to calculate activation thresholds for relevant neural populations including local motoneurons (following realistic rostro-caudal distributions) and fibers-of-passage. Our results demonstrate that targeted activation is possible but highly sensitive to both electrode position (necessitating high-density interfaces) and stimulation parameters. Our results provide critical context to the existing literature on ISMS for restoring hand function and can be applied to inform the design of neurotechnologies to restore hand control following paralysis.

Disclosures: C. Röse: None. **E. Rogers:** None. **J.E. O'Doherty:** A. Employment/Salary (full or part-time): Neuralink. **M. Capogrosso:** 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.; Neuralink.

Poster

PSTR129: Neuroprosthetics: Stroke

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.05/X1

Topic: F.05. Brain-Machine Interface

Support: NIH Grant UG3NS123135-01A1

Title: What is the nature of long-term changes in strength and spasticity observed in people with post-stroke hemiparesis who received spinal cord stimulation?

Authors: *S. BHATIA[1,2], R. DE FREITAS[2], E. SORENSEN[3], E. CARRANZA[3], A. BOOS[4], G. F. WITTENBERG[4], L. E. FISHER[5], J. W. KRAKAUER[6], D. J. WEBER[7], P. C. GERSZTEN[2], E. PIRONDINI[5], M. CAPOGROSSO[2];
[2]Neurolog. Surgery, [3]Bioengineering, [4]Neurol., [5]Physical Med. and Rehabil., [1]Univ. of Pittsburgh, Pittsburgh, PA; [6]Neurol., Johns Hopkins Univ., Baltimore, MD; [7]Mechanical Engin. and Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Stroke remains the leading cause of upper limb paralysis in the United States, with approximately 800,000 new cases annually. Nearly half of these individuals are left with persistent upper limb deficits that severely impair their quality of life. Notably, stroke survivors rank the recovery of arm and hand function as their highest unmet clinical priority. The post-stroke hemiparesis syndrome is characterized by both positive motor signs, such as *i)* abnormal flexor synergies and *ii)* spasticity, and negative signs, including *iii)* weakness and *iv)* loss of dexterity. Among these, *ii)* spasticity and *iii)* weakness are some of the most disabling and least understood sequelae of stroke. Unfortunately, current clinical rehabilitation methods fall short in effectively promoting motor recovery, posing a critical clinical need for this vulnerable population. In this context, epidural spinal cord stimulation (SCS) has recently emerged as a promising intervention to modulate spinal circuits and restore voluntary motor control. In a first-in-human clinical trial, our group evaluated the preliminary efficacy of cervical epidural SCS in participants with chronic post-stroke hemiparesis (n=7). Each participant was implanted with a pair of cervical SCS leads from the C3-T1 spinal segments for a 4-week period to assess the impact of SCS on upper limb strength and spasticity. During stimulation, all participants demonstrated improvements in isometric maximum voluntary contraction, with an average increase of 32% across movements (shoulder extension/flexion, elbow extension/flexion, and/or grip). Importantly, 6/7 participants improved in spasticity up to -6.75 points as measured by the Modified Ashworth Scale (MAS). Our preliminary data suggest that these improvements may be due to increased potentiation of the corticospinal tract (CST). Specifically, analysis of Motor Evoked Potentials (MEP) elicited by transcranial magnetic stimulation (TMS) pre- and post-study showed that in participants who had residual CST function (MEP+, n=3), there was a consistent reduction in the MEP latency, as measured from the TMS pulse to MEP onset, across multiple upper limb muscle groups. Furthermore, across multiple contacts of the implanted electrodes, there was a uniform decrease in motor thresholds during SCS muscle recruitment curves. Taken together, these results suggest that SCS changes corticospinal and spinal circuit excitability over time, offering preliminary evidence of disease modifying effects underlying the improvements in strength and spasticity among individuals living with chronic post-stroke hemiparesis.

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Poster

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Program #/Poster #: PSTR129.06/X2

Topic: F.05. Brain-Machine Interface

Support: NIH UG3NS12313501A1

Title: Configurations of epidural spinal cord stimulation to facilitate motor unit activity and improve motor function post-stroke

Authors: *N. VERMA[1], E. SORENSEN[6], L. BORDA[2], E. CARRANZA[7], J. A. BEAUCHAMP[3], P. YADAV[4], R. DE FREITAS[6], M. P. POWELL[12], A. BOOS[8], P. GERSZTEN[8], L. E. FISHER[9], E. PIRONDINI[10], M. CAPOGROSSO[11], D. J. WEBER[5]; [1]Mechanical Engin., Carnegie Mellon Univ., PITTSBURGH, PA; [2]Mechanical Engin., [4]Mechanical Engin. and Machine Learning, [5]Mechanical Engin. and Neurosci. Inst., [3]Carnegie Mellon Univ., Pittsburgh, PA; [7]Bionegineering, [6]Univ. of Pittsburgh, Pittsburgh, PA; [8]Univ. of Pittsburgh, PITTSBURGH, PA; [9]Physical Med. and Rehabil., [10]Rehabil. and Neural Engin. Labs., [11]Neurolog. Surgery, Univ. of Pittsburgh, Pittsburgh, PA; [12]Reach Neuro, Inc., Reach Neuro, Inc., Bristol, RI

Abstract: Stroke damages the connections between the brain and body, impairing motor control. Previously, we reported that subthreshold tonic epidural spinal cord stimulation(SCS) improves strength and dexterity in the arm and hand of people with chronic hemiparesis post-stroke.While tonic stimulation enhances recruitment of targeted muscles, manual tasks of daily life involve coordinated and sequential activation of muscles throughout the limb. We therefore investigated alternate SCS strategies to facilitate arm function better. We hypothesized that closed-loop SCS, adjusting stimulation parameters based on movement phases, would outperform tonic stimulation. Additionally, the neural mechanisms by which SCS improves voluntary motor function are poorly understood. Here, we directly examined the effects of SCS on motor unit(MU) excitability and firing-rate modulation. We hypothesized that SCS recruits sensory afferents to deliver excitatory postsynaptic potentials (EPSPs) to motoneurons, enhancing their excitability and responsiveness to residual supraspinal inputs. These SCS-mediated EPSPs would partially entrain motoneuron activity, synchronizing their firing. We then tested biomimetic stimulation (BioS) to mimic naturalistic, asynchronous motoneuron firing patterns.Six participants with chronic post-stroke hemiparesis were implanted with 2 x 8-channel SCS leads in the epidural space of the cervical spinal cord. High-density EMG was used to obtain MU activity during isometric arm and hand contractions, both with and without SCS. We compared evoked responses and MU firing patterns with traditional single-pulses to amplitude-modulated, high-frequency bursts. The participants also performed planar reaching movements with and without SCS, where tonic and closed-loop SCS were applied.Our results showed an increased MU firing probability 7-15 ms after each SCS pulse, partially entraining their activity, which differs from natural stochastic processes. SCS also decreased recruitment thresholds(up to 70%) and normalized impaired MU firing-rate modulation. Early evidence showed that BioS induced more graded recruitment and asynchronous MU firing patterns as compared to single-pulse SCS.

Lastly, closed-loop SCS improved reaching kinematics by increasing maximum hand speed (up to 250%), reducing movement duration(up to 40%), and smoothing hand trajectories(up to 36%) as compared to tonic SCS.Collectively, these findings provide crucial insights into the neurophysiological basis of SCS-mediated motor recovery and suggest strategies to further enhance its effects.

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Poster

PSTR129: Neuroprosthetics: Stroke

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.07/X3

Topic: F.05. Brain-Machine Interface

Title: Long-term efficacy of epidural cervical spinal cord stimulation on motor function in individuals with chronic post-stroke hemiparesis

Authors: *R. M. DE FREITAS[1], S. BHATIA[1], E. SORENSEN[1], E. CARRANZA[2], A. BOOS[3], P. GERSZTEN[4], G. F. WITTENBERG[5], L. E. FISHER[6], J. W. KRAKAUER[9], E. PIRONDINI[7], M. CAPOGROSSO[8];
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Abstract: Stroke stands as the leading cause of paralysis in the U.S.A., often resulting in irreversible impairments to both upper limb motor and sensory functions. Motor impairments caused by stroke are characterized by signs of hemiparesis, such as weakness and the intrusion of abnormal synergies, whereas sensory impairments may include loss of tactile sensation and chronic pain. Although low-dose motor training is the most common option offered to chronic post-stroke motor rehabilitation in clinic, it fails to effectively enable motor recovery. In this context, neuromodulation technologies have emerged as an alternative approach to catalyze the effects of motor rehabilitation and assist residual motor functions, serving as a permanent neuroprosthetic device. We recently demonstrated that cervical spinal cord stimulation (SCS), applied using a pair of lead electrodes implanted in the spinal epidural space, could significantly improve upper limb motor function in all participants with chronic hemiparesis after stroke. In

this pilot clinical trial, off-label electrodes were used for delivering stimulation in a laboratory setting for 4 weeks, after which they were explanted. While our aim was to test the rehabilitative effects of SCS on motor function, an unexpected side effect was reduction of the upper limb pain experienced by some participants. Following the trial, n = 3 participants who experienced reduction of pain during SCS received, under medical prescription, an on-label fully implantable SCS system (Intellis, Medtronic), which is FDA-approved for pain management. For these participants, SCS electrode leads were implanted in a similar position to the one shown to be effective for pain relief during the clinical trial. As SCS has been supporting these participants in performing motor tasks required for activities of daily living, we have been periodically assessing long-term changes in their motor functions. Remarkably, even 2.5 years after the SCS system was implanted, one participant retained the motor function improvements observed at the end of the clinical trial. Importantly, the effects of the stimulation have remained similar, yielding a 7-point improvement in Fugl-Meyer Assessment scores immediately upon activation of SCS. To date, no serious adverse events have been reported. These unprecedented outcomes support the potential of SCS as an FDA-approved device for motor in chronic stroke patients.

Disclosures: R.M. de Freitas: None. **S. Bhatia:** None. **E. Sorensen:** None. **E. Carranza:** None. **A. Boos:** None. **P. Gerszten:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reach Neuro, Inc. **G.F. Wittenberg:** None. **L.E. Fisher:** None. **J.W. Krakauer:** None. **E. Pirondini:** None. **M. Capogrosso:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reach Neuro, Inc.

Poster

PSTR129: Neuroprosthetics: Stroke

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Program #/Poster #: PSTR129.08/X4

Topic: F.05. Brain-Machine Interface

Support: NIH R01NS131428
SnSf P500PT_225455

Title: Optimizing Motor Thalamus Deep Brain Stimulation to restore upper limb and hand motor functions

Authors: *N. MACELLARI[1], A. DAMIANI[2], L. TANG[3], E. M. GRIGSBY[2], J. E. TING[2], J. HO[4], Z. XU[3,7], S. NOUDURI[3], T. CONSTANTINE[8], M. CAPOGROSSO[5], D. J. CRAMMOND[9], J. A. GONZÁLEZ-MARTÍNEZ[5], E. PIRONDINI[6];
[1]Physical medinice and rehabilitation, [2]Physical Med. & Rehabil., [4]Rehab and Neural Engin. Labs, [5]Neurolog. Surgery, [6]Rehabil. and Neural Engin. Labs., [3]Univ. of Pittsburgh, Pittsburgh, PA; [7]Tsinghua Med., Tsinghua Univ., Beijing, China; [8]UPMC, Pittsburgh, PA; [9]Dept Neurolog Surg, Univ. Pittsburgh, Pittsburgh, PA

Abstract: In the United States, 2.5 million individuals experience chronic upper limb and hand deficits following neurological injuries. Deep brain stimulation of the motor thalamus (DBS) has been shown to enhance cortical motor output to the upper limb in both non-human primates and humans. However, the optimal stimulation parameters and thalamic targets that maximize motor facilitation remain unclear. For this, we frist characterized the effects of different stimulation targets and frequencies intraoperatively in 16 patients undergoing DBS implantation in the motor thalamus. We recorded neural activity within three motor thalamus nuclei: ventral oralis posterior (VOP), ventral oralis anterior (VOA), and ventralis intermediate (VIM) at multiple depths along the electrode trajectory, while patients performed upper limb/hand tasks. We also recorded motor-evoked potentials (MEPs) in upper limb/hand muscles induced by direct cortical stimulation (DCS) of the primary motor cortex while stimulating the thalamic nuclei at different frequencies. Our intraoperative data show that VOP neurons display the highest firing rates during upper limb movements across all nuclei, suggesting a crucial role in movement generation. Low-frequency stimulation (50-80 Hz) in the VOP more consistently potentiated DCS-MEPs than high-frequency stimulation, linked to a higher degree of DCS-MEP suppression, and compared to the other nuclei. We hypothesize that this difference is due to a higher concentration of fibers projecting towards the motor cortex compared to VIM and VOA. We then validated these findings in two individuals with chronic DBS implants and severe motor deficits (P1: 70yo with subcortical stroke P2: 45yo with TBI). Low-frequency stimulation and electrode configurations designed to target the most anterior aspects of the motor thalamus (VOP) resulted in **increased upper limb motor performance and increased hand dexterity** during standardized clinical tests compared to stimulation OFF, high frequencies, and configurations targeting the posterior aspect of the motor thalamus. By identifying optimal stimulation target locations and parameters, this technology achieves unprecedented improvements in hand dexterity and further refines DBS therapy for individuals with post-stroke and TBI-related motor impairments.

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Poster

PSTR129: Neuroprosthetics: Stroke

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.09/X5

Topic: F.05. Brain-Machine Interface

Title: Direct Motor Thalamus Deep Brain Stimulation Alters Motor Fiber Recruitment Modality

Authors: *L. W. TANG[1], J. E. TING[2], A. DAMIANI[2], E. M. GRIGSBY[2], N. MACELLARI[3], S. NOUDURI[1], T. CONSTANTINE[1], D. J. CRAMMOND[6], M. CAPOGROSSO[4], J. A. GONZÁLEZ-MARTÍNEZ[4], E. PIRONDINI[5];

[2]Physical Med. & Rehabil., [3]Physical medicine and rehabilitation, [4]Neurolog. Surgery, [5]Rehabil. and Neural Engin. Labs., [1]Univ. of Pittsburgh, Pittsburgh, PA; [6]Dept Neurolog Surg, Univ. Pittsburgh, Pittsburgh, PA

Abstract: Neuromodulation using Deep Brain Stimulation (DBS) is an established therapy for movement disorders. Our recent work in non-human primates and human subjects demonstrated that low-frequency (50-80 Hz) DBS of the motor thalamus (mThal) recruits afferent fibers to the motor cortex to enhance the excitability of the corticospinal (CST) and corticobulbar tracts (CBT). This increased excitability potentiates cortical output to upper-limb and orofacial muscles, leading to immediate improvements in hand function, swallowing, and speech—even after CST/CBT injury. These assistive effects occurred immediately upon turning on the thalamic stimulation and stopped as soon as the stimulation was turned off. However, the neurophysiological mechanisms by which DBS drives this potentiation in motor output remain unclear. To investigate these mechanisms, we conducted intraoperative experiments during awake mThal DBS implantation in n=15 patients undergoing treatment for essential tremor. We placed two subdural electrocorticography (ECoG) electrodes over the hand and facial representation of the primary motor cortex to perform direct cortical stimulation. We then paired varying durations of mThal stimulation with direct cortical stimulation, while recording motor-evoked potentials (MEPs) from facial and arm muscles using surface EMG. We generated muscle recruitment curves and analyzed MEP features, including peak latency, duration, and waveform shapes, to infer changes in fiber recruitment and motor unit activation with respect to duration of mThal stimulation. Our findings demonstrated that mThal stimulation increased MEP complexity by broadening latency distributions and increasing variability in waveforms. Specifically, prolonged mThal stimulation at low-frequency increased MEP the quantity, amplitude, and latency of peaks across both facial and arm muscles, suggesting a direct increase in activation of descending motor fibers of the CST/CBT. These results demonstrate a potential mechanism by which mThal DBS enhances cortical excitability and alters motor recruitment dynamics to promote upper-limb and orofacial motor function recovery.

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Poster

PSTR129: Neuroprosthetics: Stroke

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Program #/Poster #: PSTR129.10/X6

Topic: F.05. Brain-Machine Interface

Title: Targeting Spinal Circuit Dysfunction in Spinal Muscular Atrophy with Epidural Stimulation: Preliminary Evidence of Upper Limb Motor Improvement

Authors: *S. DONADIO[1,8], G. PRAT ORTEGA[2,8], S. ENSEL[3,8], J. OSTROWSKI[9,8], L. BORDA[10,11], A. BOOS[4,8], D. J. WEBER[12,11], P. GERSZTEN[5], G. Z. MENTIS[13,14,15], R. M. FRIEDLANDER[16], E. PIRONDINI[3,6,8], M. CAPOGROSSO[7,3,8];
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Abstract: Spinal Muscular Atrophy (SMA) is an inherited neurodegenerative disease characterized by motor deficits that vary from severe muscle weakness and respiratory failure in infancy to milder limb weakness and fatigue in later-onset cases. The hallmarks of this condition are motoneuron (MN) death and spinal circuit dysfunction. Although three therapies exist that slow neurodegeneration and prevent mortality, individuals with SMA still experience severe motor deficit.This highlights the need for complementary strategies to address unresolved MN dysfunction.
Studies using SMA mouse models have shown that a reduction in proprioceptive sensory synapses to spinal MNs triggers maladaptive changes that lead to MN hyperexcitability, and, paradoxically, a decrease in firing rates due to prolonged refractory periods. Spinal Cord Stimulation (SCS) is neurotechnology that activates sensory afferents, driving excitatory input to MNs through reflex pathways. We hypothesize that in SMA, SCS may strengthen the connection between sensory afferents and MNs, reversing the maladaptive changes in the membrane properties of MNs and improving motor function. We previously showed that combining SCS with physical exercise improved strength and gait quality in three ambulatory adults with SMA, alongside increased MN firing rates and shortened refractory periods. Although promising, these findings may be influenced by exercise effects and need confirmation in a larger cohort.
As many individuals with SMA are non-ambulatory and primarily affected in upper limb function, we designed the next study to focus on this population. In a follow-up trial (STUDY21080158), we temporarily implanted epidural leads in the cervical spinal cord of three non-ambulatory adults with SMA for 29 days. To isolate the effects of SCS from exercise, stimulation was applied unilaterally, with the opposite arm as control. Participants received 2 hours of daily stimulation during strength and kinematic testing. Despite differences in age and impairment severity, all participants showed progressive improvements in maximum strength (up to +184%), as well as enhanced movement smoothness, range of motion, and velocity during 3D reaching tasks, as measured by kinematic analysis. Notably, improvements were greater in the stimulated arm, suggesting that exercise alone cannot drive these gains. Finally, all participants showed increased reflex responses to single SCS pulses in arm muscles, indicating strengthened sensory-motor pathways. The results highlight SCS as a strategy to restore motor function by targeting spinal circuits, offering a valuable addition to current SMA interventions.

Disclosures: S. Donadio: None. **G. Prat Ortega:** None. **S. Ensel:** None. **J. Ostrowski:** None. **L. Borda:** None. **A. Boos:** None. **D.J. Weber:** None. **P. Gerszten:** None. **G.Z. Mentis:** None. **R.M. Friedlander:** None. **E. Pirondini:** None. **M. Capogrosso:** None.

Poster

PSTR129: Neuroprosthetics: Stroke

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.11/X7

Topic: F.05. Brain-Machine Interface

Support: 1R01NS122927-01A1- Gonzalez-Martinez

Title: Pulvinar-driven modulation of thalamocortical connectivity in drug-resistant epilepsy: a translational framework for targeted neuromodulation

Authors: *S. NOUDURI[1], A. DAMIANI[2], J. CHEN[3], J. E. TING[2], J. A. GONZÁLEZ-MARTÍNEZ[3], E. PIRONDINI[4];
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Abstract: Drug-resistant epilepsy (DRE) affects approximately 30% of individuals with epilepsy, posing significant treatment challenges, especially when resective surgery is not feasible. Neuromodulation offers a promising alternative, but its success relies on precise target selection. The pulvinar nucleus (PUL), with its extensive posterior cortical connectivity, is an emerging yet understudied candidate for posterior quadrant epilepsy (PQE). Its functional subregions and their roles in seizure dynamics remain poorly defined. We hypothesize that medial and lateral PUL subregions exhibit distinct, dynamic interactions with cortical epileptogenic zones (EZs), which can be mapped using stereoelectroencephalography (SEEG) and intraoperative physiology. We will analyze 20 patients with PQE who underwent SEEG with depth electrodes targeting both medial and lateral PUL. Using h^2 correlation coefficients, we will quantify functional connectivity between PUL contacts and cortical EZs across preictal, ictal, and postictal periods to capture time-resolved thalamocortical dynamics. To refine subregional targeting, intraoperative multi-unit activity (MUA) will be recorded via microelectrode recordings (MER) from 3 patients undergoing response neurostimulation (RNS) implantation. Neuronal firing rates will identify low- and high-activity zones within PUL subregions, and subscalp EEG will be used to assess frequency-specific cortical responses to stimulation. We expect to observe preferential 4-8 Hz connectivity between lateral PUL and temporal EZs, and between medial PUL and occipital EZs, with this asymmetry decreasing toward seizure termination. MER-identified low-activity zones are anticipated to correspond with increased cortical delta power, suggesting thalamocortical slowing. This study aims to uncover functional specialization within the PUL and establish its subregions as dynamic nodes in seizure propagation. Findings will inform connectivity-guided strategies for neuromodulation in PQE and lay the groundwork for future clinical trials evaluating the safety and efficacy of PUL-targeted DBS and RNS.

Disclosures: S. Nouduri: None. **A. Damiani:** None. **J. Chen:** None. **J.E. Ting:** None. **J.A. González-Martínez:** None. **E. Pirondini:** None.

Poster

PSTR129: Neuroprosthetics: Stroke

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.12/X8

Topic: F.05. Brain-Machine Interface

Support: NIH SPARC OT2OD030537

Title: 3d quantification of feline dorsal root ganglia using high-resolution mri

Authors: ***Z. XU**[1,2], L. LIANG[3], L. E. FISHER[4], E. NEUFELD[7], T. K. HITCHENS[8], C. L. KOLARCIK[5], E. PIRONDINI[6];
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Abstract: The dorsal root ganglion (DRG) contains neuronal somata of afferent neurons, situated on the dorsal root, which merges with the ventral root to form the spinal nerve. Given the high abundance of peripheral sensory neurons, the DRG serves as an ideal access point for direct interaction with the sensory circuit. Despite the crucial role of DRGs in treating sensory-related disorders and applying neuromodulation, investigations of cell distribution within this structure remain limited due to the complexity of immunohistological procedures. Therefore, a comprehensive, three-dimensional (3D) analysis across spinal levels was conducted to characterize the neuronal somata distribution throughout the DRG. High-resolution (50 μm) MRI was utilized to acquire *ex vivo* T2-weighted images of DRGs from four feline spine specimens (n = 32 DRGs across cervical, thoracic and lumbosacral levels), which were then validated against immunohistology observations of the same specimens (n = 3 lumbosacral DRGs). The spatial cell density distribution patterns were analyzed within and across different DRGs, and among spinal levels (i.e. cervical, thoracic and lumbosacral), through sector-based quantification and spatial clustering analysis. Our MRI acquisitions showed high correspondence with histological slices, as demonstrated by the strong correlation ($rs > 0.8$) in sector-based somata distribution quantification between the two modalities in lumbosacral DRGs. Three-dimensional analysis of lumbosacral DRGs confirmed previous reports on mid-axial distribution patterns, while revealing novel variations in the organization along the longitudinal axis of the DRG. Cross-level comparisons revealed a conserved tendency of higher somata density in the mid-axial DRG, especially in the outer layer, with level specific dorsal-ventral and medial-lateral distribution patterns and potential clustering characteristics. By validating high-resolution MRI against histology and further quantifications, this study expands the methodological toolkit for studying the microstructure of sensory ganglia and contributes to our understanding of the anatomical organization of neuron distribution within the DRG, with potential applications for targeted neuromodulation therapies and understanding sensory disorders.

Disclosures: Z. Xu: None. **L. Liang:** None. **L.E. Fisher:** None. **E. Neufeld:** None. **T.K. Hitchens:** None. **C.L. Kolarcik:** None. **E. Pirondini:** None.

Poster

PSTR129: Neuroprosthetics: Stroke

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.13/X9

Topic: F.05. Brain-Machine Interface

Support: NIH Grant UG3NS123135

Title: Modeling synaptic dynamics to optimize the efficacy of neurostimulation technologies

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Abstract: Electrical stimulation of the nervous system is a growing field of research with the potential to greatly improve the quality of life of patients suffering from motor control disorders. Epidural spinal cord stimulation (SCS) is one of these novel therapeutic techniques, promising to dramatically help patients regain voluntary motor control. In epidural SCS, electrode leads lay on top of the bundle of fibers that compose the spinal cord, applying electrical current to modulate the activity of these nerves. It is believed that SCS functions by activating proprioceptive afferent fibers in the dorsal column of the spinal cord, which in turn convey this excitation to motoneurons where it summates with descending inputs to produce volitional movement (Seáñez & Capogrosso, 2021).

Although it is widely accepted that the afferent-motoneuron synapse plays a crucial role in the efficacy of SCS for movement disorders, the details of synaptic transmission from SCS-induced afferent firing to motoneuron response are often overlooked. Specifically, it is known that repetitive stimulation can deplete the available neurotransmitter in the afferent fibers, resulting in progressively smaller responses in the motoneuron (Wan et al., 2006). This phenomenon, known as rate-dependent depression (RDD), restricts the transmission of stimulation from the afferent fibers to the motoneuron, thereby imposing a potential limitation of SCS.

Here, we consider the role that rate-dependent depression (RDD) plays in determining the efficacy of SCS and explore methods for optimizing stimulation using models of RDD in spinal circuitry. We quantify spinal RDD in non-human primates and human patients implanted with SCS by using electromyography (EMG) to measure the depression in evoked responses at a range of stimulation frequencies. Next, we develop a computational model of RDD in spinal circuitry and fit it to our experimental data. Using this model, we predict optimized paradigms that minimize synaptic depletion and maximize the transmission of stimulation. We test these SCS paradigms in non-human primates in order to determine which parameters result in the largest increases of evoked-EMG responses across the stimulation window. Ultimately, this project evaluates the role of synaptic dynamics in limiting transmission of stimulation and proposes methodology to optimize stimulation given this restriction. While this project focuses on SCS, its implications extend beyond, as understanding synaptic transmission is essential for

optimizing the targeted responses to electrical modulation across all forms of neurostimulation technologies.

Disclosures: J. Ostrowski: None. **L. Liang:** None. **J. Balaguer:** None. **M. Capogrosso:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.01/X10

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: FAPESP Grant 2023/02531-5
CNPq Grant 404806/2021-6

Title: Presence of MCH-immunoreactive neurons during lactation in the ventromedial preoptic area of the swine model

Authors: *J. C. BITTENCOURT[1,2], A. Y. HELOU[3], C. CARVALHO[4], F. AGUIAR COELHO[5], C. POSPISSIL GARBOSSA[6], P. TATEMOTO[4];
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Abstract: This study examines the distribution of melanin-concentrating hormone-immunoreactive (MCH-ir) neurons in the ventromedial preoptic area (vmMPOA) across different species, with a focus on lactation. In rats, lactation is linked to a temporary increase in MCH-ir neurons in the vmMPOA; however, it remains unclear if this pattern is consistent in other mammals closely related to humans. The domestic pig (*Sus scrofa domesticus*) is an ideal model due to its anatomical and functional brain similarities to humans. Although earlier research has identified MCH neuron distribution in pigs, located in the lateral hypothalamic area (LHA), and MCH projections to all cortical areas and in the amygdaloid complex, a comprehensive mapping of MCH-ir neurons is lacking. To test the hypothesis that lactation triggers a temporary increase in MCH-ir neurons in the vmMPOA, we utilized an immunohistochemical method across five experimental groups. Brain samples from adult pigs were categorized into nulliparous gilts, lactating sows at postpartum day 21, sows weaned at day 21 (but slaughtered at 28 days), sows 28 days post-weaning, and age-matched males. Our stereological analysis indicated that lactating pigs displayed a specific recruitment of MCH-ir neurons in the vmMPOA, paralleling findings in rats and suggesting conserved neuroendocrine mechanisms for maternal adaptations. Notably, MCH-ir neurons were also found in male pigs in the LHA and vmMPOA, implying that factors besides lactation, like genetic selection for hyper-prolificacy, might affect the baseline presence of this peptidergic population. Additionally,

cohabitation with oxytocin-ir neurons in the supraoptic nucleus reinforces the pig's potential as a translational model for studying MCH's role in lactation and neuroendocrine plasticity.

Disclosures: J.C. Bittencourt: None. **A.Y. Helou:** None. **C. Carvalho:** None. **F. Aguiar Coelho:** None. **C. Pospissil Garbossa:** None. **P. Tatemoto:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.02/X11

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NSF 2123574

Title: Comparative expression of P450c17 and Cytochrome b5 in primate brains

Authors: E. N. HART[1], D. GONZALEZ[2], M. K. EDLER[1], W. C. J. CHUNG[2,3], C. C. SHERWOOD[4], M. RAGHANTI[1,3], ***R. S. C. TAKESHITA**[1,3];
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Abstract: The adrenal androgens dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS) are steroid hormones involved in stress regulation, neurogenesis, neuroprotection, and serve as gonadal steroid hormone precursors. They are the most abundant circulating steroids in humans and some non-human primates. Humans have the highest circulating concentrations, followed by chimpanzees and cercopithecoids (e.g., macaques and baboons). In contrast, marmosets are characterized by low DHEA levels, particularly males, whose adrenal glands lack expression of P450 17A1 (P450c17) and cytochrome b5 (cyt b5), two enzymes necessary for DHEA synthesis. Apart from the adrenal gland, DHEA and DHEAS (DHEA(S)) are synthesized *de novo* in the brain, where they promote neurogenesis, neuroprotection, and may be involved in memory enhancement. However, whether species' differences in adrenal synthesis of DHEA(S) also occurs in the brain remains unknown. This research sought to compare expression of P450c17 (marmoset: 1:40,000; macaque and chimpanzee: 1:20,000; chicken polyclonal; Dr. A. J. Conley, Department of Public Health and Reproduction, University of California-Davis) in three primate species: common marmoset (*Callithrix jacchus*), rhesus macaque (*Macaca mulatta*), and chimpanzee (*Pan troglodytes*). We used immunohistochemistry and stereology (MBF Bioscience; optical fractionator) to quantify immunopositive cell densities in the striatum (caudate, putamen, and nucleus accumbens), amygdala, hippocampus (dentate gyrus and CA1-3), and premotor cortex (layers 1-6) of 6 adult individuals (3 male, 3 female) from each species (N = 18). Our preliminary results showed that P450c17 was expressed in each brain region of the common marmoset, rhesus macaque, and chimpanzee. In all species, the dentate gyrus exhibited a higher expression of P450c17 immunoreactive cells than other regions with a significant difference detected in the macaques ($X^2 = 11.40$; $p = 0.04$) but not in the marmosets ($X^2 = 9.60$;

$p = 0.09$) or the chimpanzees ($X^2 = 8.21$; $p = 0.15$). Although not consistently significant, this regional difference calls for further investigation and may reveal a role for memory formation. Our results indicate that neural expression of P450c17 is conserved among primates, despite marked interspecies variation in adrenal DHEA(S) production. P450c17 is only one enzyme involved in DHEA(S) synthesis, and ongoing analyses are investigating expression of cyt b5. If a shift can be detected, it may suggest that central DHEA(S) production contributed to lineage-specific adaptations in stress physiology, cognition, or lifespan.

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Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.03/X12

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

Title: Evaluating DHEA administration as a preclinical model of PCOS: Diagnostic and non-diagnostic effects on metabolism, cognition, and neurophysiology

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Abstract: Polycystic Ovary Syndrome (PCOS) is the most common reproductive disorder in pre-menopausal women, yet it remains under-researched and poorly understood. Preclinical PCOS models often rely on androgen administration (e.g., testosterone) to mimic the hyperandrogenic state observed clinically in humans. Dehydroepiandrosterone (DHEA), the most abundant circulating androgen in humans, is also used, but its reliability in creating PCOS-like symptoms in rodents has been inconsistent. Here, we assessed the validity of DHEA as a PCOS model in female Long Evans rats (N = 25), focusing on behavioral, cognitive, and neurophysiological outcomes. Rats received daily subcutaneous injections of either DHEA or sesame oil and were given access to a 10% fructose solution (an external obesity factor) or water, yielding four experimental groups; separate home-cage controls received no manipulation. We hypothesized that DHEA administration would induce both diagnostic and non-diagnostic PCOS-like symptoms, with fructose intake and resulting obesity exacerbating these effects. However, metabolic data showed minimal group differences, including no evidence of insulin resistance ($p = 0.140$) or adiposity differences ($p = 0.130$), nor did hormone administration affect anxiety-like behavior ($p = 0.976$) or spatial working memory ($p = 0.269$). Despite the absence of common non-diagnostic symptoms, DHEA-treated animals met Rotterdam Criteria for PCOS diagnosis; these females exhibited disrupted estrous cycles as evident by a shortened estrus phase ($p < 0.001$), as well as elevated testosterone levels ($p < 0.001$), regardless of fructose intake.

Thus, while DHEA administration created diagnostic PCOS-like features, non-diagnostic symptoms were not observed; this suggests that this model may be useful for studying hyperandrogenism or estrous cycle disruption, but likely does not capture the full range of the human experience with PCOS. Current work in our lab is investigating whether these effects extend to the brain, examining regions involved in stress, cognition, and metabolic regulation, to test the hypothesis that DHEA may induce neuroinflammation and oxidative stress in females with PCOS. This approach will elucidate whether DHEA is a suitable model for future PCOS preclinical work.

Disclosures: C.E. Miller: None. **E. Met Hoxha:** None. **K. Kinzig:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.04/X13

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: R01HD104345

Title: Voltage-gated calcium channel activity of gonadotropin-releasing hormone (GnRH) neurons is altered by prenatal androgen exposure in female mice

Authors: *X. CHEN[1], R. A. DEFAZIO[2], S. M. MOENTER[3];
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Abstract: Polycystic ovary syndrome (PCOS), the most common endocrine cause of female infertility, is marked by persistently high luteinizing hormone (LH)-pulse frequency, presumably driven by high-frequency GnRH pulses. High-frequency GnRH suppresses follicle-stimulating hormone and follicular maturation, and the LH pulses raise androgen production. Prenatally androgenized (PNA) mice mimic many PCOS symptoms including high LH-pulse frequency. Adult PNA mice have higher spontaneous GnRH neuron firing rates than vehicle (VEH) mice, but prepubertal (3-wk-old) PNA mice have lower GnRH neuron activity despite more excitatory GABAergic inputs to these cells both before and after puberty. This implicates a role for intrinsic properties. We hypothesized voltage-gated Ca^{2+} currents (I_{Ca}) play critical roles in intrinsic excitability of GnRH neurons and are altered by development and/or PNA treatment. Whole-cell patch-clamp was used to measure GnRH neuron I_{Ca} in 3wk-old and adult VEH and PNA mice. PNA treatment increased I_{Ca} density (3-way ANOVA, $p<0.01$), but developmental stage had no influence. Development did alter the time-dependent inactivation of a fast I_{Ca}, which was more rapid in 3-wk than adult groups regardless of treatment (2-way ANOVA $p<0.01$). In VEH mice, the potential at which half the I_{Ca} was activated was more depolarized in cells from adult vs 3-wk mice (2-way ANOVA/Fisher's LSD, $p<0.05$), but this developmental change was absent in PNA mice. In response to current step injections, GnRH neurons from VEH, but not PNA, mice had

higher firing rates at 3-wks than in adulthood (3-way ANOVA/Fisher's LSD $p<0.01$). We tested the role of Ca^{2+}-activated K^+ channels on firing by blocking them with apamin. During 6 min of repeated current steps, spike frequency decreased in untreated control cells. Apamin prevented this loss and increased firing rate in GnRH neurons from adult VEH mice (2-way ANOVA/Fisher's LSD $p<0.001$); in adult PNA mice, apamin mitigated time-dependent loss of firing frequency but did not increase firing rate. Apamin also changed the post-spike-train membrane response from hyperpolarization to depolarization and this shift was smaller in GnRH neurons from PNA mice (2-way ANOVA apamin*PNA treatment $p<0.05$). These results suggest that while GnRH neurons from PNA mice at both ages have increased Ca^{2+} influx, which may enhance GnRH release, they lack some developmental changes in I_{Ca} kinetics and intrinsic excitability observed in VEH mice. Despite increased $I_{Ca,}$ Ca^{2+}-activated K^+ currents are less effective in prolonging the intraspike interval in GnRH neurons from adult PNA mice, perhaps contributing to their increased spontaneous firing rate.

Disclosures: X. Chen: None. **R.A. DeFazio:** None. **S.M. Moenter:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.05/X14

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant DA055105

Title: The influence of prepubertal ovariectomy on estrogen receptor β and parvalbumin neurons in the rat medial prefrontal cortex.

Authors: *E. HOFFMAN[1], J. M. JURASKA[2], A. S. BRINKS[3];
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Abstract: Neural circuitry in the medial prefrontal cortex (mPFC) is fine-tuned during adolescence. One change is increased activity of parvalbumin expressing (PV) cells, the source of fast-acting inhibitory transmission in the region. Reorganization of the rat mPFC during adolescence often occurs around puberty in a sex-dependent manner (Willing & Juraska, 2015; Drzewiecki & Juraska, 2020). PV and estrogen receptor β (ERβ) mRNA (esr2) expression are colocalized throughout the cortex, and PV expression and function fluctuate across the estrous cycle (Clemens et al., 2019). However, a previous study has shown that adult ovariectomy does not influence density of ERβ in the mPFC (Blurton-Jones & Tuszynski, 2002). We have found that *esr2* expression abruptly decreases in density at female pubertal onset and is sustained into adulthood (Drzewiecki et al., 2019). Here we examine whether a lack of estrogen starting before puberty influences *esr2* expression, especially in PV neurons in adulthood. Pre-pubertal ovariectomy (OVX) at P20 was performed in female Sprague Dawley rats. In adulthood (P70),

esr2 and PV mRNA (*pvalb*) expression are being quantified via *in situ* hybridization in the mPFC, as well as adjacent anterior cingulate and the nucleus accumbens, using RNAscope®. Preliminary findings indicate that prepubertal OVX decreases the proportion of *pvalb*+/*esr2*+ cells in the mPFC in adulthood, while *esr2* density appears to be similar between groups, prior work (Koss et al., 2015) found that prepubertal OVX results in a larger mPFC volume. We will be parcellating the volume of the mPFC so that the number of receptors can be calculated.

Disclosures: E. Hoffman: None. **J.M. Juraska:** None. **A.S. Brinks:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.06/X15

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Molecular mechanisms underlying the regulation of metabolic function by ovarian hormones

Authors: *L. OULDIBBAT[1], M. C. TICKERHOOF[1], M. SUZUKI[2], M. KUNDAKOVIC[1]; [1]Fordham Univ., Bronx, NY; [2]Texas A&M Univ., College Station, TX

Abstract: Women are at increased risk for metabolic dysfunction compared to men, especially during the menopausal transition and postmenopause. Estradiol plays a critical role in regulating body weight, food intake, physical activity, and body composition through its actions in the hypothalamus. However, the specific gene regulatory mechanisms involved remain poorly defined. To investigate this, we first characterized metabolic phenotypes in ovariectomized (OVX) and ovary-intact (cycling) C57BL/6 female mice aged 9 to 21 weeks, focusing on the proestrus (high estrogen, low progesterone) and diestrus (low estrogen, high progesterone) phases of the estrous cycle. We tracked weight, food intake, activity levels, and body composition. By 21 weeks, OVX mice had gained approximately 40% more weight than cycling animals, driven by increased food consumption and decreased activity. Conversely, cycling females showed decreased food intake during proestrus, consistent with estrogen's known anorexigenic effects. Additionally, OVX animals displayed a significant increase in fat mass. To begin exploring the molecular mechanisms underlying these observed metabolic phenotypes, we assessed hypothalamic expression of metabolically relevant genes, including estrogen receptor 1 (*Esr1*), agouti-related peptide (*Agrp*), and pro-opiomelanocortin (*Pomc*) and found expression differences across the cycle and between OVX and cycling groups. To investigate the molecular and cellular basis of these phenotypic changes with increased precision, we have furthered performed 10X Genomics single-nucleus RNA sequencing of the hypothalamus of OVX, proestrus, and diestrus female mice (N=6 mice or 3 biological replicates/group). By targeting 20,000 nuclei per replicate and using Seurat, so far, we have identified 22 distinct cell types, including within *Esr1*-expressing and metabolically relevant hypothalamic subregions. Ongoing single-nucleus analyses aim to define how ovarian hormone status influences both cellular

composition and gene expression dynamics in the female hypothalamus. By integrating phenotypic measurements with cell-type-specific gene expression profiles, this work provides a comprehensive framework for understanding how ovarian hormones shape both metabolic phenotype and cellular states in the hypothalamus. Ultimately, these insights may reveal novel, female-specific targets for treating metabolic syndromes.

Disclosures: L. Ouldibbat: None. **M.C. Tickerhoof:** None. **M. Suzuki:** None. **M. Kundakovic:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.07/X16

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Effects of microenvironmental forces on spontaneous migration of immortalized GnRH cells

Authors: *A. HOLLIMAN[1], L. MACKAY[1], R. VAGHASIYA[2], P. MISTRIOTIS[2], C. D. FORADORI[1];
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Abstract: Gonadotropin releasing hormone (GnRH) cells have a unique developmental origin**.** GnRH cells develop in the nasal placode and migrate across the nasal mesenchyme through the cribriform plate. After crossing the cribriform plate, the cells enter the forebrain and move toward the preoptic area and hypothalamus. Throughout their migration, GnRH neurons encounter a variety of physical forces with differing physical constraints, hydrostatic pressures, and substrate rigidities. It is not known how these physiologic conditions affect GnRH cells and their migration. To address this knowledge gap, we have employed a novel microfluidic cell culture technology. This system enables tight control of the degree of confinement, the generation of biochemical gradients, adjustable substrate stiffness, and control of shear flow, thereby recapitulating microenvironmental cues encountered by GnRH cells during *in vivo* migration. We hypothesize that the forces that GnRH cells overcome as they traverse from the nasal placode to the hypothalamus alters their morphology, migratory agency, and cell physiology. In addition, these microenvironmental-induced alterations are required for proper cell maturation and function. In preliminary studies, GN11 cells (an immortalized, immature GnRH cell line) were seeded within polydimethylsiloxane-based microfluidic devices composed of parallel channels separated by microchannels aligned in a ladder-like configuration with increasingly restrictive internal geometries of 10x10 μm^2, 6x10 μm^2, or 3x10 μm^2 (height x width). Cells were imaged every 15 minutes for 16 hours to determine migratory dynamics and morphological changes present during migration. Video images and statistical analysis were performed with ImageJ/Fiji, MatLab, and Prism. As physical confinement increased the

migration speed of GnRH cells decreased. Cells migrating in 10x10 μm^2 channels move significantly faster than cells migrating in 6x10 μm^2 channels (41.96±2.09 μm/hr v. 32.81±2.11 μm/hr, p=0.0027) and in 3x10 μm^2 channels (41.96±2.09 μm/hr v. 29.13±2.51 μm/hr, p<0.0001). Increasing restriction did not significantly alter persistence, circularity, or aspect ratio of migrating cells. This ongoing project will develop and validate a new tool to enhance clinical relevance and translational impact of *in vitro* neural cell migration studies and allow for a more complete understanding of GnRH cell migration and the forces which affect their development.

Disclosures: A. Holliman: None. **L. Mackay:** None. **R. Vaghasiya:** None. **P. Mistriotis:** None. **C.D. Foradori:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.08/Y1

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Using immortalized ovine and murine hypothalamic cell lines to explore effects of sex steroids, seasonal cues, and metabolic factors on reproduction

Authors: A. NIELSEN[1], M. DEAJ[2], C. E. ROSELLI[3], K. HOKANSON[1], ***P. E. CHAPPELL**[2]; [1]Biochem. and Biophysics, [2]Biomed. Sci., Oregon State Univ., Corvallis, OR; [3]Chem. Physiol. & Biochem., Oregon Hlth. Sci. Univ., Portland, OR

Abstract: The multiphenotypic hypothalamic KNDy neurons, releasing kisspeptin (KP), neurokinin B (NKB/Tac3), and dynorphin (Dyn), play a critical role in the neuroendocrine regulation of reproduction via stimulation of pulsatile GnRH release, and are requisite for fertility. *In vivo* evidence in mice also identifies this arcuate population in mediating negative feedback effects of gonadal steroids. We previously generated murine immortalized KNDy neuronal cell lines (KTaR-1) to explore molecular mechanisms underlying steroid hormone regulation, and recently generated and characterized an analogous immortalized line (oKNDy) derived from fetal female sheep brain. These neurons express ovine *kiss1*, *tac3*, and *pdyn*, as well as *esr1*, *esr2*, and *pgr*. Similar to observations in the mouse, low doses (5-50pM) of 17β-estradiol (E2) significantly repress *kiss1* and *tac3* expression. Since these neurons were derived from short-day seasonally breeding sheep, they can inform how pituitary circannual timing cues may exert gating signals on the reproductive axis as modeled *in vivo*. Consistent with this, we find high levels of thyroid hormone receptor (*thra*) expression in oKNDy neurons, and find *kiss1/tac3* expression inhibited by exogenous T3. Additionally, both mouse and sheep KNDy neurons express receptors for metabolic factors like adiponectin, leptin, and IGF-1, while only murine lines express receptors for GLP-1 and ghrelin. In the sheep, adiponectin increases *kiss1* expression in a dose- and E2-dependent fashion, while leptin inhibits its expression, in contrast with what is observed in the less-responsive mouse lines. Continuing our comparative efforts in these lines, we have performed electrophysiological characterization using both single-cell patch

clamp and multielectrode array techniques. Ovine oKNDy neurons possess lower resting membrane potential, and express more voltage-gated Na^+ and K^+ channels than their murine counterparts. Since the rapid growth rate of KTaR-1 cells in normal 10%FBS may preclude these cells from adopting a more neuronal phenotype, we cultured these murine cells under different serum substitute conditions and using dibutyryl-cAMP. We used Sholl analysis to determine morphological changes induced by differentiation, and observed commensurate increases in activity in these immortalized cells. Preliminary results indicate E2-modulated changes in activity in both lines following *in vitro* differentiation. Use and comparison of these cultured neuronal cell models will provide insight into GnRH pulse generation and aid in constructing molecular models of direct neuronal responsiveness to steroid hormones and metabolic inputs.

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Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

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Program #/Poster #: PSTR130.09/Y2

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: CONAHCYT GRANT BM 850453

Title: Regulation of sex hormone receptor expression in brain regions associated with chinning behavior in male rabbits

Authors: *B. MOLINA[1], L. HERNÁNDEZ LÚA[1], J. QUINTERO-GALLEGOS[1], K. HERNÁNDEZ ORTEGA[1], G. GONZALEZ-MARISCAL[2], I. CAMACHO-ARROYO, Sr.[1,3]; [1]Facultad de Química, Univ. Nacional Autónoma de México, Mexico, Mexico; [2]Researcher Emeritus, Natl. Syst. of Investigators, Mexico, Mexico; [3]Unidad de Investigación en Reproducción Humana, Inst. Nacional de Perinatología, Mexico, Mexico

Abstract: Estradiol, progesterone, and testosterone are crucial for vertebrate brain functions by interacting with their specific receptors. In rabbits, these hormones regulate various behaviors, including scent marking, a characteristic rabbit behavior called “chinning”, which involves rubbing the chin to deposit chin gland secretions. Male and female rabbits use this behavior to socially communicate and send information to other rabbits regarding sex, social status, or reproductive conditions. Chinning can be eliminated through gonadectomy, and it can be restored in males by administering testosterone propionate (TP) or a combined treatment of dihydrotestosterone (DHT) and estradiol benzoate (EB). TP implants in the medial preoptic area of male rabbits induce chinning. Despite this knowledge, physiological mechanisms implicated in the display of male chinning behavior are still unknown. Therefore, we examined intracellular progesterone (PR), estrogen (ER), and androgen receptors (AR) protein (WB) and mRNA expression (RT-qPCR) in different brain regions (olfactory bulb, prefrontal cortex, hippocampus,

preoptic area, hypothalamus, mesencephalon, and cerebellum) of adult male rabbits that were gonadectomized and treated daily with vehicle, TP (1mg), or DHT (1mg) + EB (1µg) (n=5) for 16 days. We observed that sex hormone receptors were present in all analyzed regions. Notably, TP increased AR expression in all examined regions, whereas DHT + EB increased AR levels in the olfactory bulb, prefrontal cortex, preoptic area, and hypothalamus. This illustrates a potential participation of AR in chinning display in the male rabbit.

Disclosures: B. Molina: None. **L. Hernández Lúa:** None. **J. Quintero-Gallegos:** None. **K. Hernández Ortega:** None. **G. Gonzalez-Mariscal:** None. **I. Camacho-Arroyo:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

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Program #/Poster #: PSTR130.10/Y3

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: BUAP
CONAHCYT

Title: Expression of 17β-estradiol in five prevertebral ganglia of lean and obese zucker rats throughout the estrous cycle

Authors: *M. RIVERA CASTRO[1], M. CHÁVEZ RINCON[2], J. M. BRAVO[3], C. MORAN[4]; [1]Benemerita Univ. Autonoma de Puebla, Puebla, Mexico; [2]BENEMERITA UNIVERSIDAD AUTONOMA DE PUEBLA, Puebla, Mexico; [3]INSTITUTO DE CIENCIAS DE LA UNIVERSIDAD AUTONOMA DE PUEBLA, BENEMERITA UNIVERSIDAD AUTONOMA DE PUEBLA, PUEBLA, Mexico; [4]Benemérita Univ. Autonoma de Puebla, Puebla, Mexico

Abstract: Obesity has become a major public health issue due to its role in the development of various comorbidities, especially those related to cardiovascular and endocrine disorders. While recent research has emphasized the relationship between the central nervous system and obesity, there is growing evidence that peripheral nervous system structures, such as prevertebral ganglia, also play important roles in metabolic regulation and adipose tissue homeostasis. We analyzed the presence of 17β-estradiol in five prevertebral ganglia in female Zucker rats, both lean and obese, across the estrous cycle. These ganglia are known to influence the enteric nervous system, adrenal glands, and abdominal organs, and are also anatomically and functionally linked to the ovaries and reproductive tract. Given that the ovary, a key producer of steroid hormones, may alter its hormonal output in response to changes in both central and peripheral neural signaling, we sought to examine how 17β-estradiol levels within these ganglia fluctuate during the estrous cycle. Female Zucker rats (3 months old, n = 20) were housed under controlled conditions, and their estrous cycle stages were carefully monitored. On each day of the cycle, five animals were selected for ganglia extraction. The collected tissues were preserved and processed for analysis using immunofluorescence techniques to assess 17β-estradiol immunoreactivity in neurons of the

prevertebral ganglia throughout the estrous cycle. All experimental procedures were approved by the Mexican Council for the Care and Use of Laboratory Animals. Obese rats exhibited disrupted estrous cycles, characterized by prolonged diestrus I stages, whereas lean rats maintained regular cycles. In lean animals, 17β-estradiol-immunopositive neurons peaked during diestrus II and proestrus and were lowest during diestrus I. Additionally, we observed asymmetric immunoreactivity between paired suprarenal and celiac ganglia. Soma size varied significantly throughout the cycle, with the largest neurons found during proestrus and the smallest during diestrus I. In contrast, obese rats exhibited a significantly reduced number of 17β-estradiol-positive neurons across all ganglia, with no significant variation in soma size or left-right asymmetry. These findings suggest that 17β-estradiol expression in prevertebral ganglia is dynamic and estrous-cycle-dependent in lean animals but remains relatively static under obese conditions. This hormonal modulation may influence lipid metabolism and contribute to reproductive pathologies such as polycystic ovary syndrome (PCOS), endometriosis, and infertility.

Disclosures: M. Rivera Castro: None. **M. Chávez Rincon:** None. **J.M. Bravo:** None. **C. Moran:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

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Program #/Poster #: PSTR130.11/Y4

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Circadian misalignment via timed restricted feeding disrupts estrous cyclicity in female mice

Authors: *M. A. ADESINA, W. C. J. CHUNG, E. M. MINTZ;
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Abstract: Circadian rhythms synchronize internal physiology with environmental cues. In mammals, feeding is a potent zeitgeber for peripheral clocks. When food intake occurs during the inactive phase—as in daytime restricted feeding (RF) for nocturnal rodents—it can desynchronize peripheral clocks from the central pacemaker in the suprachiasmatic nucleus (SCN), potentially disrupting neuroendocrine regulation of reproduction. In addition, a caloric deficit can also contribute to reproductive dysfunction in females. We hypothesized that restricting food availability during the normal rest period of the day would suppress the estrous cycle without a major loss of body weight. To test this, adult female C57BL/6J mice were assigned to ad libitum (AL), 6-hour, or 8-hour RF schedules for 28 days. Wheel-running activity tracked food anticipatory behavior. Daily food intake and weekly body weight were monitored. Vaginal cytology was performed daily to assess estrous cyclicity, and plasma was collected at two time points—before feeding and after — to measure circulating steroid hormone concentrations (estradiol, progesterone, corticosterone).

Preliminary data show that both RF groups consumed significantly less food than AL controls, though intake remained within a physiological range (AL: 3.61 ± 0.099 g; 6HR: 3.20 ± 0.096 g, $p < 0.05$; 8HR: 3.08 ± 0.086 g, $p < 0.05$). Body weights remained stable across all groups, with no significant differences at Week 5 (AL = 25.6 ± 0.4 g; 6hrs RF = 25.1 ± 0.5 g, $p > 0.05$; 8hrs RF = 25.0 ± 0.6 g, $p > 0.05$). Analysis of estrous cyclicity revealed a marked reduction in the percentage of proestrus days: AL mice averaged 20.8% ± 4.4, while 8HR and 6HR groups exhibited 16.9% ± 5.7 and 10.8% ± 6.0, respectively representing a 19% and 48% reduction compared to controls. These findings suggest that reproductive disruption is not solely due to reduced caloric intake but may result from circadian misalignment affecting hypothalamic GnRH and kisspeptin signaling. Brain tissue from these mice will be analyzed using immunohistochemistry (IHC) to examine cellular activation in reproductive neurocircuits (preoptic area, arcuate nucleus, and SCN), alongside histological analysis of reproductive tissues. These results underscore how feeding at biologically inappropriate times can impair reproductive function, and hence fertility.

Disclosures: M.A. Adesina: None. **W.C.J. Chung:** None. **E.M. Mintz:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

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Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Sally McDonnel Barksdale Honors College
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Title: Analyzing the neuroprotective effects of phytoestrogens and aromatase on male zebra finch cerebellum post-lesion.

Authors: *A. IROVIC[1], G. THOMPSON[2], E. MCFATRIDGE[3], R. BREAUX[3], L. B. DAY[4]; [1]Univ. of Mississippi, Waterloo, IL; [2]Univ. of Mississippi, Ocean View, NJ; [3]Univ. of Mississippi, Oxford, MS; [4]Biol., Univ. of Mississippi, UNIVERSITY, MS

Abstract: Estradiol (E2) promotes neuroplasticity and can be enzymatically derived from testosterone via aromatase (AROM) at neural injury sites. However, E2 disrupts testicular function and elevates stroke and cancer risk in women. Phytoestrogens like Genistein (GEN), plant-derived compounds with E2-like effects and higher affinity for ERβ than ERα, may offer neuroprotection without adverse effects. Using male zebra finches as a model, we compared E2 and GEN's neuroprotective effects after cerebellar injury while assessing testicular impact. The zebra finch cerebellum, a highly plastic brain region with low baseline AROM that increases post-lesion, expresses ERβ abundantly, making it ideal to isolate injury-induced and experimental AROM activity. Adult males received silastic rope implants with GEN, E2, or vehicle (CON). Twelve days later, we performed stereotaxic puncture lesions to the cerebellum

and locally injected either saline (SAL) or letrozole (LET), an AROM inhibitor. This created six treatment groups: GEN+SAL, E2+SAL, GEN+LET, E2+LET, CON+SAL, and CON+LET. Birds were weighed on implant days 0, 5, 12, and 14; testes were extracted and processed for hematoxylin/eosin. Although testes express ERα and ERβ, only E2 reduced testis mass and disrupted spermatogenesis. GEN birds did not show this effect, nor did they experience the stress-related weight loss seen in CON and E2 groups. Seventy-two hours post-lesion, birds were sacrificed; brains were cut at 30 µm on a cryostat and stained with Fluoro-Jade B (FJ) to visualize degeneration. Lesions were identified by disrupted morphology and FJ-positive cell zones. Lesion+FJ volume is being quantified using the Cavalier point-counting method with Stereologer (SRC, Tampa, FL). Currently, we have collected preliminary data of two specimen for FJ, showing their relative lesion volumes, and intend to use this data and future data to make comparative analysis to TUNEL stained samples. We expect the smallest lesions in GEN+SAL and E2+SAL, moderate in GEN+LET, E2+LET, and CON+SAL, and largest in CON+LET, where AROM upregulation is blocked. If AROM's role extends beyond E2 synthesis, CON+SAL may show lesion reduction. If GEN matches E2's neuroprotection without reproductive side effects, this will support phytoestrogens as promising therapeutic alternatives for brain injury and neurodegeneration, while also showing potential for the zebra finch model as a model for neuroscience research.

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Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

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Topic: G.02. Neuroendrocrine Processes and Behavior

Support: R01DK135212
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DOD HT94252310156

Title: Contrasting roles of PVH^{CRH} neuron neurontransmission in diet-induced obesity

Authors: *Y. CAO[1,2], Z. JIANG[2], J. CAI[2,1], Y. XU[2], L. DE LECEA[3], B. R. ARENKIEL[4], Q. TONG[2,1];
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Abstract: Stress-induced obesity has become an increasingly prevalent and realistic issue in today's society. The hypothalamic-pituitary-adrenal (HPA) axis is known to connect psychological stress to peripheral bodily responses. Chronic stress can disrupt HPA axis function, leading to increased cortisol or corticosterone (Cort) levels, promoted appetite, the preference for calorie-dense foods, and abdominal fat accumulation. Conversely, obesity itself can act as a stressor, triggering psychological distress and further activating the stress response. While this bidirectional relationship between obesity and stress is well recognized, the underlying neural mechanisms remain unclear. Corticotropin-releasing hormone (CRH)-expressing neurons in the paraventricular hypothalamus (PVH^{CRH} neurons) are critical components of the HPA axis, releasing CRH to stimulate adrenocorticotropic hormone (ACTH) secretion from the pituitary and subsequent Cort release from the adrenal cortex. PVH^{CRH} neurons are responsive to stress, but their activity can be suppressed by consuming calorie-dense foods, suggesting a role in stress-related obesity. These neurons release both CRH and glutamate. Embryonic deletion of the CRH gene in PVH^{CRH} neurons leads to adrenal gland deficits, underscoring the essential role of CRH in development, whereas the role of glutamate release from these neurons is less understood. In this study, we found that disrupting glutamate release from PVH^{CRH} neurons in adulthood reduced diet-induced obesity (DIO), whereas deleting CRH had no effect. Conversely, increasing CRH release promoted DIO, but enhancing glutamate release did not. Notably, CRH deletion in PVH^{CRH} neurons did not affect basal corticosterone levels, but it did reduce corticosterone levels under stress. These findings demonstrate the contrasting roles of CRH and glutamate release from PVH^{CRH} neurons in DIO and suggest that CRH is not required to maintain basal corticosterone levels in the absence of stress.

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Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

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Title: A complete map of peptidergic cell-cell communication in the human arcuate nucleus

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Abstract: The arcuate nucleus (AN) is situated in the mediobasal hypothalamus and comprises diverse neuronal populations, including POMC, AgRP, GHRH, TIDA, and KNDy neurons, which are integral to energy balance and the regulation of pituitary hormones. Despite their importance, the heterogeneity and molecular profiles of these neurons, particularly their neuropeptide-based cell-to-cell interactions, remain largely unexplored in humans. Advances in single-nucleus RNA sequencing (snRNA-seq) have made it possible to comprehensively examine the AN's transcriptomic landscape and offer insights into its diverse roles and intercellular communication. We performed snRNA-seq on a pooled sample of human ANs from eight healthy donors and identified 22 distinct cell clusters, including well-characterized glial and ependymal populations. Furthermore, we combined our pool of arcuate neurons with previously sequenced arcuate neurons to refine neuronal subclusters further and increase the depth of information. Subclustering of the neurons revealed 35 subpopulations with significant heterogeneity in neurotransmitter and neuropeptide expression. Analysis of differential gene expression in neuronal populations revealed the predominance of GABAergic neurons and smaller subsets of glutamatergic neurons with minimal expression of cholinergic and histaminergic markers. Analysis of ligand-receptor interactions provided further insight into intercellular communication, revealing extensive signaling networks between neuronal populations. Clustering neurons based on their inputs and outputs revealed those primarily engaged in food intake, reproductive control, and growth. Neuropeptides and their receptors exhibited distinctive expression patterns, suggesting intensive interactions between AN neurons, which we examined using a novel, comprehensive approach. This study presents a single-nucleus transcriptomic map of the human arcuate nucleus, elucidating its molecular diversity, intercellular communication, and unique subpopulations. Our findings highlight the complexity of peptidergic interactions between arcuate nucleus neurons and advance our understanding of the AN's critical role in homeostasis. They also open new avenues for exploring therapeutic targets in endocrine and metabolic disorders.

Disclosures: A. Dobolyi: None. **F. Dóra:** None.

Poster

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Topic: G.02. Neuroendrocrine Processes and Behavior

Support: T32MH093311
5R01MH059911-26

Title: Male (but not Female) Glucagon Gene Knockdown (Gcg-KD) Rats Display Increased Sucrose Intake and Preference

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Abstract: The therapeutic effects of semaglutide and other glucagon-like peptide-1 (GLP-1) receptor agonists to treat obesity are linked to the drugs' ability to reduce daily caloric intake, perhaps by shifting dietary preferences for fat, protein, sugar, and alcohol. Multi-agonist drugs that target receptors for additional peptide products of the *Gcg* gene (including glucagon, oxyntomodulin, glicentin, and GLP-2) may be even more effective in reducing daily energy intake. Interestingly, while semaglutide-treated rats lose body weight, they consume significantly more low-concentration sucrose compared to vehicle-treated rats (Cawthon et al., 2023), for reasons that remain unclear. We reported that homozygous Sprague-Dawley *Gcg*-KD rats have markedly reduced expression of *Gcg* mRNA, and a near-total KD of central and peripheral *Gcg*-derived peptides (Zheng et al., 2022). To examine whether endogenous *Gcg*-derived peptides influence sucrose intake and preference, adult male and female *Gcg*-KD and wild-type (WT) rats received 22hr access to chow, water, and six ascending concentrations of sucrose solution (0.03-1 M), with each concentration presented for two consecutive days. Average 2-day sucrose intake and preference for each sucrose concentration (vs. chow) as a source of calories was analyzed using a mixed between- and within-subjects ANOVA (sex × genotype × concentration; N = 4-6 rats per sex/genotype subgroup). Results revealed a significant main effect of sex, an interaction between genotype and sex, and a three-way interaction among genotype, sex, and concentration on sucrose intake and preference (vs. chow). Compared to WT controls, male (but not female) *Gcg*-KD rats consumed more sucrose across several concentrations and displayed higher preference for sucrose vs. chow as a caloric source. Interestingly, female *Gcg*-KD rats consumed less sucrose than WT females, an effect opposite to that in males, with no effect of genotype on female preference for sucrose vs. chow. A follow-up study revealed no main or interacting effects of genotype or sex on chocolate Ensure intake, although male *Gcg*-KD rats tended to consume more Ensure than WT rats (P=0.1). Overall, these results indicate that endogenous *Gcg*-encoded peptides contribute to limiting sucrose intake and preference for sucrose solution as a caloric source in male but not female rats.

Disclosures: I.E. Guerrero: None. **M. Bales:** None. **L.M. Rinaman:** None.

Poster

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Title: Effects of dietary and object enrichment of behavior, physiology, and morphology of zebra finch (Taeniopygia castanotis) juveniles and adults of both sexes.

Authors: *L. B. DAY[1], C. CRAIG[2], G. MORRIS[3], M. THARP[3], L. WEST[3];
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Abstract: Husbandry influences physiology and behavior of lab animals and is essential for animal welfare and data reliability. We conducted two experiments to examine: 1) how post-fledging chicken egg (Diet) supplementation, and 2) object environmental enrichment (OEE) impact baseline and reactive stress circulating corticosteroids (CORT), growth, and spatial cognition in juvenile (Juv) and adult male and female zebra finches (ZF). In the Diet study we measured male cheek patch size, which is positively related to attractiveness. In the OEE study, we measured abnormal repetitive behaviors (ARBs) and neophobia. Birds were raised in mixed sex flight cages and transferred to single-sex cages at post-fledging nutritional independence (35 days). Juvs were moved directly to treatment cages (60 x 40 x 40 cm, 5-8 birds/cage). Adults were housed in flight cages and fed a standard diet (SDiet) of seed, biweekly bread and egg, and cuttlefish prior to experiments. Juvs were parent fed. Diet birds were given the SDiet minus egg treats (NEgg) or supplemented with 4g whole boiled egg/bird (Egg) for 62 days for Juvs and 90 days for adults (1-3yo). All OEE birds were fed our SDiet and acclimated to treatment cages for 10-14 days. Our no object enrichment group (NOE) had two dowel perches. Object enrichment (OE) birds received 3 toys, a natural perch, and nest material. After Diet treatment, Diet birds were moved to flight cages for exercise and fed our SDiet 10 days prior to spatial tests. Diet and Object enrichment, as we implemented them, had modest and mixed influences on physiology and behavior, with enrichment-, sex- and age-specific effects. Egg increased body mass in Juvs and adults and in Juvs buffered against reactive stress, with females showing relatively greater benefits. Neither Diet nor Objects lowered baseline levels of CORT. Oddly, check patch size increased in Egg vs NEgg adults but not Juvs with side-specific interactions with diet in both age groups. Diet and Object birds demonstrated spatial learning. All Diet birds had lower spatial skills compared to prior studies. Oddly, Egg males had the least spatial skills, but OE improved adult female spatial skill. OE reduced ARBs in Juvs and increased exploration in Juvs and adults in novel object tests with females being more exploratory. Our study supports Object and Diet enrichment for ZF husbandry for Juvs and adults even if non-breeding protein demands are low. Ours is the first study to reveal how sex and age impact Diet and OEE effects on morphological, physiological, and behavioral tests and verifies that post-fledgling diet and “play” may positively impact body condition, attractiveness, anxiety, and cognition in Juvs and adults.

Disclosures: L.B. Day: None. **C. Craig:** None. **G. Morris:** None. **M. Tharp:** None. **L. West:** None.

Poster

PSTR130: Neuroendocrine Systems: Anatomy and Physiology II

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.17/Y10

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: University of Mississippi College of Liberal Arts
University of Mississippi Department of Biology
National Institute of General Medical Sciences of the National Institutes of Health Mississippi INBRE Institutional Development Award (IDeA) P20GM103476
Sally McBarksdale Honors College
P20GM103460 supporting the Glycoscience Imaging Core

Title: Neuroprotective effects of estradiol and a phytoestrogen and interactions with aromatase inhibition post cerebellar lesion in male zebra finches (Taeniopygia Guttata)

Authors: *G. THOMPSON, A. IROVIC, R. BREAUX, E. MCFATRIDGE, L. B. DAY;
Biol., Univ. of Mississippi, University, MS

Abstract: When brain cells are injured, secondary apoptosis occurs. Glia cell aromatase (AROM) upregulates post-injury increasing estradiol (E2) synthesis from testosterone. E2 limits apoptosis but reduces male fertility and increases breast cancer risk mainly via estrogen receptor alpha (ERα). Genistein (GEN), a phytoestrogen, may be neuroprotective without E2 negative reproductive effects or cancer risk as GEN has stronger affinity for ER beta (ERβ) than ERα. To test neuroprotective effects of systemic GEN and E2, we used adult male zebra finch (ZF) cerebellar lesions as a model due to robust neuroplasticity in other songbird brain regions and high ERβ with low constitutive AROM in the cerebellum (CB), allowing for local inhibition of E2 synthesis. We implanted subdermal silastic ropes (E2-500ug, GEN-1000ug, or silastic (CON)) 12 days prior to stereotaxic guided needle (21g) puncture lesions, accompanied by local injection of 50µg of 1% letrozole/saline (LET), an AROM inhibitor or saline (SAL). For these 6 treatments (n=7/group), E2+LET, E2+SAL, GEN+LET, GEN+S, CON+LET, and CON+SAL, birds were weighed and implant retention was checked on day 0, 5, 12 (lesion), and 14 (sacrifice). At sacrifice, testes were weighed, sliced, and stained with H&E. E2 reduced testis mass and decreased spermatozoa compared to CON and GEN. E2 and CONs reduced body mass across days 0-14, but GEN birds did not, possibly due to GEN lipogenic effects. Brains were cut at 30um, slide-mounted, and apoptotic cells labeled with Terminal Deoxynucleotidyl Transferase dUTP Nick End Labeling (TUNEL) according to protocol (Merck KGaA, Darmstadt, Germany) and methylgreen counterstain. Initial volume measurements (n=3-4/group) partially supported the hypothesis that GEN and E2 are similarly neuroprotective with lesion sizes ranging from small to large: GEN+SAL and E2+SAL < GEN+LET and E2+LET < CON+SAL < CON+LET. However, measures inconsistently conflated lesion path, characterized by absent or distorted cells, with TUNEL+ cell clusters, and could not be reproduced. Using Cavalieri point-counting in Stereologer (SRC, Tampa, FL) two individuals jointly identified regions of interests, lesion path and non-adjacent TUNEL+ cells, and independently estimated volumes. Point-counts between individuals varied by only a few points per slice, but new estimates were significantly larger than originals. Our study suggests GEN protects body mass loss and testis morphology vs. E2. If GEN provides similar or neuroprotection as E2, this establishes the importance of our

model for investigating phytoestrogens as safer alternatives to E2 for local and dietary neuroprotection and study of underlying mechanism.

Disclosures: G. Thompson: None. **A. Irovic:** None. **R. Breaux:** None. **E. McFatridge:** None. **L.B. Day:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.01/Y11

Topic: G.03. Stress and the Brain

Support: NIH Grant R35 (Neuromodulation and Robustness of Neurons and Networks)
Schiff Undergraduate Research Fellowship (Brandeis)
Provost Undergraduate Research Fellowship (Brandeis)

Title: Response of the cardiac rhythm of the crab, Cancer borealis, to long-term temperature perturbations in vivo

Authors: *G. D. YANG, K. SCHAPIRO, G. HARRIS, S. D. VAN HOOSER, E. MARDER; Biol., Brandeis Univ., Waltham, MA

Abstract: Crucial rhythmic motor patterns such as walking or breathing are driven by central pattern generators (CPGs). These must respond to climate-induced temperature changes. Humans depend on CPG-driven rhythms for critical tasks like walking or breathing, and the crab, *Cancer borealis*, is a useful model organism that could help us better understand human rhythmic motor patterns and how they respond to temperature increases. Temperature robustness of the crab, *Cancer borealis*, has been studied extensively *in vitro*, but these studies lack the neuromodulatory input of the intact animal. *In vivo* assays reveal inhibitory bouts, a little-studied phenomenon in which the crab's heart spontaneously slows or stops before recovering (Kushinsky et al., 2019). The function of these bouts is not well understood. Acclimation studies, in which the living crab is first acclimated at different temperatures, have found changes in robustness *in vitro* (Tang et al., 2012). However, this project was the first to study how the animal responds in real time during temperature acclimation.
The cardiac rhythm, a CPG-driven rhythm of the crab, was noninvasively recorded *in vivo* with photoplethysmography (PPG) at 11 °C, 15°C, and 19°C over the span of weeks. A significant difference was found in instantaneous frequency (Hz) of 100 beats before and after each temperature increase from 11-15 °C (Crab 1: 0.2599 before, 0.3041 after, $p < 0.0000$; Crab 2: 1.0074 before, 1.3415 after, $p = 5.78E-05$) and 15-19 °C (Crab 1: 0.2937 before, 0.4234 after, $p < 0.0000$; Crab 2: 0.4326 before, 0.3803 after, $p = 2.54E-02$). Qualitative results found both spontaneous and temperature-induced variations in waveform, suggesting not all such variations are direct responses to the environment. Inhibitory bouts were observed in all three conditions

and appeared to have a “reset” function in which cardiac waveform or regularity of frequency differed before and after bouts. They often occurred repeatedly over extended durations, matching previous findings (Kushinsky et al., 2019). Preliminary analysis shows cardiac and pyloric rhythms from animals with frequent inhibitory bouts and variability of waveform are robust to temperature perturbations *in vitro*.
The finding that frequency changes with temperature validates previous findings *in vivo* and *in vitro*. This project builds on previous work on the effects of temperature acclimation on neuronal systems (Tang et al., 2012), and is the first time crabs are recorded during the acclimation process. Future research will further investigate the potential “reset” function of inhibitory bouts.

Disclosures: G.D. Yang: None. **K. Schapiro:** None. **G. Harris:** None. **S.D. Van Hooser:** None. **E. Marder:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.02/Y12

Topic: G.03. Stress and the Brain

Support: Kavli Foundation

Title: Mechanisms of temperature robustness in acclimated crustacean neuronal pattern generators

Authors: *C. STEIGER, W. STEIN;
Biol. Sci., Illinois State Univ., Normal, IL

Abstract: Rapidly changing temperatures are a major challenge to neuronal function because temperature can impact the nervous system in a multitude of ways - altering ionic conductances, ion channel kinetics, and the activity of entire neuronal circuits, which can result in severe neuronal dysfunction or failure with fatal consequences. Nevertheless, some animal species possess physiological mechanisms that can mitigate the effects of acute temperature changes in the nervous system and as a result have the ability to sustain neuronal activity across a wide range of temperatures. This is particularly the case for poikilothermic species that experience rapid environmental temperature fluctuations, like natural and climate-change related weather extremes. However, whether there are mechanisms that can sustain neuronal activity during long-term temperature changes remains unknown. To study long-term temperature robustness, we use the stomatogastric nervous system in Green crabs (Carcinus maenas), a species that experiences rapid temperature fluctuations and also slow seasonal temperature changes in its natural habitat. Following the climate variability hypothesis, we hypothesized that neurons in this species show a broad temperature robustness that can vary with long-term temperature acclimation. To test this, we record the rhythmic activity of the pyloric central pattern generator in cold- and warm-acclimated green crabs (for two months) and test its robustness to temperature

perturbations. We determine the temperature ranges at which rhythmic activity persists as a measure for temperature robustness. Our data indicate that both cold- and warm-acclimated animals showed a large temperature robustness (cold-acclimated: 31.9±1.0°C, N=9; warm-acclimated: 34.3±1.0°C, N=9). However, in warm-acclimated animals, rhythmic pyloric activity was sustained at higher temperatures (up to 38.0±1.0°C, N=9), while in cold-acclimated animals it failed at lower temperatures (up to 35.1±2.1.0°C, N=9, $P<0.05$, t-test). These results suggest that long-term acclimation expands and shifts neuronal responses to better fit the new temperature conditions. Our data also indicate that the neuronal responses of animals acclimated for a shorter period (two weeks) do not change, suggesting that the mechanisms that acclimate neuronal activity act on a slow time scale (weeks to months). We are currently testing the cellular mechanisms underlying long-term temperature acclimation, with particular focus on the regulation of ionic currents and the excitability of the pyloric neurons as those have been suggested to provide temperature robustness to the pyloric circuit.

Disclosures: C. Steiger: None. **W. Stein:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.03/Y13

Topic: G.03. Stress and the Brain

Support: Kavli Foundation Exploration Award

Title: Identifying a Tachykinin-Related Peptide Receptor Mediating Temperature Robustness in Crustacean Neurons

Authors: *M. SEYMOUR, W. STEIN;
Sch. of Biol. Sci., Illinois State Univ., Normal, IL

Abstract: Hyperthermia can dramatically impair sensorimotor processing and motor control. Investigating the cellular and circuit effects of temperature changes and the long-term ramifications of acclimation to hyperthermia is thus crucial to our understanding of neuronal pathologies and associated behavioral consequences. Some poikilothermic motor circuits are endowed with an ability to maintain function across broad temperature changes. This temperature robustness is partly mediated through the release of neuromodulators, including a family of neuropeptides known as tachykinin-related peptides (TRPs). TRPs have been shown to enhance temperature robustness in crustacean neurons by increasing the excitation/inhibition ratio, yet the receptors that mediate this effect are currently unknown. Here, we identify and functionally characterize a TRP receptor in the green crab (*Carcinus maenas*), a species with well-described temperature-robust motor circuits. Bioinformatic analysis revealed a putative TRP receptor sequence with significant alignment to other known invertebrate tachykinin receptors (E-value 1e-71 to the common octopus). Using RT-PCR, we confirmed expression of

the receptor transcript in the brain and stomatogastric ganglion (a region possessing temperature-robust motor neurons). To functionally characterize this putative receptor, we are using *Xenopus laevis* oocytes, where receptor mRNAs are expressed and tested for responsiveness to a superfused synthetic crustacean TRP using two-voltage clamp electrophysiology. Our data indicate that oocytes expressing the candidate receptor exhibit a peptide-induced ionic current in response to crustacean TRP application, and that these currents increase in a concentration-dependent manner, which is consistent with functional ligand-receptor binding. These findings uncover a key molecular mechanism contributing to temperature robustness in invertebrate neural circuits and offer new insight into how nervous systems adapt to environmental temperature changes.

Disclosures: M. Seymour: None. **W. Stein:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.04/Y14

Topic: G.03. Stress and the Brain

Support: NSF Grant 2239994

Title: Sexually Dimorphic and Clock Gene-Specific Effects of Light at Night on Drosophila Behavioural Rhythms

Authors: A. PRANEVICIUS[1], G. BIONDI[2], A. R. IYER[3], A. SEIFFE[5], A. M. DEPINO[6], ***M. FERNANDEZ**[4];
[1]Barnard Col., New York City, NY; [2]Barnard Col., NYC, NY; [3]Biol., Indiana Univ., Bloomington, IN; [4]Indiana Univ., Blooomington, IN; [5]departamento de fisiología, biología molecular y celular, IFIBYNE, UBA-CONICET, CABA, Argentina; [6]Inst. For Physiology, Mol. Biol. and Ne, Buenos Aires, Argentina

Abstract: Light pollution is a major anthropogenic environmental change and a significant threat to ecosystems. Among other detrimental effects on physiology, light at night (LAN) disrupts circadian rhythms in a wide range of species. However, the underlying neuronal and genetic mechanisms remain poorly understood. Here, we show that the loss of the circadian clock gene *period (per)* exacerbates the LAN-induced shift toward nocturnal behaviour, with a more pronounced effect on males. In contrast, the loss of *cycle* has no such effect on males or females; *cyc* null mutants are nocturnal under standard light–dark cycles, and their activity and sleep profiles are not affected by LAN exposure. CRISPR-Cas9 knockout of *per* in most clock neurons resembles the *null* mutant phenotype. Our results show that mutations in components of the positive and negative limbs of the circadian clock result in distinct responses to nocturnal light and highlight the role of genetic factors in modulating behavioural plasticity in response to environmental perturbations.

Disclosures: A. Pranevicius: None. **G. Biondi:** None. **A.R. Iyer:** None. **A. Seiffe:** None. **A.M. Depino:** None. **M. Fernandez:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.05/Y15

Topic: G.03. Stress and the Brain

Title: The role of dopamine in the resilience of collective behavior to water stress

Authors: *D. YE[1], M. N. WILSON[1], J. F. KAMHI[2], A. BEYENE[3], D. GORDON[1]; [1]Stanford Univ., Stanford, CA; [2]Denison Univ., Granville, OH; [3]Janelia Res. Campus, Ashburn, VA

Abstract: Water stress is an urgent and growing problem for all organisms. Drought conditions, with high temperatures and low humidity, cause evaporative water loss leading to significant physiological costs. Our project examines how individual forager decisions about the risk of water loss allow colonies of the desert red harvester ant (*Pogonomyrmex barbatus*) to regulate collective foraging behavior. This continues a >30-year study of behavior and ecology in a population experiencing the deepening drought in the southwest US. Colonies must spend water to obtain water and food: ants lose water while foraging but gain it by metabolizing fats from collected seeds. Forager decisions integrate cues from olfactory encounters with returning foragers, a cue to food availability, and current desiccation, a cue to the risk of water loss on the next trip. Colonies differ in managing this tradeoff. Risk-averse (RA) colonies reduce foraging in dry conditions to conserve water, sacrificing food intake. Risk-tolerant (RT) colonies continue foraging despite the cost.Previous transcriptomic and pharmacological studies showed that dopamine (DA) mediates forager decisions. Higher DA is associated with increased foraging in dry conditions. To investigate neurochemical variation among colonies, we measured DA titers in forager brains from RA and RT colonies sampled on days that differed in humidity. DA was quantified using near-infrared fluorescence assays in pooled brain samples. While average DA levels did not differ overall across the two colony phenotypes, RT foragers showed elevated DA in dry conditions, whereas RA foragers maintained stable levels. This suggests RT colonies may upregulate DA to support risky foraging under desiccation stress.We mapped dopaminergic neurons (DANs) in *P. barbatus* using tyrosine hydroxylase immunolabeling and confocal microscopy. Comparative analysis reveals conserved DAN clusters, especially in mushroom bodies and the subesophageal zone, similar to PAM and SEZ neurons in *Drosophila*. We will discuss how differences between RA and RT colonies in DAN cluster architecture may underlie differences among colonies in forager decisions about the risk of water loss.

Disclosures: D. Ye: None. **M.N. Wilson:** None. **J.F. Kamhi:** None. **A. Beyene:** None. **D. Gordon:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.06/Y16

Topic: G.03. Stress and the Brain

Support: NSF MRI Grant 2407348

Title: Cortisol-mediated modulation of synaptic transmission and behavior in C. elegans

Authors: J. LARRIVEE[1], T. STOKES[1], M. KURLAND[2], *A. J. KALLARACKAL[1];
[1]Mount St. Mary's Univ., Emmitsburg, MD; [2]Columbia High Sch., Maplewood, NJ

Abstract: Glucocorticoids are known to impact a variety of cellular processes and behaviors across many different species. Hormones such as cortisol impact various physiological systems, including the nervous system, with complex effects that vary depending on timing and concentration of exposure. We used the model organism *C. elegans* to determine the impact of short and long term cortisol exposure on receptor trafficking and behavior. Additionally, we performed a candidate gene screen to identify the molecules required for cortisol action. Together, these results highlight the utility of of using *C. elegans* to understand the underlying mechanisms of cortisol-mediated signaling.

Disclosures: A.J. Kallarackal: None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.07/Z1

Topic: G.03. Stress and the Brain

Title: The impact of stress on feeding and ethanol preference in Drosophila

Authors: *M.-C. HSIAO, R. ZHU, Y.-M. WU, H.-H. LIN;
Neurosci. and Physiol., SUNY Upstate Med. Univ., Syracuse, NY

Abstract: Stress profoundly affects brain function and behavior, leading to behavioral dysregulations, including memory deficits, emotional instability, altered feeding, and increased addiction vulnerability. However, the molecular and circuit mechanisms driving these diverse outcomes remain unclear. In this study, we leveraged the genetic tractability and comprehensive circuit wiring map of *Drosophila melanogaster* to investigate how stress affects food intake and

alcohol preference. Using an array of behavioral assays—including Excreta Quantification (EX-Q), Fly Proboscis Activity Detector (Fly-PAD), and Fly Liquid-food Interaction Counter (FLIC) to measure total food intake, feeding microstructures, and alcohol preference—we found that five days of crowding stress significantly suppressed food intake. This reduction was driven by decreases in sip number and duration, feeding bout numbers, and burst number. In addition, stressed flies showed a marked increase in preference for ethanol-containing food, with longer feeding durations on ethanol-containing food. Furthermore, these stress-induced changes were reversible: upon removal of the stressor, both eating behavior and alcohol preference returned to baseline levels. These findings demonstrate that crowding stress elicits robust, reversible changes in feeding and ethanol preference, providing a foundation for dissecting the underlying neural and molecular mechanisms of stress-induced behavioral alterations.

Disclosures: M. Hsiao: None. **R. Zhu:** None. **Y. Wu:** None. **H. Lin:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.08/Z2

Topic: G.03. Stress and the Brain

Support: JST Grant JPMJSP2108
AMED-CREST JP21gm310010
JST-CREST JPMJCR22P6
ACT-X JPMJAX242D

Title: Chronic stress targets courtship command neurons to shape behavior

Authors: *Y. NISHIZUKA[1], M. TSUJI[1], K. EMOTO[1,2];
[1]The Univ. of Tokyo, Tokyo, Japan; [2]Intl. Res. Ctr. for Neurointelligence (WPI-IRCN), Tokyo, Japan

Abstract: After experiencing frequent encounters with threats over a long period of time, animals persistently adjust their behavior so that their aversive responses to future threats are promoted, while appetitive responses to rewarding stimuli are suppressed. Such behavioral adjustment to stressful environments is likely crucial for survival and yet can become maladaptive when implemented excessively. However, how long-term stress adjusts behavior, particularly how appetitive behaviors are suppressed, remains incompletely understood. We will present our recent findings regarding how long-term stress suppresses male courtship behaviors. The male courtship behavior in Drosophila is one of the best-studied behavior in terms of its circuit basis. Indeed, work over the past decades has established the courtship circuitry extending from the sensory neurons to output neurons, where a group of neurons called P1 neurons play a commanding role. By developing a novel paradigm, we have discovered that the repeated (4-day long) electric shocks suppress the time in which males engage in the courtship behavior. This

suppression was persistent, as it was observed even one week after the shock ceased. This was likely not due to impaired basic motor/visual capabilities, since, when shocked male did chase female, it showed running speed and directionality toward female comparable to those of the control flies. We further explored the circuit underpinnings of how the repeated shocks might influence the courtship behavior. Our analysis using the recently developed neural activity reporter called CRTC *(Bonheur et al., 2023)* revealed that the repeated shocks reduce activities of the courtship command P1 neurons, thus identifying the most important node of adjustment along the courtship circuitry. We further found through photoactivation experiments that P1 neurons in shocked flies tend to require stronger light intensity to elicit courtship behavior, suggesting that shock-induced reduction in P1 activities negatively impacts courtship behavior. Overall, our data suggest that the repeated electric shocks persistently reduce courtship behavior by lowering the spontaneous activity of the courtship command P1 neurons.

Disclosures: Y. Nishizuka: None. **M. Tsuji:** None. **K. Emoto:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.09/Z3

Topic: G.03. Stress and the Brain

Support: NiCE: 2425051

Title: Atmospheric pollutants negatively impact olfactory processing and behavior

Authors: *J. RIFFELL;
Univ. of Washington, Seattle, WA

Abstract: There is growing concern about sensory pollutants impacting animal behavior and sensory processing. This is particularly true for organisms that use their olfactory system to detect odor plumes, such as night-flying insects. Anthropogenic pollutants, including oxidants like ozone and nitrate radicals (O_3 and NO_3, respectively), rapidly degrade scents, potentially reducing attraction to the odors. However, the neurophysiological and behavioral impacts are unknown. Using a nocturnal flower-moth system, we find that atmospherically relevant concentrations of NO_3, and not O_3, eliminate odor source visitation by moths, and it is the reaction of NO_3 to a subset of monoterpenes that reduces the odor's attractiveness. The elimination of behavioral attraction to the degraded odor was mediated by the changes in excitatory-inhibitory balance in the primary olfactory region of the moth brain, the antennal lobe (AL). Changes in the proportion of the key monoterpenes in the odor altered the encoding and scent representation by the AL projection neurons. Atmospheric modeling studies were conducted to understand whether these impacts could alter insect sensing capabilities in other areas of the world. Global atmospheric models of odor oxidation reveal that insects in certain urban areas may have a reduced ability to perceive and navigate to odor sources. These results

illustrate the impact of anthropogenic pollutants on an animal's olfactory ability and indicate that such pollutants may be critical regulators of olfactory behaviors.

Disclosures: J. Riffell: None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.10/Z4

Topic: G.03. Stress and the Brain

Support: NSF grant 2232789
USDA grant 2020-38422-33097
NIH/NIGMS grant R16GM153659

Title: Double-edged sword effects of environmental nitrite on fish sense of smell

Authors: M. HUERTAS;
Biol., Texas State Univ., San Marcos, TX

Abstract: Fish are continuously exposed to nitrogenous compounds in the aquatic media, such as ammonia, nitrite, and nitrate. These compounds are naturally produced by the decomposition of organic matter and the excretion of nitrogen waste by animals, but they can also result from agricultural pollutants. It is well-known that nitrogenous compounds like nitrite can harm fish species at high concentrations. However, little is known about the effect of sub-lethal concentrations of environmental nitrite on fish. We hypothesize that continuous sub-lethal exposure to nitrite can subtly affect the sensory organs of fish, particularly the nose, which contains sensitive cilia projecting from its neurons into the surrounding water. To investigate this, we studied goldfish, catfish, and Xiphophorus models under chronic nitrite exposure. Our findings reveal that nitrite first accumulates in the nose and brain, with significant concentrations appearing only in the gills, gut, and muscle at almost acute levels. We also observed that nitrite exposure alters the cellular structure of the nose, leading to an increase in mucus cells and elongation of olfactory neuron cilia. Moreover, it induces changes in the nose microbiome. Surprisingly, we also found that nitrite has a" double-edged sword effect". Thus, at very low concentrations, nitrite improves olfaction and feeding behavior. However, damage appears in the olfactory epithelium at increasing nitrite concentrations, and feeding behavior declines. Since the sense of smell is critical for long-term fish survival, these findings provide valuable insights into safe levels of environmental nitrite exposure for aquatic vertebrates. Moreover, understanding the mechanisms of transport through the nose and its role in nervous function can help to understand the resilience of vertebrates in changing aquatic environments.

Disclosures: M. Huertas: None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.11/Z5

Topic: G.03. Stress and the Brain

Support: Texas Ecolabs Award
UT Austin Undergraduate Research Fellowship

Title: Resilient brains: Behavioral and physiological homeostasis in highly variable environments

Authors: P. A. WONG, A. HUSAIN, ***H. A. HOFMANN**;
Integrative Biol., The Univ. of Texas at Austin, Austin, TX

Abstract: Anthropogenic climate change increases environmental variability (e.g., prolonged droughts, more severe weather events), posing potent challenges to maintaining homeostasis, reproduction, and behavior of countless species. Yet the neural and molecular systems that enable diverse organisms to adapt to these challenges remain woefully understudied. For example, across vertebrates, the evolutionarily conserved hypothalamic preoptic area (POA) is central to organismal homeostasis and reproduction, and the hippocampus is critical for spatial behavior. How do these brain regions respond to increased environmental variability, in real time and on seasonal and decadal time scales, enabling animals to survive - and even thrive - in highly variable environments? To gain insight into the cellular and molecular plasticity mechanisms that afford neural systems resilience as they respond to ever-increasing environmental perturbations in a rapidly changing world, we take advantage of the Longear Sunfish (*Lepomis megalotis*), a colonially breeding freshwater fish commonly found from the Great Lakes region to Northern Mexico. We first used remote sensing data and data obtained from water quality monitoring stations along streams to quantify environmental variability for 20 well-established *L. megalotis* habitats along the longitudinal precipitation and latitudinal temperature gradients that characterize the diverse eco-regions of Texas. We found remarkable short- and long-term variability within and across sites. Next, we employed drone-based automated video tracking to quantify space use and reconstruct the social networks of nest-holding *L. megalotis* males and discovered that spatial and social behavior is remarkably resilient in even extreme environments. Finally, we used single nucleus RNA-sequencing of the POA/hypothalamus to reveal the neuromolecular mechanisms underlying organismal resilience across highly variable environments. We discovered that the activity numerous pathways involved in energy and temperature homeostasis as well as the stress physiology co-vary with environmental variability and behavior at different time scales. Taken together, our research integrates neurogenomics, behavior, and ecology to provide novel insights into the brain's ability to survive and thrive in changing environments.

Disclosures: P.A. Wong: None. **A. Husain:** None. **H.A. Hofmann:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.12/Z6

Topic: G.03. Stress and the Brain

Support: Allen Frontiers
NSF GRFP

Title: Mapping neural gene expression of the sea urchin, Lytechinus pictus, through development

Authors: *C. L. JENNICHES[1], A. HAMDOUN[2];
[1]Ctr. for Marine Biotech. and Biomedicine, Scripps Inst. of Oceanography, UCSD, La Jolla, CA;
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Abstract: Marine organisms exhibit dramatic diversity of nervous system organization and function. The transition of the sea urchin's neural architecture from a bilateral larva to a pentaradial juvenile deviates dramatically from that of the traditional animal models of neurobiology. Relatively little is known about the neuroethology of this unusual nervous system due to a lack of stable genetics and tools for high throughput analysis of gene expression patterns.Using a new, genetically-enabled sea urchin model, *Lytechinus pictus,* we developed a semi-automated, high-throughput imaging pipeline, and screened 68 neural genes in the embryo and early larval stages, aiming to better characterize the spatial transcriptomics of the nervous system and to define targets for development of transgenic lines. Based on patterning and strength of expression seen in this screen, as well as supplemental *in situ* data from juvenile stages, we narrowed in on five broadly neuronal genes - *synaptotagmin-1, elav-like protein 3, CUGBP elav-like family member 1, choline O-acetyltransferase-like, and GKamide* - as promoter targets and five genes that marked putative neuronal subgroups - *synaptic vesicular amine transporter-like (VMAT), tyrosine 3-monooxygenase, neuronal acetylcholine receptor subunit alpha-3-like (CHRNA3), thyrotropin releasing hormone (TRH), and SALMFamide*. The juvenile centralized nervous system consists of five symmetrical, densely bundled radial nerve cords (RNCs), united by a central nerve ring (CNR). Our results reveal internal complexities in these nerve cords, via spatial restriction of genes that represent putative neuronal subtypes. *Tyrosine-3-monooxygenase,* a putative marker for dopaminergic neurons, expresses on flanking sides of the RNCs, but does not express down the midline. *CHRNA3* was specifically expressed in the innervated, chemosensory podia. Spatially restricted expression was observed in the larval nervous system as well. *VMAT,* for example, expresses throughout the "peripheral" nervous system of the sea urchin larva, but is not expressed in the central apical ganglion.Using these data, along with a growing panel of neuronal and sensory genes, we are constructing a preliminary, but expanding map of neural gene expression in this species, presenting a more complex picture of the cell types and molecular organization of the *L. pictus* nervous system. This spatial transcriptomic data is now being used in the generation of transgenic and mutant lines that will allow for mechanistic study of sea urchin chemosensation, behavior, and vulnerability to environmental change.

Disclosures: C.L. Jenniches: None. **A. Hamdoun:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.13/Z7

Topic: G.03. Stress and the Brain

Support: Kavli Discovery Fellowship to CTGM
Allen Discovery Center for Neurobiology in Changing environments

Title: Elucidating the neurobiology of coral larvae in changing environments.

Authors: *C. GALINDO MARTINEZ[1,2], M. RANGARAJAN-PAUL[3,2], N. SWINHOE[4,2], C. KENKEL[5,2], M. TRESGUERRES[3,2];
[1]Scripps Inst. of Oceanography, Scripps Inst. of Oceanography, Univ. of California San Diego, LA JOLLA, CA; [2]Allen Discovery Ctr. for Neurobio. in Changing Environments (ADC-NiCE), La Jolla, CA; [3]Scripps Inst. of Oceanography, Univ. of California San Diego, La Jolla, CA; [4]Dept. of Embryology, Carnegie Inst. for Sci., Baltimore, MD; [5]Dept. of Biol. Sci., USC, Los Angeles, CA

Abstract: Coral reefs are hotspots for marine biodiversity that also provide nourishment, livelihoods, and coastal protection to tropical communities worldwide. Coral larval recruitment is a critical component of reef resilience to both natural and anthropogenic disturbances, as they have the potential to repopulate reefs, thus offsetting the mortality of adult coral colonies. However, very little is known about the neurological mechanisms utilized by coral larvae to sense their environment and decide where to settle and establish a new colony, or how these mechanisms are impacted by environmental variability. As part of The Allen Discovery Center for Neurobiology in Changing Environments, our project aims to characterize and explore the neural circuits that drive the chemosensing of settlement cues in coral larvae. Using immunohistochemistry (IHC), we found a high abundance of cell bodies and processes containing the neuropeptide FMRFamide in the aboral epidermis of larval *Galaxea fascicularis*. This suggests the presence of a nerve net that may play a role in detecting chemical cues, which matches previous reports of an “apical organ” in larvae from other Cnidarians. We are currently generating a neural map of *G. fascicularis and Acropora cervicornis* larvae through IHC using commercially available antibodies against other neuropeptides, as well as novel GLWamide antibodies we are developing. We are also employing Hybridization Chain Reaction Fluorescence In Situ Hybridization to visualize the expression of genes in neuronal cell types. Additionally, we aim to identify genetic markers of neural cells using single-nuclei RNA sequencing and develop GCaMP biosensors to characterize neural dynamics in live larvae in changing environments.

Disclosures: C. Galindo Martinez: None. **M. Rangarajan-Paul:** None. **N. Swinhoe:** None. **C. Kenkel:** None. **M. Tresguerres:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.14/Z8

Topic: G.03. Stress and the Brain

Support: NIGMS (R35 GM137888)
Beckman Young Investigator Award
Pew Scholar in Biomedical Sciences Award
Klingenstein-Simons Fellowship Award in Neuroscience

Title: Post-biting behavioral reprogramming underlies reproductive efficiency in Aedes aegypti mosquitoes

Authors: *L. DONG, L. B. DUVALL;
Biol. Sci., Columbia Univ., New York, NY

Abstract: The global spread and increasing populations of disease-vector mosquitoes expose hundreds of millions of people to mosquito-borne illnesses each year. Female *Aedes aegypti* mosquitoes, global vectors of dengue, require blood protein to support egg development and undergo repeated cycles of blood-feeding and egg-laying. After a blood meal, females temporarily suppress their activity and host-seeking while using blood-derived nutrients to develop eggs. Host-seeking suppression ends once eggs are successfully laid. While this period has generally been thought of as one of behavioral inactivity, we report that it instead reflects behavioral reprogramming, which transitions post-blood-meal inactivity into active searching for egg-laying sites. Females with mature eggs exhibit a distinct behavioral state characterized by increased locomotor activity and a shift in circadian behavioral timing, leading to nocturnal humidity-seeking and egg-laying in an otherwise diurnal species. We further show that the circadian clock gene *cycle* is critical for regulating this transition; its absence disrupts the timing and persistence of oviposition behavior, leading to poor site selection and reduced predicted offspring survival. These findings suggest that, during egg development, internally-driven behavioral reprogramming dependent on the circadian clock triggers nocturnal hyperactivity and oviposition site search, an essential process for mosquito reproduction and population viability. Because the choice of egg-laying site determines the fate of dozens of offspring from a single blood meal, oviposition represents an efficient target for mosquito population control.

Disclosures: L. Dong: None. **L.B. Duvall:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.15/Z9

Topic: G.03. Stress and the Brain

Support: Picower Institute

Title: Neuropeptidergic control of jellyfish behaviors

Authors: *B. GRONE[1], S. LIANG[2], B. WEISSBOURD[3];
[1]Biol., [2]MIT, Cambridge, MA; [3]MIT, Cambridge, MA.

Abstract: Neuropeptide transmission is prominent in all nervous systems, suggesting deeply conserved roles in neural function. Clytia hemisphaerica is an emerging jellyfish model for evolutionary, systems, and regenerative neuroscience. Here, we introduce Clytia as a small, transparent, genetically tractable organism and describe ongoing, foundational work focused on mapping behaviors to neural subpopulations and the neuropeptides that they produce. Our strategy is to target genetic tools for inducible ablation and calcium imaging to each neural subpopulation using regulatory genomic DNA upstream of neuropeptide precursor genes. Each subpopulation will be ablated to determine which are required for each of the major behavioral outputs (swimming, quiescence, margin folding, and crumpling). In parallel, we have tested behavioral effects of the predicted neuropeptides via bath application of synthesized peptides. Strikingly, we have identified peptides that lead to a variety of behaviors. For example, one peptide induced rapid “crumpling” behavior, which is a high-intensity defensive response. These animals then transition from crumpling to a distinct swimming state in which they fully retract their tentacles and swim rapidly. These neurons are therefore an exciting target population that may be involved in controlling or modulating aspects of defensive behaviors. Our screening has identified several additional promising peptide candidates that influence each of the major behavioral types in Clytia. This information creates a foundation for further studies of the neural control of behavior in this decentralized and radially symmetric nervous system. By applying genetically encoded tools which had not previously been used in jellyfish, we may uncover new biological mechanisms of behavior or general principles of nervous systems that are shared by cnidarian and bilaterian animals.

Disclosures: B. Grone: None. **S. Liang:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.16/Z10

Topic: G.03. Stress and the Brain

Support: The Picower Institute for Learning and Memory

Title: Jellyfish Model for Neural Regeneration

Authors: *J. O. KIMURA, B. WEISSBOURD;
Biol., MIT, Cambridge, MA

Abstract: A major goal of biomedicine is to gain the ability to regenerate damaged nervous systems. Full control of this process would revolutionize the treatment of a variety of neurological disorders and injuries. Regenerating nervous systems comes with major challenges, as nervous systems possess emergent properties not present in other tissues. Neurons make precise physical and chemical connections among themselves to generate coordinated activation patterns that execute functions. Thus, to gain high-resolution insights into neural regeneration, we must bridge across multiple levels of complexity, from the molecular mechanisms driving neural differentiation and guidance, to the systems-level activity patterns driving behavior and function. To get at these mechanisms, we are leveraging the simple neural architecture of the hydrozoan jellyfish *Clytia hemisphaerica*. *Clytia* are transparent animals that continuously scale and grow their largely 2-dimensional nervous system using stem cells that reside in specific niches. *Clytia* also come equipped with tools such as transgenesis, RNAi, and whole-animal live imaging. It was previously found that a RFamide peptide expressing (RFa+) subnetwork was responsible for the execution of food-passing behavior, and was capable of regenerating upon genetically inducible ablation. This connection of a highly regenerative neural subnetwork to a specific behavior provides a functional readout for proper neural reintegration upon injury. Here, we are studying the regenerative capacity of the *Clytia* RFa+ subnetwork to uncover principles of neural regeneration. Preliminary characterization of RFa+ subnetwork regeneration revealed elevated rates of RFa+ neuron generation compared to that of normal growth, and that neural regeneration was driven by the migration of RFa+ neurons. Dissection of the RFa+ neuron migration patterns identified different classes of RFa+ neurons based both on migration rates and morphology. We found that food-passing behavior recovered in a continuum, with animals capable of executing “partial” behaviors during network regeneration. Recording of RFa+ network activity during regeneration then showed that the neurons were capable of firing, and the statistics of activation patterns were predetermined early during regeneration. Altogether, the data shows unexpected complexity and flexibility of RFa+ neurons, as they are simultaneously capable of migrating and firing during regeneration. Future work involves generating a single cell RNAseq timecourse dataset across regeneration to identify what progenitor populations are generating this elevated level of RFa+ neuron generation.

Disclosures: J.O. Kimura: None. **B. Weissbourd:** None.

Poster

PSTR131: Environmental Stressors in Invertebrates

Location: SDCC Halls B-H

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Program #/Poster #: PSTR131.17/Z11

Topic: G.03. Stress and the Brain

Support: Whitehall Foundation
NIMH R01 MH128688
Scialog Award

Title: Neural mechanisms for maternal behavior adaptations to changes in ambient temperature

Authors: Z. ADAHMAN[1], **R. OYAMA**[2], J. S. RICEBERG[3], *I. CARCEA[4];
[1]Rutgers, The State Univ. of NJ - Newark, Newark, NJ; [2]Pharmacology, Physiol. & Neurosci., Rutgers Brain Hlth. Inst., Brooklyn, NY; [3]Neurosci., Mount Sinai & Albany Med. Col., New York, NY; [4]Rutgers, Newark, NJ

Abstract: Newborns of many mammalian species are partial poikilotherms and require adult thermoregulatory care for survival. In mice, pup survival in cold and cool ambient temperature depends on the ability of adult caregivers to huddle pups and bring them into a high-quality nest. It is therefore essential that adult mice adjust parental care as a function of changes in ambient temperature. Here, we investigated how mouse maternal care adapts to a range of temperatures, from cold to warm. We show that changes in ambient temperature affect several individual and co-parenting maternal behaviors in both dams and virgin female mice, and modulate activity of vasopressin neurons. Furthermore, we establish that the effects of ambient temperature on both maternal care and the activity of vasopressin neurons depend in part on thermosensation, specifically on the TRPM8 sensor. Using trans-synaptic anterograde tracing and whole-brain activity mapping, we find that vasopressin neurons from the paraventricular hypothalamic nucleus connect synaptically with temperature-responsive brain structures implicated in maternal care. We then show that optogenetic activation of vasopressin projections to the central amygdala, a structure activated by cold ambient temperature, recapitulates the effects of cold on co-parenting behaviors. Our data provide a biological mechanism for maternal thermoregulatory behavior in mice with translational relevance to the reported association between ecosystem temperature fluctuations and variations in human child neglect cases.

Disclosures: Z. Adahman: None. **R. Oyama:** None. **J.S. Riceberg:** None. **I. Carcea:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.01/Z12

Topic: H.01. Fear and Aversive Learning and Memory

Support: UConn InCHIP FY22 Seed Grant

Title: Cannabidiol (CBD) reduces reinstatement of fear in individuals with social anxiety

Authors: *F. L. ZAKAS[1], S. M. SKLENARIK[2], K. TREADWELL[1], R. S. ASTUR[1]; [1]Psychological Sci., Univ. of Connecticut, Storrs, CT; [2]Psychological Sci., Central Connecticut State Univ., New Britain, CT

Abstract: Anxiety disorders affect over 20% of 18-29-year-olds annually and commonly impair daily functioning. Exposure therapy, based on classical fear extinction, is a frequently utilized treatment but has high relapse rates (~50%), highlighting the need for adjunctive treatments. Cannabidiol (CBD), a non-psychoactive cannabinoid, has been shown to exert anxiolytic effects and enhance extinction in nonhumans, suggesting potential utility in augmenting extinction-based interventions. We tested whether CBD enhances fear extinction and attenuates fear reinstatement in undergraduates with social anxiety. Twenty-five participants (16 female; 9 male) underwent fear conditioning with faces paired (CS+) or unpaired (CS-) with an aversive forearm shock. Following acquisition, participants received an oral dose of 600mg CBD or placebo. After a 45-minute activation period, participants completed a single extinction session, followed by a reinstatement session. Galvanic skin response (GSR) was measured throughout. Additionally, participants were given surveys assessing anxiety, uncertainty tolerance, cannabis use, and contingency awareness. There were no significant differences in GSR during extinction. However, CBD significantly attenuated GSR reinstatement of fear relative to both acquisition and extinction ($p < 0.05$). Drilling deeper into this effect, reinstatement, by administering an unpaired shock, increased GSR responses to both the CS+ and CS-, but this GSR fear increase was much greater for the CS- compared to the CS+. CBD decreased the GSR response during reinstatement, but this decrease in response was dramatically stronger for the CS- resulting in no differential fear to the CS+ compared to the CS- following reinstatement. Hence, CBD enhances the effect of extinction and attenuates reinstatement of fear in people with high social anxiety. These results suggest that CBD given before extinction may be an effective adjunct to treat both specific and generalized anxieties. Additional analyses will be presented that examine the extent of to which differential learning, baseline anxiety levels, tolerance for uncertainty, and sex differences affect the strength of this CBD effect. Further studies will examine whether CBD acts to enhance extinction learning, attenuate generalized anxiety, or both. Moreover, future studies will examine the optimal timing of CBD administration to maximize extinction and extinction durability.

Disclosures: F.L. Zakas: None. **S.M. Sklenarik:** None. **K. Treadwell:** None. **R.S. Astur:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.02/AA1

Topic: H.01. Fear and Aversive Learning and Memory

Support: National Institutes of Health Grant RO1NS106915
VA grant BX003893
Brown Foundation G.K.611019

Title: Purkinje Cell Gq Signaling Impairs Fear Memory Reconsolidation Through Endocannabinoid Release

Authors: *G. KOGIAS;
LSU Hlth. Sci. Ctr. Cell Biol. & Anat., New Orleans, LA

Abstract: The cerebellum plays a vital role in the formation of associative fear memories. Our recent findings show that fear conditioning reduces the level of endocannabinoid 2-Arachidonoylglycerol (2-AG) in cerebellar lobules V/VI, and this is necessary for memory consolidation. Once consolidated, memories can be altered. Upon reactivation, memory becomes temporarily unstable before stabilizing again through reconsolidation, a process during which memories can be either strengthened or weakened. Cerebellar activity is crucial during this phase, as inhibiting protein synthesis in the cerebellar vermis during reconsolidation disrupts memory recall. To investigate the function of cerebellar Purkinje cell in this process, we exposed male L7::Gq(+)-DREADD (Designer Receptors Exclusively Activated by Designer Drugs) mice to fear conditioning (tone + shock), followed by memory reactivation with a tone-alone stimulus in a novel context 10 days later. Mice received J60 or saline 30 min after reactivation and fear memory retention was tested three days later. We found that the activity of cerebellar Purkinje cells regulates the reconsolidation of fear memory, as pharmacogenetic activation of GqDREADD in Purkinje cells disrupted reconsolidation, interfering with reinstatement of fear memory. These effects were observed exclusively in male L7::Gq(+)-DREADD mice and not in females. Activation of GqDREADD in Purkinje cells evoked endocannabinoid release, and we therefore determined whether this is responsible for Gq-induced memory loss. Mice treated with the endocannabinoid receptor inhibitor AM4113 (3 mg/kg) immediately after memory reactivation and 30 minutes before receiving a DREADD receptor agonist (J60) did not show reduction in freezing responses compared to controls (L7::Gq(-)-DREADD mice received saline injection before J60). In contrast, male mice expressing Gq(+)-DREADD in Purkinje cells and receiving saline and J60 showed reduced freezing responses relative to Gq(-)-DREADD. This indicates that blocking endocannabinoid signaling rescues memory deficit due to the disruption of fear memory reconsolidation mediated by Purkinje cell activation. Therefore, suppressing endocannabinoid signaling in the cerebellum is essential for fear memory reconsolidation in male mice. This highlights the importance of cerebellar activity and endocannabinoid signaling in modulating emotional memory processing.

Disclosures: G. Kogias: None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.03/AA2

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant (RO1NS106915)
VA Grant (BX003893)

Title: Stress-induced reduction in cerebellar endocannabinoid tone potentiates fear memory

Authors: *M. S. SAYED[1,3], C. J. DUBOIS[1], J. FAWCTT-PATEL[1,3], M. A. FAROOQ[2,3], J. LIU[2,3];
[1]Cell Biol. & Anat., [2]Cell Biol. and Anat., LSU Hlth. Sci. Ctr. Cell Biol. & Anat., New Orleans, LA, LA; [3]Southeast Louisiana VA Healthcare Syst., New Orleans, LA

Abstract: The cerebellum has emerged as a key player in cognition and emotion. Our lab previously showed that fear conditioning elevates the level of the enzyme monoacylglycerol lipase (MAGL), which degrades the endocannabinoid 2-arachidonoylglycerol (2-AG). This reduction in cerebellar 2-AG is required for fear memory formation. Given that stress enhances fear memory, we hypothesized that stress reduces cerebellar eCBs to promote subsequent fear memory. We found that exposing mice to predator odor stress significantly decreased levels of DAGL, the enzyme that synthesizes 2-AG, in cerebllar cortex lobule 5/6 by around 40% while leaving the activity of degradative enzyme MAGL unaltered. Consequently, electrophysiological data revealed changes in tonic eCB signaling. In naive mice, the CB1R antagonist NESS0327 increased miniature inhibitory postsynaptic current (mIPSC) frequency in cerebellar cortex lobule 5/6 Molecular Layer Interneurons (MLIs), indicating a tonic eCB signal. However, NESS0327 failed to alter mIPSC frequency in stressed mice, suggesting that stress reduced tonic eCB signal. This was not due to deficient CB1 receptor signaling, as the CB1R agonist WIN55212-2 reduced mIPSC frequency by 30% in both naive and stressed animals. At a behavioral level, we demonstrated that mice subjected to predator odor stress 3 hours before fear conditioning exhibited enhanced fear memory the next day. Critically, systemic administration of the CB1R agonist ACEA after the stress exposure prevented this enhancement. These results establish that a stress-induced decrease in cerebellar eCB signaling promotes the consolidation of subsequent fear memories. Building on these findings, we are now investigating if directly increasing cerebellar eCB signaling can prevent stress-induced memory enhancement. Our current research utilizes L7-Gq transgenic mice, which express Gq-coupled DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) specifically in cerebellar Purkinje cells. By administering the DREADD activator J60, we can selectively activate the Gq signaling pathway in these neurons. This Gq pathway activation facilitates the synthesis of 2-AG within these cells. Preliminary results suggest that this targeted, chemogenetic elevation of cerebellar 2-AG appears to counteract the effects of stress and block the potentiation of fear memory. Therefore, stress reduces 2-AG levels by impairing its synthesis, enhancing subsequent memory formation.

Disclosures: M.S. Sayed: None. **C.J. Dubois:** None. **J. Fawctt-Patel:** None. **M.A. Farooq:** None. **J. Liu:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.04/AA3

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant R15MH129932-01

Title: Sex differences in elevating endocannabinoid signaling in hippocampal-dependent fear conditioning in adolescent rats

Authors: S. SHAHI[1], S. BALLAN[1], K. MOLINA[1], P. KALAIDJIAN[2], *C. G. REICH[1];
[1]Ramapo Col. of New Jersey, Mahwah, NJ; [2]Ramapo Col., Mahwah, NJ

Abstract: Sex differences in responses to chronic stress are implicated in the higher prevalence of major depression and PTSD in females. Evidence of sex differences in endocannabinoid (eCB) physiology suggests that eCB signaling contributes to sexual disparities in fear conditioning. In the present study, we assessed the effects of increasing hippocampal eCB levels on hippocampal-dependent contextual fear conditioning (CFC) in adolescent female and male Sprague-Dawley rats. Through inhibition of MAGL, hippocampal levels of the eCB, 2-AG, were elevated either prior to acquisition or to memory recall of CFC. Female and male adolescent rats were surgically implanted with cannula targeted to the dorsal hippocampus. Following a one-week recovery period, animals were administered 0.5 µl (2 µg/ µl) JZL184, a monoacylglycerol-lipase inhibitor through the cannulas either prior to acquisition (Day 1) or memory recall (Day 2). All sample sizes were n= 8 or greater, the size needed for 80% statistical power. In males, administration of JZL184 on either day increased freezing behavior compared to vehicle injected males during memory recall (Day 2). In intact females. JLZ184 administration on either day decreased freezing during memory recall testing, however JZL184 during Day 1 produced a larger effect. Ovariectomy (OVX) significantly decreased freezing during CFC recall compared to intact females. Administration of intrahippocampal JZL184 during Day 1 in OVX females resulted in less freezing during Day 2 recall compared to vehicle-treated OVX rats. Surprisingly, JZL184 administered on Day 2 on OVX females increased freezing levels. Next, we assessed the effects of enhancing tonic levels of Anandamide (AEA) through inhibition of FAAH (URB597, 0.5 µl, 1 µg/µl). In intact and OVX females, intrahippocampal injection of URB597 prior to Day 1 learning led to a significant decrease of freezing during Day 2 recall compared to vehicle controls. However, in intact females, URB597 injection did not affect Day 2 freezing levels and led to an increase in OVX freezing levels compared to OVX vehicle controls. The findings suggest that in females both tonic 2-AG and AEA signaling modulate CFC acquisition. Only 2-AG appears to modulate CFC recall in females depending on gonadal status. Continuing studies are focused on the interaction of estrogen and eCBs. These findings have implications in the use of medical cannabinoid treatment of disorders such as PTSD, as well as recreational cannabis use in adolescent/young adult females.

Disclosures: S. Shahi: None. **S. Ballan:** None. **K. Molina:** None. **P. Kalaidjian:** None. **C.G. Reich:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.05/AA4

Topic: H.01. Fear and Aversive Learning and Memory

Support: Baylor University Graduate School

Title: Fluoxetine Reduces Hyperglycemia-Induced Facilitation of Fear Memory in Mice

Authors: *R. OOI[1], M. PINO, IV[2], S. NELSON[2], C. YEAGER[2], A. FROMMACK[2], K. LONG[2], G. HALL[3], L. E. KUSUMO[4], K. GILLEY[2], E. G. VICHAYA[5];
[1]Biol. & Chem., [2]Liberty Univ., Lynchburg, VA; [3]Texas A&M Univ., College Station, TX; [5]Psychology & Neurosci., [4]Baylor Univ., Waco, TX

Abstract: Diabetic patients are approximately twice as likely to develop affective and cognitive dysfunction. While preclinical models reliably demonstrate heightened freezing behavior in the fear conditioning test (FCT), this response is generally interpreted as enhanced memory. However, increased freezing in the hyperglycemic model may instead reflect a depressive-like phenotype, characterized by heightened sensitivity to negative stimuli. To explore this possibility and refine behavioral interpretations in preclinical models of depression, this study investigates whether treatment with the antidepressant fluoxetine (FLX) modulates freezing behavior, aiming to determine whether FCT behavior may serve as a more clinically relevant indicator of affective disturbance in this model. We hypothesized that streptozotocin (STZ)-induced hyperglycemia would increase neuroinflammation, reduce activity, and heighten freezing in the FCT. Inversely, we expected that FLX would reverse these effects, modulating freezing behaviors to control levels. This study used male C57 mice in a 2×2 factorial design, with two independent variables: hyperglycemia (STZ vs. buffer-control) and antidepressant treatment (FLX vs. saline). Behavior included Open Field (OF), Marble Burying (MB), and FCT. Hippocampal qPCR analyses assessed *Tnf* gene expression to evaluate neuroinflammation. Results showed that hyperglycemia reduced burying in the MB task ($p = .005$), with FLX treatment further reducing these scores ($p = .004$). Hyperglycemia was also associated with a significant reduction in OF exploration ($p = .004$), with no FLX impact. Results support a reduction in locomotor activity associated with hyperglycemia. As expected in the FCT, hyperglycemia exaggerated freezing behavior ($p = .030$), indicating an increased salience to aversive stimuli as this effect was significantly attenuated by FLX ($p = .046$), modulating freezing behaviors to the controls. Lastly, as hypothesized, qPCR analyses revealed that hyperglycemia increased *Tnf* expression ($p = .028$), which was not influenced by FLX, suggesting an alternate mechanism. Overall, our results suggest that increased freezing behavior observed in hyperglycemic mice reflects heightened sensitivity to negative stimuli rather than enhanced memory, as FLX treatment effectively reduced freezing to control levels. This reinterpretation challenges the cognitive-based assumptions in the FCT and highlights the need for more affectively sensitive measures in preclinical models. Future studies should refine behavioral assays for depression-related phenotypes and improve translational relevance in clinical research.

Disclosures: R. Ooi: None. **M. Pino:** None. **S. Nelson:** None. **C. Yeager:** None. **A. Frommack:** None. **K. long:** None. **G. Hall:** None. **L.E. Kusumo:** None. **K. Gilley:** None. **E.G. Vichaya:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.06/AA5

Topic: H.01. Fear and Aversive Learning and Memory

Title: The 5-HT1A receptor agonist 8-OH-DPAT impairs fear memory formation but does not affect anxiety-like behavior

Authors: P. KALITKA, S. SHONG, S. CHAPLIN, *A. ZUNIGA;
The Col. of Wooster, Wooster, OH

Abstract: Our ability to form, store, and recall memories is critical for our survival. Memories of traumatic experiences or fearful events can promote defensive behaviors that allow organisms to better cope with similar situations in the future or avoid them all together. The retrieval of these memories at inappropriate times can be maladaptive, however. Indeed, anxiety disorders and PTSD are characterized in part by the inability of patients to suppress the recall of traumatic memories, even under safe conditions. Although serotonin is most known for its role in affective disorders, expanding evidence suggests that serotonin and its receptors contribute directly and indirectly to learning and memory. The 5-HT1A receptor is of particular interest, as prior work has shown that modulation of this receptor affects contextual fear learning and anxiety-like behavior. Thus, the goal of this study was to examine the effects of a 5-HT1A receptor agonist on the formation a contextual fear memory and on anxiety-like behavior in the elevated plus maze (EPM). To test this, male and female C57BL/6J mice were used in two separate experiments. In experiment 1, mice were treated with the 5-HT1A receptor agonist 8-OH-DPAT (DPAT, 1mg/kg, I.P.) 15-min prior to contextual fear conditioning, and their behavior during the training session was monitored. In experiment 2, mice were given DPAT (1mg/kg, I.P.) 15-min prior to the being exposed to the elevated plus maze. In experiment 1, we found that activation of 5-HT1A receptors decreased freezing during the training session. Specifically, when compared to vehicle-treated animals, mice treated with DPAT froze significantly less during the inter-shock intervals and after the delivery of the last shock. In experiment 2, we found that DPAT treatment significantly decreased locomotor activity but had no effect on the percent of time spent in the open or closed arms of the EPM. Our results provide further evidence for the involvement of the serotonergic system in the formation of fearful memories and suggest that at this dose, activation of 5-HT1A receptors does not affect anxiety-like behavior. When taken together, our data suggests that the inhibitory effect that 5HT-1A agonism has on fear learning is not mediated by changes to anxiety-like behaviors. Future studies are needed to better understand the mechanisms by which these receptors affect memory processes and PTSD-related symptoms, and to assess their viability as therapeutic targets.

Disclosures: P. Kalitka: None. **S. Shong:** None. **S. Chaplin:** None. **A. Zuniga:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.07/AA6

Topic: H.01. Fear and Aversive Learning and Memory

Support: NINDS IRP

Title: Engagement of basal forebrain cholinergic neurons during social behavior

Authors: *G. WATKINS[1], D. A. TALMAGE[2], L. W. ROLE[3], A. MCCRAY[3];
[2]Section on Genet. of Neuronal Signaling, [3]Section on Circuits, Synapses, and Mol. Signaling, [1]NIH/NINDS, Bethesda, MD

Abstract: Across species, proper engagement with and the ability to distinguish between novel and familiar individuals are crucial for threat detection, mate selection, and other complex social interactions necessary for survival, and changes in both sociability and social memory have been observed across aging in mammals. The CA2 subregion of the hippocampus is necessary for the acquisition and expression of normal social behavior. The projection neurons of the medial septum and diagonal band (MS/DB) in the basal forebrain provide cholinergic inputs to the hippocampus, including the CA2 and CA3 subregions, and while cholinergic signaling has been shown to modulate a range of hippocampus-dependent functions, the contribution to social behavior is less clear. To address this, we collected data from both behavioral and immunohistochemistry experiments at different points across the lifespan of wildtype mice. We assayed social memory and social discrimination, after which we measured activation of MS/DB cholinergic and CA2/CA3 neurons by quantifying cFos expression. Additionally, we measured the density of cholinergic axonal fields in these hippocampal subregions. We found that mice who successfully perform a social discrimination task have an increased percentage of activated cholinergic neurons relative to a control population, as well increased activation in CA2, suggesting that cholinergic signaling from MS/DB neurons is important for social memory and novelty preference.

Disclosures: G. Watkins: None. **D.A. Talmage:** None. **L.W. Role:** None. **A. McCray:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.08/AA7

Topic: H.01. Fear and Aversive Learning and Memory

Support: NINDS IRP

Title: Intrinsic plasticity of basal forebrain cholinergic neurons in threat memory encoding

Authors: *F. LUO[1], G. V. WATKINS[2], L. JIANG[3], N. S. DESAI[2], D. A. TALMAGE[3], L. W. ROLE[2];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; [2]Circuits, Synapses, and Mol. Signaling Section, [3]Genet. of Neuronal Signaling Section, NINDS, Bethesda, MD

Abstract: Neurons in the basal forebrain provide major cholinergic inputs to the basolateral amygdala (BLA) and hippocampus. These projections constitute critical components of the neural circuitry underlying threat processing. Acetylcholine release in the BLA is essential for both the acquisition and recall of cued threat memories; notably, inhibition of BLA-projecting cholinergic neurons during either training or recall significantly suppresses threat responses. A subset of cholinergic neurons in the nucleus basalis and posterior substantia innominata (NBM/SIp) becomes incorporated into the threat memory engram, such that their activation is required for both the formation and retrieval of the associated memory. Moreover, these neurons become more intrinsically excitable following threat learning, suggesting that intrinsic plasticity is an important physical substrate of engram encoding. It is unclear, however, whether the changes in intrinsic excitability are as long-lasting as the memory trace. We also would like to know do other populations of basal forebrain cholinergic neurons participate in this memory. To address these questions, we examined the physiological properties of cholinergic neurons in the NBM/SIp and the medial septum/vertical diagonal band (MS/vDB) using three groups of mice. The first group served as a control and did not undergo any behavioral training. The second and third groups were subjected to cued threat training and recall. In the second group, we analyzed neurons 2.5 hours after recall; in the third group, 48 hours after recall. To identify activated cholinergic neurons, we used an activity-dependent and Cre-dependent (ADCD) viral construct in Chat-Cre x Fos-tTA/GFP mice. The ADCD method allowed us to label cholinergic neurons that were activated during training or recall. We found distinct electrophysiological differences between naïve, training-activated and recall-reactivated cholinergic neurons. Training-activated neurons began to show increased intrinsic excitability compared to naïve neurons. The most robust changes occurred in cholinergic neurons from both NBM/Sip and MS/DB activated by training and later reactivated by recall within 2.5 hours: these changes included increased maximum firing rates, reduced firing thresholds and afterhyperpolarization potentials. The intrinsic excitability started to decline 48 hours post-recall when these physiological features began to shift back towards the state observed in the naïve group. These results suggest that enhanced intrinsic excitability is part of NBM/SI cholinergic physiology shortly after the memory is formed, but not later.

Disclosures: F. Luo: None. **G.V. Watkins:** None. **L. Jiang:** None. **N.S. Desai:** None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.09/AA8

Topic: H.01. Fear and Aversive Learning and Memory

Support: This work was supported by funds from the NINDS IRP

Title: Quantitative analysis of Ca^{2+} dynamics reveals cholinergic signaling in vHipp participating in threat learning

Authors: *C. ZHONG[1], N. S. DESAI[1], D. A. TALMAGE[2], L. W. ROLE[1];
[1]Circuits, Synapses, and Mol. Signaling Section, [2]Genet. of Neuronal Signaling, NIH/NINDS, Bethesda, MD

Abstract: The cholinergic neurons of the medial septum and ventral diagonal band of Broca (MS/vDB) are implicated in learning and memory by modulating activity of the hippocampal network. Previous studies indicated the MS/vDB cholinergic inputs to ventral hippocampus (vHipp) might be involved in auditory cued threat memory. Here we combined imaging of a genetically encoded calcium indicator (GCaMP, axonGCaMP) and an ACh sensor (Red-GRABACh1.7) with transcriptional activity markers to investigate the specific roles for cholinergic regulation of vHipp mediated cue-conditioned threat learning. Mice went through a classic auditory cue-conditioned threat training and recall paradigm (tone paired to shock and then recall to tone alone). Following different aspects of this paradigm, the animal was sacrificed and we imaged cholinergic neurons within acute ex-vivo MS/vDB slices or cholinergic projections within vHipp slices. With GCaMP6f expressed specifically in cholinergic neurons in Chat-Cre mice, and a tTA-dependent activity labeling system (Robust Activity Marker, or RAM) to label neurons activated during the training session, we found: 1) an increased number of RAM-labeled cholinergic neurons after cue-conditioned threat training; 2) an increase in Ca^{2+} dynamics, measured as frequency of Ca^{2+} transients, in RAM labeled cholinergic neurons; 3) 24 hours after training, Ca^{2+} dynamics were significantly enhanced in RAM labeled cholinergic neurons following presentation of the recall tone, as compared to RAM labeled cholinergic neurons without tone recall or in mice presented with the tone without prior tone-shock pairing. With axonGCaMP6s expressed specifically in MS/vDB cholinergic axons in Chat-Cre mice, we observed spontaneous active (Ca^{2+} dynamics) cholinergic axon segments within ex vivo vHipp slices. Ongoing studies are focused on imaging the activity of cholinergic axons within the vHipp after fear training / recall. With imaging of axonGCaMP6s expressing cholinergic axons and Red-GRABACh1.7 expressing neurons within vHipp, we will also define whether these observed active cholinergic axon segments are releasing ACh. Taken together, these data are consistent with an important role for MS/vDB-vHipp cholinergic signaling participating in both the acquisition and retrieval processes in this auditory cued threat learning paradigm.

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Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.10/AA9

Topic: H.01. Fear and Aversive Learning and Memory

Title: Investigating the Interaction of CRD Nrg-1 and Acetylcholine in Threat Memory

Authors: *A. G. GEORGE, M. R. ANANTH, R. KIM, L. JIANG, L. W. ROLE, D. A. TALMAGE;
Natl. Inst. of Neurolog. Disorders and Stroke, NIH/NINDS, Bethesda, MD

Abstract: The activity of basal forebrain cholinergic neurons in the nucleus basalis/substantia innominata (NBM/SI) that project to the basolateral amygdala (BLA) is required for threat memory encoding. Cysteine rich domain-containing neregulin-1 (CRD Nrg-1) is a transmembrane bi-directional signaling protein that is important for cholinergic signaling in the BLA. Here we investigate whether reductions in CRD Nrg-1 in BLA-projecting cholinergic neurons affect the function of the NBM/SI to BLA circuit in threat memory encoding. To investigate the importance of CRD Nrg-1 to threat memory, we evaluated the performance of WT mice and mice with heterozygous disruption of CRD Nrg-1 (CRD-Het) in a cued fear conditioning task. While both groups of animals performed normally during the training session, preliminary data revealed CRD-Het mice displayed impaired responsiveness (reduced freezing) to learned threat during the recall session compared to littermate controls. We next asked whether reductions in CRD Nrg-1 affect the engagement of the NBM/SI to BLA circuit in response to threat learning. We quantified the number of activated cholinergic neurons in the NBM/SI and the number of activated neurons in the BLA. Preliminary analysis revealed there were fewer cholinergic neurons in the NBM/SI of CRD-Het mice, however the proportion of recall-activated cholinergic neurons remained the same. Ongoing studies evaluate the function of the NBM/SI to BLA circuit by monitoring the activity of cholinergic neurons and ACh release in the BLA during the cued fear conditioning assay. Our studies evaluate the role of CRD Nrg-1 in the maintenance of cholinergic circuits, and the consequences of its absence on NBM/SI to BLA circuit activity and threat memory encoding. Understanding this relationship will provide valuable insight into the formation of salient memories, and the molecular mechanisms that underlie these processes.

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Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.11/AA10

Topic: H.01. Fear and Aversive Learning and Memory

Support: NINDS IRP

Title: Reductions in CRD Neuregulin 1 Affect Basal Forebrain Cholinergic Neurons During Development

Authors: *D. A. TALMAGE;
NINDS, Bethesda, MD

Abstract: Neuregulin-1, a member of the epidermal growth factor family, is critical for neuronal differentiation, migration, and survival. Of the many Neuregulin-1 isoforms, the cysteine rich domain (CRD; a.k.a Type III) Nrg1 is unique in its potential for juxtacrine, bidirectional signaling. Previous studies from our lab have found that synapse formation and survival of spinal cord cholinergic neurons is compromised in CRD-Nrg1-/- mice. Whether reductions in CRD-Nrg1 affect the survival and/or target innervation of basal forebrain cholinergic neurons (BFCNs) in the central nervous system remains unknown. To test this, we first evaluated the density of BFCNs in young adult (2.5 mo. old) WT mice and mice with heterozygous disruption of the CRD Nrg1 gene (CRD-HT). We found fewer ChAT+ neurons in CRD-HT mice the posterior basal forebrain (NBM/SI) as compared to WT mice. When separated by sex as well as by parent-of-origin (parent from which with the CRD Nrg1 mutant allele was inherited), this deficit in the NBM/SI was strongest in CRD-HT males that inherited the allele from mutant fathers (paternally inherited CRD-HT mice, CRD-HT^{PI}). To understand the developmental trajectory of this loss of cholinergic neurons, we evaluated the number of ChAT+ neurons across the basal forebrain at 1 mo. and 6 mo. of age in male WT and CRD-HT^{PI} mice. We found accelerated ChAT+ neuron loss in CRD-HT^{PI} mice. In WT mice we found a natural age-related decrease in cholinergic neuron number from 1 to 6 months (1 mo. > 2.5 mo. > 6 mo.). At 1 mo. ChAT+ neuron numbers in CRD-HT^{PI} animals were the same as in WT, but significantly lower at 2.5 mo. There was no further decline at 6 mo. Next, we asked whether the decrease in cholinergic neuron number in CRD-HT^{PI} males impaired innervation of target regions. We found reduction in cholinergic terminal field density in the BLA of CRD-HT^{PI} mice compared to their WT littermates. Given this substantial deficit in the cholinergic circuit between the basal forebrain and the BLA, we next asked whether reductions in CRD-Nrg1 affected ACh release in the BLA or BLA-related behaviors. We used a genetically encoded ACh sensor, GRAB$_{ACh}$, to follow changes in ACh release in the BLA during a learned threat paradigm (cued fear conditioning assay) or following exposure to an innately threatening olfactory stimulus. Preliminary data reveal CRD-HT^{PI} males have less ACh release in the BLA and impaired behavioral responses to learned and innate threat. Ongoing studies are using simultaneous recording of ACh release and calcium activity in the BLA to gain additional insight into the effects of decreased CRD-Nrg1 signaling on BLA-related behaviors.

Disclosures: D.A. Talmage: None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.12/AA11

Topic: H.01. Fear and Aversive Learning and Memory

Title: Cholinergic dynamics across the medial prefrontal cortex during fear experience

Authors: *J. A. NORIEGA-PRIETO[1,2], J. P. FADOK[1,2];
[2]Psychology and Tulane Brain Inst., [1]Tulane Univ., New Orleans, LA

Abstract: Acetylcholine (ACh) plays a critical role in modulating neural circuits that govern fear learning and defensive behaviors. However, the precise dynamics of ACh release across distinct subregions of the medial prefrontal cortex (mPFC) during fear conditioning remain underexplored. Using fiber photometry with a genetically encoded ACh sensor in mice, we monitored ACh release in the prelimbic (PL), infralimbic (IL), and dorsal peduncular (DP) cortices during fear conditioning with the serial compound stimulus (SCS) paradigm. The SCS paradigm enables a dissociation of active (flight) and passive (freezing) fear responses, offering a unique framework for investigating the functional role of ACh in response selection. Our findings reveal PL exhibits heightened ACh release during SCS presentation, correlating with both passive and active fear responses. IL shows no detectable ACh response, while DP displays distinct cholinergic dynamics linked to flight behaviors, emphasizing its role in adaptive defensive strategies. Additionally, optogenetic experiments leverage these cholinergic dynamics for physiologically relevant manipulations, offering deeper insights into prefrontal cholinergic mechanisms in fear processing. These findings may inform therapeutic strategies for anxiety and trauma-related disorders.

Disclosures: J.A. Noriega-Prieto: None. **J.P. Fadok:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR132.13/AA12

Topic: H.01. Fear and Aversive Learning and Memory

Support: Korea Institute of Science and Technology Intramural Program (2E33701)
K-brain Project (RS-2023-00262880) of National Research Foundation funded by the Ministry of Science and ICT, Korea

Title: A computational modeling approach to the role of serotonin in cued fear learning and extinction

Authors: *A. BADRIPOUR[1], T. KIM[2];
[1]KIST, Seoul, Korea, Republic of; [2]Brain Sci. Inst., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: Although serotonin has long been implicated in mood and anxiety regulation, its mechanism remains insufficiently understood. Cued-fear conditioning (CFC), a well-controlled framework for examining how organisms learn to associate neutral cues with aversive outcomes, has been widely used. While several computational approaches have explored circuit dynamics involving neuromodulators such as serotonin, the specific mechanisms by which serotonin modulates threat learning and memory in CFC have yet to be fully characterized. This study aims to understand how serotonin modulates aversive learning to uncover the neurocomputational basis of fear-related behaviors. We present a computational framework that specifically investigates serotonergic modulation in CFC. Our two-phase approach combines a behavioral-level model of punishment-based reinforcement learning with a circuit-level model of amygdala-hippocampus-medial prefrontal cortex interactions. In the first phase, we simulate how serotonin influences the acquisition and extinction of cue-associated fear responses across two temporal time-scales and control learning rates and the risk discounting factor, which modulates sensitivity to aversive prediction errors and the timing of conditional fear responses. In the second phase, we incorporate circuit-level dynamics to examine how these two serotonergic temporal dynamics affect memory encoding and retrieval processes across key brain regions. This framework provides a novel account of how serotonin may bias learning and forgetting in response to discrete threats, offering insights into the neural computations underlying affective disorders such as PTSD.

Disclosures: A. Badripour: None. **T. Kim:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR132.14/AA13

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant R01NS129217

Title: Dopamine neuromodulation in the ventral hippocampus during aversive associative learning

Authors: *A. FINNERTY-HAGGERTY[1], B. J. WILTGEN[2];
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Abstract: The ventral hippocampus (vHPC) has extensive connections with regions involved in emotion processing and is necessary for the acquisition and recall of aversive memories. Recent work has also established dopamine as a critical neuromodulator for aversive learning, yet we know little about how dopamine release in the vHPC contributes to the formation of aversive memories. The current study aims to characterize the specific dopamine projections and receptor subtypes within the vHPC that underlie aversive learning and memory. This study used an

aversive memory task in mice called trace fear conditioning (TFC), which is known to depend on the vHPC. Using a genetically encoded fluorescent sensor (GRAB-DA), we show that dopamine is released into the ventral CA1 subregion during TFC. To investigate the source of this dopamine release in the vHPC, we used targeted genetic tools to lesion the two main dopaminergic projections to the vHPC, the ventral tegmental area (VTA) and the locus coeruleus (LC). We are currently monitoring dopamine release in these lesioned animals. Next, we studied the dopamine receptor subtypes involved in TFC using classic pharmacological techniques to target the activity of both D1-like and D2-like receptors in the vHPC during training. The results from the first experiment suggest that the source of dopamine to the vHPC involves the interaction between VTA and LC dopaminergic terminals. The results from the second experiment show that inhibiting D1-like receptors impairs memory, whereas inhibiting D2-like receptors enhances memory. Together, these results suggest that dopamine release in the vHPC is essential for forming aversive memories. Future work in our lab will combine calcium imaging with GRAB-DA to examine the impact of dopamine release on excitatory and inhibitory neural activity in the vHPC during TFC training. This work is significant in that altered catecholamine release in the HPC accompanies schizophrenia, bipolar disorder and ADHD, which are often comorbid with fear and anxiety disorders.

Disclosures: A. Finnerty-Haggerty: None. **B.J. Wiltgen:** None.

Poster

PSTR132: Neuromodulators in Fear Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR132.15/AA14

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant # R01NS129217

Title: Stimulus discrimination is modulated by norepinephrine and dopamine release in the dentate gyrus

Authors: *S. M. MAW;
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Abstract: The ability to form distinct episodic memories about similar events in our lives allows us to distinguish between our many day-to-day experiences. The dentate gyrus (DG), a subregion of the hippocampus, is essential for this discrimination process, performing what is often called pattern separation. Previous research indicates that the catecholamines, dopamine (DA) and norepinephrine (NE), have different effects on DG function. However, the precise timing of catecholamine release into the DG during discrimination learning and whether DA or NE plays a more important role is currently unknown. There are two main catecholaminergic projections to the DG, the ventral tegmental area (VTA) and the locus coeruleus (LC). The VTA has a sparse dopaminergic projection to the DG while a dense projection from the LC releases both NE and

DA. The current study aims to understand how these regions interact with the DG to promote stimulus discrimination during learning. Previous work from our lab has shown that the primary source of dopamine release in the dorsal CA1 subregion of the hippocampus is the LC. Therefore, in this work, I will first determine if this is also the case for the dentate gyrus. To do this, I will use a trace fear conditioning task (TFC) that depends on the dorsal hippocampus. Preliminary data indicates that mice with LC lesions show significantly less DA release in the DG, while VTA lesioned animals were not different from control mice. Next, we examined the contribution of NE and DA to pattern separation using a trace discrimination task. In this task, mice were trained to discriminate between two auditory cues of different frequencies, one that predicted shock and one that did not. We found that lesioning the DG or using chemogenetic tools to inhibit granule cell activity impaired performance on this task. Moving forward, we aim to determine the precise timing of DA and NE release into the DG during the trace discrimination task. We will correlate this data with behavior to determine if catecholamines release predicts performance during training and memory testing.

Disclosures: S.M. Maw: None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.01/AA15

Topic: H.03. Motivation

Support: NIH 068283

Title: Potentiation of striatal dopamine release after voluntary physical activity in both sexes.

Authors: *M. K. TANNER[1], A. A. HOHORST[2], J. WESTERMAN[1], E. B. OLESON[1], B. N. GREENWOOD[3];
[1]Psychology, [2]Integrative Biol., Univ. of Colorado Denver, Denver, CO; [3]Psychology, Univ. of Colorado Denver, DENVER, CO

Abstract: It is well established that regular exercise produces many beneficial effects. It is thought that exercise recruits midbrain dopamine systems, which play a role in exercise performance, motivation, and reinforcement, as well as the mental health and cognitive benefits of exercise. Long-term exercise produces both presynaptic and postsynaptic adaptations in midbrain dopamine cell body regions and their projection areas, such as the nucleus accumbens (NAc), dorsomedial striatum (DMS), and dorsolateral striatum (DLS). These adaptations are consistent with greater dopamine responses to stimuli. For example, exercise increases dopamine content, increases TH, and reduces D2 autoreceptors. Given these changes, potentiated dopamine release in striatal subregions following exercise could contribute to exercise performance and it's beneficial effects. However, whether exercise produces a hyperdopaminergic state has not been evaluated. Here, we used fast-scan cyclic voltammetry to test the hypothesis that stimulus-

evoked DA release is potentiated in the DMS, DLS and NAc of both sexes following 28 days of voluntary wheel running (VWR). Adult male and female Long-Evans rats were given either locked (Sedentary) or unlocked (VWR) running wheels for the duration of the study. After 28 days of either condition, stimulus-evoked DA release was measured in all rats. Under urethane anesthesia, rats were implanted with a carbon fiber microelectrode into the NAc, DMS or DLS, while a bipolar stimulating electrode was placed into the medial forebrain bundle. Dopamine release was evoked using electrical stimulations consisting of 24 biphasic rectangular pulses delivered at 60 Hz and recordings were taken from the NAc, DMS and DLS. In males, we found that dopamine release was potentiated in the DMS and DLS of VWR rats compared to Sedentary rats. Analysis of stimulus-evoked dopamine release in the NAc of males and in all 3 regions of females is currently ongoing. Results so far confirm the hypothesis that exercise produces a hyperdopaminergic state. These findings could have important implications for understanding the broad benefits of exercise.

Disclosures: M.K. Tanner: None. **A.A. Hohorst:** None. **J. Westerman:** None. **E.B. Oleson:** None. **B.N. Greenwood:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.02/AA16

Topic: H.03. Motivation

Support: NIH Grant R01MH125898

Title: Sex and estrous phase influence functional connectivity between brain regions during fear extinction resulting in hyperconnectivity in proestrus female rats

Authors: *C. SANCHEZ[1], A. A. HOHORST[2], J. D. WESTERMAN[1], M. K. TANNER[1], J. FREUND[1], S. OBERTO[1], B. N. GREENWOOD[3];
[2]Integrative Biol., [1]Univ. of Colorado Denver, Denver, CO; [3]Psychology, Univ. of Colorado Denver, DENVER, CO

Abstract: The inability to suppress fearful memories contributes to symptoms of trauma-related disorders such as post-traumatic stress disorder. Extinction-based exposure therapy is a common treatment for trauma-related disorders, but the efficacy of exposure therapy is limited by fear relapse phenomena including renewal (the return of fear in a different context than where fear extinction initially took place) and spontaneous recovery (the return of fear after the passage of time). Women are more susceptible than men to trauma-related disorders, but the sex differences mediating this phenomenon are understudied. Fear extinction is sex- and reproductive phase-divergent. For example, female rats exposed to fear extinction during the proestrus or estrus phases of the estrous cycle (Pro/Est, high hormones) have less relapse compared to females exposed to fear extinction in metestrus or diestrus (Met/Di, low hormones). We recently found

that activity of substantia nigra dopamine (DA) neurons during fear extinction is highest during Pro/Est, and inhibition of the substantia nigra to dorsolateral striatum (DLS) DA pathway during fear extinction restores fear relapse in females exposed to fear extinction during Pro/Est. These data implicate a role for DLS DA in estrous cycle-modulation of fear extinction and relapse. However, whether estrous cycle influences the activity of other midbrain catecholaminergic regions during fear extinction, and how estrous phase might influence the interactions between nigrostriatal and mesolimbic DA systems and canonical fear extinction circuitry is unknown. To investigate these questions, adult, male and female rats were exposed to fear extinction and the neural activation marker cFos was quantified in extinction-related brain regions. Females were grouped by estrous phase during fear extinction (Pro/Est or Met/Di). Pearson correlation coefficients were used to create correlation networks of extinction-related brain regions. Fear extinction elicited the greatest increase in cFos within ventral tegmental area DA neurons, but not noradrenergic neurons of the locus coeruleus, in females exposed to fear extinction during Pro/Est relative to Met/Di females and males. Additionally, there was greater functional connectivity between brain regions in females exposed to fear extinction in Pro/Est compared to Met/Di and males. The DLS and nucleus accumbens were identified as hubs. Results suggest that the presence of ovarian hormones during fear extinction could enhance extinction and reduce relapse by increasing functional connectivity through a mechanism involving midbrain DA.

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Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Program #/Poster #: PSTR133.03/BB1

Topic: H.03. Motivation

Support: R01MH125898

Title: Exercise modulates inescapable stress-induced cFos expression within dorsal raphe nucleus inputs

Authors: *M. A. ABDIN[1], S. M. MELLERT[1], J. D. WESTERMAN[1], J. R. FREUND[2], B. N. GREENWOOD[3];
[1]Univ. of Colorado Denver, Denver, CO; [2]Univ. of Colorado Denver, Golden, CO; [3]Psychology, Univ. of Colorado Denver, DENVER, CO

Abstract: Stress-induced anxiety and depression are highly prevalent and pose a major global health challenge. Exercise is a powerful stress resistance factor that reduces the risk of developing stress-related mental health disorders. Voluntary wheel running in rodents prevents the behavioral consequences of inescapable stress that resemble anxiety and depression. Wheel running produces these stress protective effects by constraining the activity of serotonergic

neurons in the dorsal raphe nucleus (DRN). Nevertheless, the mechanisms through which wheel running regulates the DRN response to stress remain unknown. One possibility is that wheel running modulates the activity of DRN inputs during stress, either by enhancing the inhibitory drive or diminishing the excitatory input to DRN 5HT neurons. To understand the impact of wheel running on activity of DRN inputs during stress, we injected a red fluorescent retrobead tracer into the DRN that travels retrogradely and labels DRN-projecting neurons in regions that project to the DRN. Following 3 weeks of sedentary or voluntary wheel running conditions, adult, female Sprague Dawley rats (n = 10/group) were exposed to inescapable stress. Immunohistochemistry for c-Fos was conducted to determine which DRN inputs are modified by prior wheel running. Females were selected for this study because wheel running induces rapid stress-protective effects in females. Data collection is ongoing. The results may reveal specific DRN projections that are influenced by exercise, providing insights into the mechanisms through which exercise constrain the DRN response to stress and promote stress resistance.

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Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Program #/Poster #: PSTR133.04/BB2

Topic: H.03. Motivation

Support: NIH R01MH125898

Title: The protective effects of exercise against the behavioral consequences of inescapable stress depend on the time of day that exercise occurs

Authors: *A. J. VALDEZ[1], M. K. TANNER[2], J. WESTERMAN[3], A. A. HOHORST[2], B. N. GREENWOOD[4];
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Abstract: It has been well established that exercise reduces the risk for future stress-related mental health disorders such as anxiety. Despite the powerful stress-protective effects of exercise, little is known regarding how much exercise is necessary for stress resistance, or whether the time of day at which exercise occurs influences its stress-protective effects. Rodents can be used to study features of exercise-induced stress resistance, as male and female rats allowed voluntary access to in-cage running wheels for several weeks are protected from the behavioral consequences of future inescapable stress, such as exaggerated shock-elicited fear. Prior work has given rats unlimited access to running wheels; thus, it is unknown whether restricted access to certain times of the day can also enable stress resistance. Exercise-induced stress resistance involves adaptations in central serotonergic systems, which display strong

circadian rhythms of neural activity and gene expression. This suggests that the development of stress resistance might depend on the time of day that exercise occurs. The goals of this experiment are to first determine whether restricting wheel running access to 3 hours per day can enable stress resistance, and if so, whether the time of day that exercise occurs impacts the stress protective effects. Adult, male and female, Sprague Dawley rats were randomly assigned to either sedentary or exercise groups. Rats in the exercise groups were allowed access to their wheels for either the first 3 hours or the last 3 hours of each active cycle. After 3 weeks (females) or 6 weeks (males) of daily wheel running restricted to these times, rats were left in their home cages or were exposed to inescapable tail shock stress. We found that, like unrestricted wheel running, wheel running restricted to 3 hours per day is still able to prevent stress-induced exaggerated shock-elicited fear in both sexes, but only if the wheel running occurs during the first 3 hours of the active cycle. Wheel running during the last 3 hours of the active cycle failed to produce stress-protective effects despite rats in each group running similar daily distances. These results indicate that the time of day at which exercise occurs influences the development of stress resistance, and that morning exercise may be more beneficial to mental health compared to exercise in the evening.

Disclosures: A.J. Valdez: None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.05/BB3

Topic: H.03. Motivation

Support: NIH Grant R01MH125898

Title: The role of the substantia nigra to dorsolateral striatum dopamine pathway in voluntary exercise depends on exercise history and sex

Authors: *J. FREUND[1], J. FRITZ[5], M. K. TANNER[1], N. M. BROWN[6], A. A. HOHORST[2], J. WESTERMAN[5], E. C. LOETZ[3], B. N. GREENWOOD[4];
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Abstract: While the mental and physical benefits of exercise have been well documented, two-thirds of the population fails to achieve the recommended minimum amount of physical activity. A better understanding of the neural mechanisms involved in the acquisition and maintenance of exercise behavior could lead to novel strategies to increase participation in exercise and maximize its benefits. The dorsal striatum plays a role in the formation of habits and has been implicated in the acquisition of voluntary wheel running in rodents. Interestingly, we have found that different subregions of the dorsal striatum govern wheel running in male versus female rats.

In males, the early acquisition of wheel running depends on the dorsomedial striatum (DMS), a region involved in goal-directed action, whereas the long-term maintenance of wheel running depends upon the dorsolateral striatum (DLS), a region implicated in habits. The DMS also contributes to the acquisition of wheel running in females, but females recruit the DLS to govern wheel running much more readily than do males. The preference for the DLS could explain the rapid escalation to habitual wheel running seen in females compared to males. The mechanisms driving the switch to DLS control over wheel running, and the more rapid switch to DLS control in females, are unknown. Dopamine (DA) from the substantia nigra contributes to the functions of the DLS, but the role of DLS DA in mediating the acquisition and maintenance of wheel running is unknown. This study aims to identify how inhibition of the SN-DLS DA pathway might affect the acquisition and maintenance phases of exercise in adult, male and female, Long Evans rats. An intersectional chemogenetic approach was used to inhibit the SN-DLS pathway on day 1 and day 28 of voluntary wheel running. Running data was collected (Vital View) and wheel running architecture (distance, duration, speed, bouts) were analyzed with a custom code. We hypothesize that inhibition of the SN-DLS pathway on day 1 of wheel running will reduce wheel running in females but not males, whereas inhibition of this pathway on day 28 will reduce wheel running in both sexes. If the data support this hypothesis, it highlights a novel sex-divergent role for DLS dopamine in rodent voluntary physical activity.

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Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

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Program #/Poster #: PSTR133.06/BB4

Topic: H.03. Motivation

Support: Whitehall Foundation

Title: Dopaminergic and serotonergic signaling in the nucleus accumbens to appetitive and aversive stimuli

Authors: *C. M. CORBETT[1], C. J. E. DENNING[2,3], B. P. DUNHAM[2,3], M. NIEDRINGHAUS[2,3], E. A. WEST[2,3];
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Abstract: Dopamine (DA) and serotonin (5-HT) are two neuromodulators known to play a critical role in associative learning, such as cue-outcome associations. Specifically, dopamine and serotonin signaling in limbic structures such as the nucleus accumbens (NAc) underlie the learning mechanisms linking the presentation of a reward (unconditioned stimuli; US) and the reward predictive cue preceding the reward (conditioned stimuli; CS). However, it is unknown

how dopamine and serotonin signaling in the NAc is modulated by cues that predict a mild aversive stimuli. Here, we investigated NAc dopamine and serotonin dynamics to positive and negative outcomes as well as their predictive cues. Specifically, adult male (n=4) and female Long-Evans rats (n=4) underwent surgery to inject genetically-encoded biosensors (AAV-hsyn-DIO-GRAB$_{DA}$ and AAV-hsyn-DIO-GRAB$_{5\text{-}HT}$) and an optic ferrule targeting the nucleus accumbens core. Using fiber photometry, fluorescence (deltaF/F) was recorded during a Pavlovian task (15 d, 5 d/week) where three spatially distinct cues predicted three different outcomes: one cue predicted a food reward (CS^+), a second cue predicted no outcome (CS^-), and a third cue predicted mild aversive stimuli (CS^A; flashing lights and sounds). First, animals rear more during the aversive stimuli compared to all other outcomes (reward, no outcome) and this behavior persisted throughout conditioning. Interestingly, we found an increase in serotonin signaling during the aversive stimuli on the first day of Pavlovian conditioning that persisted through the first week of conditioning. We also found an increase in both dopamine and serotonin to the food reward by the end of conditioning. These findings highlight the critical role of serotonin in cue-outcome associations to a mild aversive stimuli.

Disclosures: C.M. Corbett: None. **C.J.E. Denning:** None. **B.P. Dunham:** None. **M. Niedringhaus:** None. **E.A. West:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.07/BB5

Topic: H.03. Motivation

Support: NJ Health Foundation
R00DA042934

Title: Aging correlates with deficits in differential components of attention in transgenic Alzheimer's disease rats vs controls

Authors: S. BOZARTH[1], A. O'SHALL[1,2], C. DENNING[1,2], E. A. WEST[1,2], *M. NIEDRINGHAUS[1,2];
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Abstract: Patients with Alzheimer's disease (AD) often have impaired attention, which can be observed before classic memory deficits. Thus, we sought to determine whether there is an age-dependent increase in AD inattention. Here, 7-16-month-old transgenic rats (Tg-F344, n=9), developed to recapitulate early Alzheimer's disease pathology and wild-type littermate control rats (n=11) completed a three-choice serial reaction-time task. In this task, rats first self-initiated a trial, then, following a delay, one of three cue lights illuminated on the opposite side of the chamber. Shorter cue durations reflected an increase in attentional burden. A trial was registered as "correct" if the rat responded (nosepoke) in the illuminated cue, "incorrect" if the rat

responded in a non-illuminated cue, as an “omission” if there was no engagement with any cue within the set duration, or “impulsive” if the response occurred during the delay. Correct trials resulted in the delivery of a food pellet reward, while non-correct trials (impulsive, incorrect, or omission) resulted in a 5 s timeout indicated by house light illumination. In addition, the cue duration increased or decreased depending on the rat’s response (correct responses resulting in a decrease in cue presentation duration and incorrect responses and omissions resulted in an increase in cue presentation duration). Age correlated with deficits in incorrect trials (p=0.0457) and omissions (p=0.0123) in WT animals (but not AD), indicating a age-related decrease in engagement in the task. Age in AD animals correlated with increased final cue duration reached (p=0.0054) suggesting age-related decrease in attention. PFC catecholamine levels are critical for regulating attention and impulsivity in context of executive functioning, future directions include analyzing changes in catecholamine dynamics simultaneously to behavior.

Disclosures: S. Bozarth: None. **A. O'Shall:** None. **C. Denning:** None. **E.A. West:** None. **M. Niedringhaus:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.08/BB6

Topic: H.03. Motivation

Support: R00DA042934
Brain and Behavior Foundation

Title: Behavioral flexibility and gut microbiome as potential predictors of future oral oxycodone intake

Authors: C. M. CORBETT[1], T. GOHAR[1], A. O'SHALL[1,2], M. NIEDRINGHAUS[1,2], *E. A. WEST[1,2];
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Abstract: Oxycodone is regularly prescribed for pain in the United States despite its abuse liability. While many individuals will go no further than the prescribed use, others will become dependent on oxycodone and continue to seek out the drug. Behavioral measures used to assess goal-directed behaviors, such as contingency degradation, may be a useful tool in determining an individual’s oxycodone abuse liability prior to prescription. Additionally, another potential predictor of oral oxycodone use is the gut microbiome as previous studies have shown a critical role of the gut-brain axis in substance use and abuse. Here, we investigated behavioral and microbiome predictors of oral oxycodone intake. First, adult male (n=28) and female Long-Evans (n=37) rats underwent contingency degradation training where animals were trained to lever press for sucrose pellets and once animals reached criteria goal-directed behaviors were assessed. Following this, animals then underwent 21 days of oral oxycodone self-administration

(2 h/5 d week; 0.3 mg/ml decreased to 0.1 mg/ml). Fecal samples were collected prior to the start of oral oxycodone self-administration and during the final days of oxycodone self-administration. 16s rRNA sequencing was performed on all samples. First, we found performance on contingency degradation task correlates with future oral oxycodone intake. Importantly, animals that self-administered oral oxycodone had increased active hole responding during the last four days of self-administration when self-administration stabilized compared to water control animals. Interestingly, two phenotypes emerged during oral oxycodone self-administration where a subpopulation of animals self-administered more oral oxycodone over the course of the 21 days of self-administration (high takers) and a subpopulation of the animals self-administered oral oxycodone at levels similar to water controls (low takers). Notably, we found that 21 days of oral oxycodone self-administration depletes the gut microbiome, suggesting that oral oxycodone dysregulates the gut. Preliminary analyses are underway to determine if baseline gut microbiome levels (prior to oral oxycodone) are correlated with future oral oxycodone intake and if there is a correlation between high and low oral oxycodone phenotypes and gut microbiome levels. These findings highlight the relevance of behavioral tasks that are potentially predictive of future oral oxycodone intake and may be a translationally relevant tool in determining the potential for abuse liability of oxycodone in some patients.

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Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Program #/Poster #: PSTR133.09/BB7

Topic: H.03. Motivation

Support: R00DA042934

Title: The effects of oral oxycodone self-administration on drug-seeking behavior, affective processing, and decision making in rats

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Abstract: The opioid epidemic continues to be driven, in part, by the initial use of prescription medications, with oral administration serving as a common route of abuse. Despite the high prevalence of oral opioid misuse, most preclinical addiction models focus on intravenous (IV) drug delivery, thus limiting our understanding of how oral consumption of opioids affect brain function, motivation, and decision-making processes. Addressing the gap is essential for improving translational relevance and developing targeted interventions for individuals with opioid use disorder. Here, we investigated how oral oxycodone self-administration alters reward-related behavior in male and female rats. Long-Evans male (n=6) and female rats (n=8) were

trained to nose poke to receive either oxycodone (0.1mg/mL) or water through a liquid trough (female: 0.07mL; male: 0.1mL per delivery) on a fixed ratio 1 schedule (FR1) for 8 days and then a FR3 schedule for 10 days. Following each FR schedule block, rats were tested on a progressive ratio (PR), in which the response requirement increased exponentially after each reinforcer, to assess willingness to press. We found that the average number of active nose pokes across the final four days of self-administration positively correlated with breakpoints during the PR session. Additionally, average breakpoints for each group increased from the first PR session (following FR1) to the second (following FR3), indicating a progressive enhancement in drug-seeking behavior. Following the PR assessments, all subjects will undergo a Pavlovian conditioning task to measure how a history of oxycodone exposure modulates responses to appetitive and aversive cues and outcomes, followed by a reversal procedure to assess behavioral flexibility and decision-making. Taken together, these findings provide critical insight into the behavioral effects of oral opioid use and offer a translationally relevant model for studying opioid use disorder.

Disclosures: A.E. O'Shall: None. **C.M. Corbett:** None. **E.A. West:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.10/BB8

Topic: H.03. Motivation

Support: NJ health foundation

Title: Investigating medial prefrontal cortex norepinephrine and dopamine dynamics during an aversive and appetitive learning task

Authors: *B. P. DUNHAM[1,2], E. A. WEST[1], M. NIEDRINGHAUS[3];
[1]Rowan Univ. SOM, Stratford, NJ; [2]Sch. of translational biomedical engineering and sciences, Stratford, NJ; [3]Cell Biol. and Neurosci., Rowan Univ., Stratford, NJ

Abstract: The medial prefrontal cortex, including the prelimbic subregion (PrL) is a crucial hub for directing attention toward environmental predictors and motivationally significant cues. Additionally, the PrL regulates actions based on predicted outcomes. Here, we trained male and female wild-type Fischer 344 (WT) rats in a Pavlovian task with cues predicting positive (food), negative (bright flashing lights and music), and neutral outcomes. Before behavioral testing, the animals were injected with adeno-associated viruses (GRABNE and GRABDA) into the prelimbic cortex (PrL), which causes infected cells to express a protein that fluoresces when bound by their respective neurotransmitters norepinephrine (NE) and dopamine (DA). We then implanted an optical fiber into the PrL to measure changes in NE and DA dynamics. To measure escape behavior, we calculated the maximum velocity and the number of times the rats rear onto the sides of the chamber. Rats' max velocity increased significantly during the aversive outcome

when compared to the positive and neutral outcomes throughout conditioning. Additionally, animals reared up the sides of the cages significantly more during the aversive than during the other outcomes. Critically, animals only spent more time in the foodcup (a measure of approach behavior) to the positive predictive cue (not neutral or aversive) on the final day of conditioning. On day one of training, NE increased significantly during the aversive outcome. On the final day of training, NE was reduced during both the negative and positive outcomes. The duration of the NE reduction is related to the duration of the outcome. In the case of the reward, the reduction is short-lived as it concludes once the food pellet is eaten. In the case of the aversive, which lasts 10 seconds, the NE drop continues throughout the stimulus. DA does not respond to cues or outcomes on the first day of conditioning. On the final day of conditioning, DA increases with the reward delivery and decreases during the aversive stimulus. Ongoing studies include investigating the progression of PrL NE and DA in response to cues predicting either a positive or negative outcome in transgenic rats (TgF344-AD "AD rats") engineered to overexpress mutant human presenilin-1 and mutant amyloid precursor protein. Using AD animal models with translational relevance is essential for uncovering the neural circuits associated with behavioral deficits, given that the primary region supplying norepinephrine to the PrL (locus coeruleus) is the first area to exhibit tau tangle accumulation.

Disclosures: B.P. Dunham: None. **E.A. West:** None. **M. Niedringhaus:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Topic: H.03. Motivation

Support: NIH Grant R00DA042934
NIH Grant R21AG072355

Title: A loss of palatable reward processing in an Alzheimer's disease rat model

Authors: *B. LINNEMAN[1,2], L. A. ADRIAN[1], M. NIEDRINGHAUS[1,2], E. A. WEST[1,2];
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Abstract: Alzheimer's disease (AD) is typically characterized by the presence of neuropathological markers and cognitive decline, however, noncognitive AD symptoms, like apathy, are heavily implicated in disease severity and are often overlooked. In both AD patients and AD mouse models, dysfunction of the ventral tegmental area (VTA) and its upstream target, the nucleus accumbens (NAc) has been linked to deficits in reward processing. Using a transgenic AD rat model expressing both behavioral phenotypes and histological markers consistent with AD patients (TgF344-AD "AD rats"), we investigated motivated behavior. We first conducted a conditioned place preference (CPP) assay in which one side of a chamber was paired with Froot Loops, a palatable reward, and the other was paired with food chow (6 pairings

each, 1 pairing/day) in AD and wild-type (WT) littermate control rats of both sexes at ages 2-3 months (WT n=11, AD n=11) and 6-7 months (WT n=12, AD n=12). We found that 2-3-month old rats formed a conditioned place preference to the chamber paired with the palatable reward, but this preference was absent in 6-7-month-old AD rats. In addition, we found a decrease in consummatory behavior of the palatable reward relative to the food chow in AD rats relative to WT rats at 6-7-months but not at 2-3-months, suggesting that age-related deficits in conditioned place preference in AD rats could be due to an age-dependent decrease in the motivational value of the palatable reward. Thus, to bypass the consummatory aspect of the CPP, we conducted an additional experiment using direct NAc dopamine terminal stimulation. AD and WT rats (WT n=8, AD n=10, 6-7 month old) of both sexes underwent surgery for infusion of a Cre-expressing Tyrosine Hydroxylase (TH+) virus and a Cre inducible channelrhodopsin (ChR2) virus into the VTA, along with implantation of an optical ferrule into the NAc core or shell. Following recovery, animals began CPP with one side of a chamber paired with LED stimulation ("blue", 20 Hz, 465 nM, 10 mW), and the other paired with no stimulation (3 pairings each, 1 pairing/day). We found that at the 6-7-month timepoint, where AD animals do not form a preference to the chamber paired with the palatable reward, both WT and AD animals form a conditioned place preference to the chamber paired with the optogenetic stimulation. Together, these findings indicate an age-dependent decrease in motivation specific to a palatable food reward in AD animals that is not due to deficits in contextual learning.

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Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.12/BB10

Topic: H.03. Motivation

Support: Wake Forest Department of Psychology

Title: Injections of gastrin releasing peptide into the medial nucleus accumbens shell or the paraventricular nucleus of the hypothalamus inhibit eating in restricted rats

Authors: Y. TANG[1], E. IRVIN[2], W. ZHANG[2], A. NADEAU[2], R. COCHRAN[2], *W. E. PRATT[2];
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Abstract: Gastrin-releasing peptide (GRP) is a peptide that is released from the gut following food ingestion and has many peripheral digestive functions, such as stimulating gastrin release, regulating pancreatic secretions, and increasing gastrointestinal motility. Like other peripherally-associated feeding peptides, GRP mRNA is also expressed in neurons within the brain, and there

are receptors for the peptide distributed broadly throughout eating-related circuits, including the hypothalamus and the medial nucleus accumbens (Moody et al., 1988; Wada et al., 1990). These regions are involved in regulating food intake in response to energy deficit and the hedonic value of palatable foods. In the current experiments, we examined whether GRP injection into either the nucleus accumbens or the paraventricular nucleus of the hypothalamus would affect intake of rat chow in food-restricted rats. Two groups of male Sprague-Dawley rats were implanted with bilateral guide cannulas aimed at either the paraventricular nucleus of the hypothalamus (N = 5) or the medial nucleus accumbens shell (N = 7). Rats were then reduced to 90% ad libitum body weight and habituated to 2-hr of daily access to rat chow in experimental eating chambers. Diet intake, water intake, and locomotor measures were monitored throughout each session. Upon habituation to the diet and injection procedures, each rat received bilateral intracranial injections of 0, 100, 200, and 300 ng GRP/side in 0.5 microliters of isotonic saline directly into the paraventricular nucleus or the nucleus accumbens immediately prior to being placed into the feeding chambers across multiple experimental days. Consistent with past research examining the effects of GRP on food intake when administered systemically or into the amygdala (Fekete et al., 2002; Stein & Woods, 1982), GRP infusion into either targeted region caused a significant reduction in eating [effect of nucleus accumbens GRP: F (3,15) = 4.46, p = .02, η^2 = .47; GRP X time interaction: F (69,345) = 3.30, p = < 0.001, η^2 = .39; effect of paraventricular nucleus GRP F (3,9) = 4.62, p = .03, η^2 = .61; GRP X time interaction: F (69,207) = 2.81, p = < 0.001, η^2 = .48] without significantly impacting ambulation or rearing (all ps > .10). The anorexic effects observed here were similar to what we have previously observed following similar injections in non-restricted rats offered a sweetened fat diet. These findings suggest that GRP receptors in the nucleus accumbens and paraventricular nucleus regulate food intake in animals regardless of whether they are motivated by hunger or the palatability of foods.

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Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Program #/Poster #: PSTR133.13/BB11

Topic: H.03. Motivation

Support: Wake Forest Department of Psychology

Title: Blocking muscarinic (but not nicotinic) acetylcholine receptors of the nucleus accumbens decreases appetitive motivation without affecting motor impulsivity in rats

Authors: *W. ZHANG[1], Y. TANG[2], A. NADEAU[3], W. E. PRATT[4];
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Abstract: Motor impulsivity refers to the tendency to act without due consideration to long-term consequences. It is a key behavioral trait linked to several psychological disorders, including substance use disorders, binge eating, and pathological gambling. To investigate the neural circuits underlying impulsive action, rodent models have been developed using tasks that require action restraint to obtain a food reward. Multiple labs have shown that the nucleus accumbens plays a crucial role in regulating appetitive and consummatory motivation, as well as impulsive-like behavior. Previously, we have shown that acute stimulation of μ-opioid receptors of the nucleus accumbens increases impulsive action. Since opioid peptide expression in the striatum is known to be regulated by acetylcholine muscarinic receptors (Wang & McGinty, 1996, 1997; Pratt & Kelley, 2005), in these experiments we sought to determine if blocking nucleus accumbens acetylcholine muscarinic or nicotinic receptors would affect rats' impulsive action, as measured in a differential reinforcement of low rate responding (DRL-20) schedule. In this task, rats are required to withhold a response for 20 seconds to receive a sugar pellet on the next lever press. Following implantation with bilateral guide cannulas targeting the nucleus accumbens core, non-restricted male Sprague Dawley rats (N = 11) were tested after bilateral injections of scopolamine (1.0, 10.0 μg/0.5 μl/side), mecamylamine (1.0, 10.0 μg/0.5 μl/side), and saline vehicle. Each rat received all drug treatments in a random order across five experimental days, separated by at least 72 hours. Blockade of muscarinic receptors at 10.0 μg/side with scopolamine significantly reduced rats' lever presses, $F(4,40) = 9.91$, $p < .001$, and reinforcers earned, $F(4,40) = 15.34$, $p < .001$. However, the proportion of lever presses that earned a reinforcer was unchanged, $F(4,40) = 1.25$, $p = .30$, suggesting that acute muscarinic receptor blockade in the nucleus accumbens leads to less food-seeking behavior, but doesn't affect impulsive action. Blocking nicotinic receptors with mecamylamine was without effect. Reduced activity levels are unlikely to explain these effects; microanalyses showed that rats' latency to retrieve rewards once they were earned was not impaired, consistent with prior studies (Pratt & Kelley, 2004). Overall, these results support a role for nucleus accumbens muscarinic receptors in regulating the reinforcement value of palatable food, specifically facilitating appetitive motivation without influencing motor impulsivity.

Disclosures: W. Zhang: None. **Y. Tang:** None. **A. Nadeau:** None. **W.E. Pratt:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Program #/Poster #: PSTR133.14/BB12

Topic: H.03. Motivation

Support: Leon Levy Foundation

Title: Identification of semaglutide-responsive ensembles driving reductions in palatable food and alcohol preference

Authors: *L. ROGERSON[1], E. J. KYZAR[2], R. SETARA[3], A. RAMIREZ[4], S. VIRKAR[6], M. EISENGART[6], C. D. SALZMAN[5];
[2]Psychiatry, [1]Columbia Univ., New York, NY; [3]Columbia Univ., Bronx, NY; [4]Psychiatry, Columbia Univ., New York City, NY; [5]Zuckerman Inst., Columbia Univ., New York, NY; [6]Columbia Univ. Zuckerman Inst., New York, NY

Abstract: Semaglutide, a GLP-1 receptor agonist, has become one of the most widely prescribed and commercially successful medications with clinical efficacy for weight loss and diabetes management. However, it also produces broader behavioral effects, including changes in subjective experiences related to food and alcohol intake—suggesting mechanisms beyond its conventional role in glucose regulation and insulin secretion. These pleiotropic effects likely involve central nervous system pathways, but the relevant brain regions remain poorly defined. Using a palatable food preference paradigm in mice, we show that semaglutide robustly suppresses preference for and consumption of palatable food both acutely and chronically. We also demonstrate semaglutide's ability to significantly decrease alcohol preference and intake. To uncover the neural correlates of these effects, we applied our novel whole-brain Two Time Point with Subtraction (TTPS) pipeline, which offers improved resolution over traditional single-time-point cFos mapping. This approach allowed us to unbiasedly identify semaglutide-responsive brain regions, with the central amygdala (CeA) emerging as the top node across both acute and chronic conditions. To evaluate the functional role of these neurons, we use TRAP2 mice to selectively express excitatory DREADDs in semaglutide-responsive CeA neurons and test whether their activation is sufficient to alter palatable food and alcohol preference. Together, our findings seek to implicate a CeA ensemble as a key population in semaglutide's central mechanism of action, with implications for treating disordered reward-related behaviors.

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Poster

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Location: SDCC Halls B-H

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Program #/Poster #: PSTR133.15/BB13

Topic: H.03. Motivation

Support: NIH/NIMH R21MH129989
R01MH131053
PA CURE Grant SAP # 4100085747

Title: Sub-second Dopamine Dynamics in Mouse Prefrontal Cortex During Socially Competitive Behaviors

Authors: *A. BENSON;
Drexel Univ., Philadelphia, PA

Abstract: Previous research has shown that prefrontal dopamine (mPFC DA) is crucial for regulating rodents' socially competitive behaviors. However, DA release dynamics relative to the behavior are unknown. This leaves the outstanding question of whether DA release drives social behaviors or is a consequence of said behaviors. Answering this question is paramount to determining how PFC DA dysregulation impacts motivational disturbances seen in various psychiatric disorders such as schizophrenia, which exhibits a significant social withdrawal. We hypothesize that DA is released at the onset of socially competitive behaviors across both sex and rank in response to the behavior. To this end, we use fiber photometry with the novel DA biosensor, GRAB-DA3h, to investigate DA dynamics in the mPFC during a social dominance tube task assay. Both male and female animals were tested, and sex differences were examined. Preliminary data found that female mice were equally capable of establishing stable dominance hierarchies compared to males, and that DA signaling in the tube task features rank-specific effects in female pushing behaviors and sex-specific effects in pushing, resistance, and open-arm entry behaviors. Based on these discoveries, future studies will include fiber photometry with a dual injection of a calcium sensor on top of the novel DA sensor to determine if PFC activity drives these behaviors, and optogenetics to evaluate if PFC activity modulates DA activation. Together, these results suggest that PFC DA is released as a consequence of social behaviors and acts in a sex-specific manner. Supported by NIH/NIMH R21MH129989, R01MH131053, and PA CURE Grant SAP # 4100085747 to WJG.

Disclosures: A. Benson: None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.16/BB14

Topic: H.03. Motivation

Support: R01AA030577

Title: Bile acids regulate accumbal circuitry through TGR5 receptor activation

Authors: *S. SHARMA[1], I. ROQUE[1], J. T. YORGASON[2];
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Abstract: Bile acids (BAs), traditionally known for their role in fat emulsification within the gastrointestinal tract, can also cross the blood-brain barrier via passive diffusion or active transport, or can be synthesized locally. Their function in central neural circuits, however, remains largely unexplored. Existing studies have focused primarily on BA effects on neurocircuitry in the hypothalamus, hippocampus, and prefrontal cortex. In situ hybridization studies reveal TGR5 BA receptor mRNA expression in the striatum, suggesting a possible role for BAs in modulating reward circuitry. This study addresses a critical gap in understanding how liver-derived BAs influence the mesolimbic dopamine (DA) system, particularly through their

effects on cholinergic interneuron (CIN) activity and DA release in the nucleus accumbens (NAc). Using fast-scan cyclic voltammetry (FSCV) to measure DA release and cell-attached patch-clamp recordings to assess CIN firing, we exposed mouse NAc slices to the BAs cholic and deoxycholic acid (combined and in equal amounts). We observed that low BA concentrations (1-10 μM) increased CIN firing and DA release, whereas higher concentrations (100 μM-10 mM) suppressed both CIN firing and DA release. The low concentration effects were mediated through TGR5 receptors, as application of the TGR5 antagonist SBI-115 blocked the excitatory, but not inhibitory, responses. These findings highlight a dose-dependent, TGR5-dependent modulation of reward circuitry by BAs. Future experiments will test if chronic ethanol alters BA related electrophysiological responses. Overall, our results identify a novel gut-liver-brain signaling axis, offering new insights into the peripheral regulation of reward processing.

Disclosures: S. Sharma: None. **I. Roque:** None. **J.T. Yorgason:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.17/BB15

Topic: H.03. Motivation

Title: Intracerebral and intranasal oxytocin administration produce context-dependent effects on maternal motivation in C57BL/6J mice

Authors: I. JACOBER, H. ADAMS, J. KITTRELL, C. WELLS, T. MCALMOND, *T. D. ROGERS;
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Abstract: Decreased social interaction and altered social communication are core symptoms of autism spectrum disorder (ASD). Oxytocin (OT) is a proposed treatment for social symptoms in ASD. However, clinical trial results are variable, suggesting context-dependent effects of OT. Our previous research has demonstrated that OT administered to adult mice interacting with peers increases social interaction when required effort to socially engage is low but decreases interaction when required effort is high. These findings demonstrate that OT differentially affects rates of sociability (low effort interaction) and social motivation (high effort interaction) providing one potential source of context-related variance. To expand our research, we aim to determine the effects of OT on low-effort and high-effort maternal behaviors. To examine a low-effort context, we implanted guide cannulas into the paraventricular nucleus (PVN) of virgin female C57BL/6J mice. Virgins were administered cannula infusions of either OT or phosphate buffered saline (PBS), and their interactions with a dam and pups were recorded. The virgin mice administered intra-PVN OT retrieved pups displaced from the nest more often as compared to PBS controls. These findings support previous research showing that OT administration increases maternal behaviors in low-effort contexts. To examine the effects of intranasal OT in a high-effort context, we used the ladder task, a novel social motivation measure recently

developed in our lab. We placed a C57BL/6J dam and either her PND1 litter (to test maternal retrieval) or another dam's PND1 litter (to compare allomaternal retrieval) at the base of the chamber and placed one pup from each litter at the top of the ladder, requiring the dam to climb for retrieval. This was repeated across five trials, separately for each litter type, with the ladder steepness increasing across trials. While no differences were found in maternal retrieval times, intranasal OT significantly increased latencies for allomaternal retrieval relative to saline. These results are consistent with our previous findings and suggest that OT increases sociability and decreases social motivation in a variety of social interaction types including adult peer-to-peer and maternal social interactions.

Disclosures: I. Jacober: None. **H. Adams:** None. **J. Kittrell:** None. **C. Wells:** None. **T. McAlmond:** None. **T.D. Rogers:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

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Program #/Poster #: PSTR133.18/CC1

Topic: H.03. Motivation

Support: NIH R01MH131858 (SAW)
Whitehall Foundation Research Grant 2022-12-059 (SAW)

Title: Effort drives reorganization of brain wide prefrontal network activity during spatial decision making

Authors: *A. SÁNCHEZ-FUENTES[1], L. A. DENARDO[2], S. WILKE[3];
[1]Dept. of Psychiatry and Biobehavioral Sci., [2]Physiol., [3]UCLA, Los Angeles, CA

Abstract: Effort-based decision making (EBD) requires integrating cost-benefit information and is thought to depend on anterior cingulate cortex (ACC) regulation of effort-related brain networks. However, the specific ACC neuronal populations and circuits engaged during EBD, and how effort costs modulate their activity, remain poorly understood. To address this, we developed a fully automated T-maze task in which mice choose whether to surmount an effortful obstacle for High Reward (HR) or take a direct path for a Low Reward (LR). Both effort cost and reward magnitude can be dynamically varied, enabling novel task designs and improving on hand-operated assays, which are low throughput and more prone to experimenter influence. We then combined this platform with activity-dependent labeling approaches to examine the ACC and brain wide neural correlates of EBD. First, we used a standard task design, but with probabilistic rewards, alongside tissue clearing, cFos immunohistochemistry, and light-sheet microscopy to map whole brain activity patterns under no-effort and effort conditions. Introducing an effort cost selectively increased activity in deep layers of ACC, without affecting neighboring prefrontal regions. In contrast, several downstream targets of ACC projections - including the ventral tegmental area, periaqueductal gray, and agranular insula - showed reduced

activity during effortful decision making. In a separate experiment, we used TRAP2-based genetic labeling combined with cFos staining to identify ACC neurons active under no-effort and effort conditions. To promote deliberative choices, HR and LR sides were switched pseudorandomly for each session. Surprisingly, effort did not recruit distinct ACC ensembles. Instead, overlapping populations may flexibly reorganize their activity, modifying downstream network engagement to support decisions involving effort. These results provide new insights into the distributed circuits underlying cost-benefit decision making.

Disclosures: A. Sánchez-Fuentes: None. **L.A. DeNardo:** None. **S. Wilke:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.19/CC2

Topic: H.03. Motivation

Support: Undergraduate Research Experience and Creative Activity Grant

Title: The effect of intranasal oxytocin on paternal motivation and aggression in C57/Bl/6J mice

Authors: *S. A. BARNETT[1], C. WELLS[2], K. EVANS[3], J. KITTRELL[2], T. D. ROGERS[1]; [1]Psychology, [2]Middle Tennessee State Univ., Murfreesboro, TN; [3]Middle Tennessee State university, Smyrna, TN

Abstract: While oxytocin (OT) is well-described for its role in maternal behaviors, oxytocin's role in paternal behaviors is less well investigated. Previous research in our lab has suggested that oxytocin increases maternal social behaviors requiring low-effort to access the social stimulus (i.e. - pups) but decreases maternal social behaviors that require high-effort. The aim of the current study is to test the effects of intranasal OT on paternal motivation and male aggression. Intranasal OT (12ug/12ul) was administered chronically for 14 consecutive days to C57BL/6J sires that were four to five months of age, that had successfully bred one to two litters, and that had been paired and housed with a dam for at least one month before the study began. On day 14, the pup exposure test and the weighted door task were used to evaluate paternal behaviors, and the aggression test and the resident intruder test were used to evaluate aggressive behaviors. During the pup exposure test, three unfamiliar pups are placed in an arena with the subject sire for 20 minutes. This exposure to the same pups is repeated for six days. On day eight, the sire is exposed to three novel pups in the same arena. Time spent investigating the familiar and novel pups is measured across each day as a measure of paternal caretaking behaviors. During the weighted door task, the sire's litter and the nest is placed on the opposite side of a one-way weighted door. The sire must push open the door to access the pups, and additional weight is added to the door across five consecutive trials providing a measure of paternal motivation. Preliminary data from these tests suggests that paternal care-taking behaviors are increased following chronic intranasal administration of OT. During the resident

intruder task, the sire was isolated in the home cage by removing the dam and the litter. An unfamiliar male was then placed in the home cage, and territorial aggressive behaviors were recorded. During the aggression task, each sire was placed in an open field arena, and, in separate trials, an unfamiliar male and unfamiliar female was placed in the arena. Interactions between the sire and either the male or female were recorded, and aggressive behaviors of the sire were measured. Preliminary data suggests that OT increases the amount of sniffing and investigation towards male and female stimulus mice but decreases aggressive behaviors. The current findings may provide needed insights into the oxytocin's role in paternal behaviors in mice.

Disclosures: S.A. Barnett: None. **C. Wells:** None. **K. Evans:** None. **J. Kittrell:** None. **T.D. Rogers:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.20/CC3

Topic: H.03. Motivation

Title: Hippocampus-ventral tegmental area structural connectivity patterns are associated with dopamine gene expression patterns in the human brain

Authors: *B. L. ELLIOTT[1], V. P. MURTY[2];
[1]Psychology and Neurosci., Temple Univ., Philadelphia, PA; [2]Psychology, Univ. of Oregon, Eugene, OR

Abstract: A dopaminergic projection from the ventral tegmental area (VTA) to the anterior hippocampus is essential for adaptive behavior, supporting functions such as novelty detection, learning, and motivational salience. While this dopaminergic circuit has been characterized in animal models, structural and molecular properties of this circuit along the human hippocampal long-axis remain unknown. Here, we examined whether spatial patterns of dopaminergic gene expression in the human hippocampus are associated with structural connectivity to the VTA. We used open-access mRNA gene expression data from the Allen Human Brain Atlas to assess expression of genes involved in dopamine transport (SLC6A3 [DAT]), storage (SLC18A2 [VMAT2]), synthesis (TH), and degradation (COMT, MAOA) along the human hippocampal long-axis. These expression profiles were then related to hippocampus-VTA structural connectivity derived from diffusion MRI tractography in a large adult sample (N = 628, Human Connectome Project). HPC-VTA connectivity was strongest with the anterior hippocampus and showed significant positive correlations with COMT, TH, and SLC6A3 expression in both hemispheres. In contrast, SLC18A2 showed a negative association, and MAOA was positively associated with right, but not left, VTA-HPC connectivity. These findings provide evidence that group-level patterns of mesolimbic structural connectivity align with spatial gradients of

dopamine-related gene expression, offering insight into the molecular organization of hippocampal-VTA pathways in the human brain.

Disclosures: B.L. Elliott: None. **V.P. Murty:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.21/CC4

Topic: H.03. Motivation

Support: NS123424-01

Title: Investigation of the Effect of Effort on Dopamine Ramping in the Nucleus Accumbens During Goal-Directed Behavior

Authors: *G. M. WINTER[1], C. BOYLE[1], K. CHINNARAJ[2], A. HAMILTON[3], S. L. COWEN[4];
[2]Physiol., [3]Chem. and Biochem., [4]Dept. of Psychology, [1]Univ. of Arizona, Tucson, AZ

Abstract: Clarifying how effort influences dopaminergic release is essential for understanding motor control, motivation, and value-driven processing, with implications for the study of depression, Parkinson's disease, and Alzheimer's disease. Dopamine release in the nucleus accumbens (NAc) responds to reward prediction errors, risk, and motivational value. Prolonged NAc dopamine release also exhibits ramping responses as animals approach a goal (Howe et al., 2013), suggesting that dopamine can represent proximity to rewards or the discounted value of distant rewards. While NAc dopamine release does not appear to be modulated by anticipated effort and effort-associated costs (Walton and Bouret, 2019), release is modulated by ongoing physical exertion. Ongoing effort could impact dopamine ramping in at least two ways. First, it could simply enhance ramping (e.g., shifting the baseline or slope upward). Alternatively, it could act to decrease the perceived value of the current state and therefore reduce the ramping response. Methods: Two male Sprague-Dawley rats were trained to traverse a linear track with blocks of trails performed under flat (Low Effort) and angled (10 degrees, High Effort) configurations. Liquid food reward (50% diluted Ensure) was dispensed upon reaching either end of the track, and the amount of reward was held constant in all conditions. Dopamine release was recorded via fiber photometry using the GRAB-DA3m sensor with virus injections targeting NAc (2 injections, AP: -1.5, ML: 1.7, DV: -7 mm and AP: -1.5, ML: 1.7, DV -5 mm). The photometry probe was implanted above the injection site (AP: -1.5, ML: -1.7, DV: -6.4mm to -7.4mm). Results: Comparison of dopamine release between the high and low effort conditions failed to identify a ramping response or an effect of effort. These data are quite preliminary, and it is conceivable that the angle of the track was not sufficient to induce notable physical exertion. While these results indicate that, at least under these specific experimental conditions, the level

of ongoing physical exertion did not modulate NAc dopamine ramping, further data collection is ongoing.

Disclosures: G.M. Winter: None. **C. Boyle:** None. **K. Chinnaraj:** None. **A. Hamilton:** None. **S.L. Cowen:** None.

Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

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Program #/Poster #: PSTR133.22/CC5

Topic: H.03. Motivation

Support: PAPIIT IN300122 (UNAM, Mexico)

Title: Administration of the dopamine D2 auto-receptor agonist quinpirole in the nucleus accumbens decreases the effects of the nicotinic acetylcholine receptor agonist cytisine on oral ethanol self-administration in rats

Authors: *J. C. JIMÉNEZ[1], R. RUÍZ GARCÍA[2], A. BARRIENTOS-NORIEGA[3], F. MIRANDA-HERRERA[4];
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Abstract: INTRODUCTION: The mesocorticolimbic dopamine (DA) system plays a crucial role in mediating the reinforcing and addictive effects of ethanol (EtOH). Other neurotransmitter systems, such as acetylcholine (Ach), modulate DAergic function in the nucleus accumbens (nAcc). Ach is released from cholinergic interneurons in the nAcc and binds to nicotinic and muscarinic Ach receptors to exert its effects. Our previous studies indicated that the intra-accumbal administration of the nicotinic Ach receptor agonist cytisine enhances oral self-administration of EtOH. Additionally, dopamine D2 auto-receptors, which are found in the DAergic nerve endings in the nAcc, inhibit the regulation of DA release into the nAcc. These auto-receptors may influence the effects of cytisine on oral EtOH self-administration. This study aims to evaluate the impact of intra-accumbal administration of the DA D2 receptor agonist quinpirole (QUIN) on cytisine's effects on oral EtOH self-administration. METHOD: Male Wistar rats were water-deprived for 23.30 hours and then trained to lever-press for water reinforcement on a fixed ratio 1 (FR1) schedule for three days. Following this, the rats were trained to lever-press for EtOH on an FR1 schedule for three days. After completing the training, the reinforcement contingency was changed to a fixed ratio 3 (FR3) schedule for EtOH access. The rats then received intra-accumbal injections of cytisine (0.0, 0.8, 1.6, 3.2 μg) or combinations of QUIN (0.0, 1.0, 2.0 μg) with cytisine (3.2 μg), or the DA D2 receptor antagonist sulpiride (0.0, 1.0, 2.0 μg) with QUIN (2.0 μg) and cytisine (3.2 μg). For each dose tested, cannulae were implanted in the nAcc shell (AP +2.0 mm of Bregma, ML ± 0.8 mm, DV -4.5

mm). RESULTS: The data indicated that intra-accumbal injections of cytisine significantly increased operant oral EtOH self-administration, while QUIN reduced the oral self-administration of EtOH induced by cytisine. Furthermore, the effects of QUIN were diminished with the administration of SULP. These findings suggest that the DA D2 auto-receptor agonist modulates the increases in oral EtOH self-administration caused by cytisine.

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Poster

PSTR133: Circuit Regulation of Motivation and Reward-Driven Behavior

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.23/CC6

Topic: H.03. Motivation

Title: Distinct roles for mesolimbic dopamine in learning and task engagement

Authors: *L. T. CODDINGTON[1], S. GONG[2], J. T. DUDMAN[3];
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Abstract: Dopamine has long been implicated in two putatively distinct components of appetitive behavior: learning and motivation. These two components also interact; for example, in the absence of sufficient motivation an agent may not gain sufficient experience for reinforcement learning. We describe this particular aspect of motivation as engagement in a task. In animal studies it is generally assumed that motivation is 'clamped' to a sufficient level via prior restriction of access to a resource (e.g. water) that can then be obtained as a reward for task performance. Periods of disengagement are appreciated to undermine performance in trained animals, yet it is not clear whether or how engagement determines acquisition learning in animals. Here, we studied naive mice learning to perform a hidden target navigation task. A navigation task is particularly germane because it allows one to estimate engagement from behavior via detailed analysis of trajectories. We observed a nearly ten-fold spread in the number of trials animals required to fully acquire the task (learning efficiency). By developing robust analysis that separates engagement from inferred learning updates we find that the probability of (dis)engagement was a primary determinant of learning efficiency across animals. Measurement and manipulation of mesolimbic dopamine signals at reward demonstrated that while very brief phasic signals modulated learning efficiency independent of engagement; however, larger sustained dopaminergic reward signals dramatically improved learning efficiency by modulating learning and eliminating periods of disengagement. These results highlight and provide mechanistic insight into a well known point of emphasis in the human education literature - engagement is a critical determinant of learning.

Disclosures: L.T. Coddington: None. **S. Gong:** None. **J.T. Dudman:** None.

Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR134.01/CC7

Topic: H.01. Fear and Aversive Learning and Memory

Support: DoD/ARO W911NF-23-1-0145
Brain and Behavior Research Foundation
NIH/NIMH Grant 5R01MH106617

Title: Tensor component analysis reveals internal state changes

Authors: *J. STEINHAUSER[1], K. SHULER[3], E. PAPALEXAKIS[2], E. KORZUS[4];
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Abstract: Understanding how to investigate and quantify the necessary neuronal networks underlying cognition and behavior is paramount to advancing the fields of neuroscience and psychology. Numerous data mining techniques have been widely applied to various neuroscience datasets, primarily non-invasive fMRI data. However, few data mining techniques have been applied to neuronal circuit-level resolution analysis to determine the modulatory dynamics necessary to produce specific and appropriate behavioral outputs. To address this, we utilized Tensor Component Analysis, an unsupervised data mining technique to reduce the data from high dimensionality to low dimensionality and discover latent variables, or components, within the data. The data is neuronal activity recorded from calcium imaging within the medial prefrontal cortex in mice. The mice underwent fear conditioning, followed by a fear discrimination learning (FDL) paradigm, in which they learned to distinguish between a safe and a threatening environment. We decomposed the tensor into three low-dimensional factors that, when combined, reconstruct the original tensor. To determine the number of components that best model the data, we used a heuristic called “Core Consistency Diagnostic” (CORCONDIA), which runs a specified number of iterations for various components to find the model that optimally represents the data's complexity without overfitting. CORCONDIA determined that three components best fit the calcium imaging data. These three components represented three unique epochs within the behavioral paradigm: neurons that were highly engaged when exposed to all environments during habituation, before fear conditioning; neurons highly engaged during FDL and exposed to the safe or the threatening environments; and neurons that were highly engaged during fear discrimination learning paradigm when exposed to a familiar neutral environment. Overall, tensor component analysis revealed groups of neurons that similarly engage during distinct time periods and/or unique environments of the behavioral paradigm.

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Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

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Program #/Poster #: PSTR134.02/CC8

Topic: H.01. Fear and Aversive Learning and Memory

Support: T32 GM135028
K99/R00 MH122228

Title: Development of an ethologically relevant rodent model of social stress

Authors: *B. FITZGERALD[1], K. A. CUMMINGS[2];
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Neurobio., Univ. Alabama at Birmingham, Birmingham, AL

Abstract: Posttraumatic stress disorder (PTSD) is a neuropsychiatric disorder that develops in ~7% of the population following exposure to highly stressful events. Most of these cases are socially derived, involving child neglect, domestic violence, sexual abuse, etc. Common symptoms of PTSD include high levels of persistent fear and the inability to suppress (e.g., extinguish) this fear. Currently, the most effective treatment is exposure therapy, which is only effective in 50% of patients. This underscores the need to more comprehensively understand these neural circuits in order to develop better treatment strategies for PTSD patients. Rodents are a great model to study fear and stress due to their numerous circuit parallels with humans. Recent evidence suggests that inhibitory GABAergic neurons are centrally involved in orchestrating fear memory encoding within the rodent medial prefrontal cortex (mPFC). In line with this role, GABAergic dysfunction is common in humans PTSD patients and in rodent models for PTSD, but the mechanisms of this dysfunction are unknown. Current rodent models for PTSD utilize components such as foot shocks or other artificial forced aversive stimuli. While these stimuli could produce stress-related phenotypes, they are not ethologically relevant and are thus difficult to translate to natural rodent behaviors. Here, we developed an ethologically-relevant rodent model for social stress in male and female mice. This paradigm harnesses three different socially-related stimuli including social defeat stress, predator odor exposure, and social housing instability. By using this model in combination with a subthreshold fear conditioning paradigm, we revealed that stress-exposed mice exhibit exaggerated fear responses and inability to extinguish fear as compared to sham control mice.Using this paradigm, we are now identifying the GABAergic mechanisms underlying following social stress-induced pathological fear memory. We are characterizing the alterations in GABAergic microcircuitry and plasticity within the rodent mPFC that allows for the persistent promotion of fear and fear extinction deficits following trauma using *in vivo*chemogenetics, fiber photometry recordings, and brain slice electrophysiology. Our results will reveal the GABAergic mechanisms underlying stress-potentiated fear in both male and female mice.

Disclosures: B. Fitzgerald: None. **K.A. Cummings:** None.

Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR134.03/CC9

Topic: H.01. Fear and Aversive Learning and Memory

Title: Investigating PFC representations in contextual fear discrimination using VR technology

Authors: *M. DEVINE[1], P. PIANTADOSI[1], A. HOLMES[2];
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Abstract: Contextual fear conditioning (CFC) can be used to measure an animal's ability to link environmental stimuli with an aversive experience, providing a model of post-traumatic stress disorder (PTSD). Although the neurobiological basis of PTSD is poorly understood, previous studies suggest that the prefrontal cortex (PFC) is important. While useful, traditional CFC paradigms have important limitations. They require the physical transfer of animals between contexts across multiple days, which prevents the continuous measurement of neuronal activity across the distinct contexts. Additionally, PTSD can be triggered by instantaneous transitions from an innocuous context to one that triggers aversion, e.g., an individual with PTSD linked to battlefield trauma may be walking in an innocuous environment before an unexpected firecracker explosion induces a fear state. Such rapid context transitions are not captured by traditional CFC paradigms. Here, we implemented a virtual reality (VR) CFC paradigm to address these limitations. Mice were placed in a cylindrical apparatus lined with LEDs that could be nearly instantaneously changed from one context to another. Mice were able to discriminate on a moment-by-moment basis between an aversive context (paired with footshock) and a neutral context (no footshocks). To demonstrate the necessity of PFC to fear discrimination, we chemogenetically inhibited PFC neurons during a discrimination session where contexts transitioned from aversive to safe. Chemogenetic inhibition of PFC resulted in elevated fear, as compared to controls. Finally, we recorded the activity of PFC neurons using 1-photon microendoscopic imaging, demonstrating that neurons are sensitive to aversive stimuli and provide contextual information.

Disclosures: M. Devine: None. **P. Piantadosi:** None. **A. Holmes:** None.

Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

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Program #/Poster #: PSTR134.04/CC10

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant MH113053
NIH Grant MH117791

Title: Prelimbic cortex firing dynamics during probabilistic fear discrimination

Authors: *M. MOADDAB, M. A. MCDANNALD;
Boston Col., Chestnut Hill, MA

Abstract: Adaptive behavior requires animals to form accurate threat predictions and use these predictions to initiate appropriate fear responses. The prelimbic cortex (PL) has been implicated in both aspects of adaptive behavior. The PL is central to threat predictions that permit differentiating threatening and neutral stimuli. Simultaneously, PL activity has been shown to track defensive behaviors such as freezing. Here, we devised a procedure to more decisively determine PL firing reflecting threat prediction and defensive behavior tracking. Long Evans rats (n = 17, 7 females) were implanted unilaterally with drivable microelectrode bundles dorsal to the PL. Following recovery, we recorded PL activity while rats underwent fear discrimination consisting of three 10-s auditory cues, predicting unique foot shock probabilities: danger ($p = 1$), uncertainty ($p = 0.25$), and safety ($p = 0$). Each session consisted of 24 trials: three danger trials, three uncertainty shock trials, nine uncertainty omission trials, and nine safety trials with an average inter-trial interval of 3.5 min. The schedule for rewarded nose poking was completely independent of cue presentation and foot shock. Fear was measured in two ways. First, conditioned suppression ratios were calculated as a general indicator of fear discrimination. Second, comprehensive ethograms spanning 10^+ behaviors (including freezing, rearing, stretching, flight, and jumping) were constructed around cue presentations in high temporal resolution, 200-ms intervals. We recorded 531 neurons over 206 fear discrimination sessions. Rats showed complete discrimination during sessions from which PL neurons were recorded. Conditioned suppression ratios were highest to danger, intermediate to uncertainty, and low to safety. Initial visualization of PL single-unit firing showed a mixture of cue-excited and cue-inhibited neurons, showing the greatest firing to danger, intermediate to uncertainty, and lowest to safety. Single-unit patterns were echoed across all 531 neurons, as principal component analysis for the cue period revealed complete differential cue firing to the defining low dimensional feature. A complete analysis of PL firing with respect to threat prediction and defensive behavior during discriminative sessions will be presented.

Disclosures: M. Moaddab: None. **M.A. McDannald:** None.

Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR134.05/CC11

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH R01MH123260-01
NSF 1924732

Title: Encoding of auditory threat valence in population-level prelimbic cortex neural activity

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Abstract: Anxiety disorders like post-traumatic stress disorder, involve impaired discrimination between threat and safety cues, resulting in fear overgeneralization. Since these disorders persist long after trauma, it is essential to understand the initial encoding, but more importantly, the long-term cortical consolidation of emotional memories. Emotional memories are initially encoded in the amygdala and later consolidated in neocortical regions, yet the characteristics of the cells that support remote memory remain unclear. Here, we investigated the role of primary auditory cortex (A1), prelimbic cortex (PL), and the connectivity between these regions in auditory fear discrimination across recent and remote time points. Mice underwent auditory fear conditioning using a tone paired with footshock (CS+) and an unpaired tone (CS−). Retrieval was tested at 1, 15, and 30 days post-conditioning using CS+, CS−, and two novel intermediate tones. Chemogenetic inhibition of A1 on day 1 disrupted discrimination, and this impairment persisted across remote time points, suggesting that early A1 activity is necessary for proper cortical memory consolidation. In contrast, A1 inhibition on day 15 caused only transient deficits, indicating that A1 is no longer required once cortical consolidation has occurred. Because fear expression depends on the prelimbic cortex (PL), we examined whether A1 projects to this region to modulate expression of sound-evoked memories. We identified an excitatory A1→PL projection terminating in layer 1 of PL. To assess its functional role, we used intersectional optogenetics to selectively silence this pathway. Inhibiting A1→PL projections impaired auditory discrimination at all retrieval time points, indicating that A1 input is necessary for specific PL-dependent fear expression. Calcium imaging of excitatory PL neurons during conditioning and retrieval revealed a population code that tracked sound valence and mirrored behavioral responses. Longitudinal tracking of sound responder neurons revealed dynamic ensemble activity among the majority of PL neurons; however, a subset of PL neurons remained consistently active across time. The subset of consistently active cells recapitulated the population's discrimination profile, whereas transiently active neurons did not. These results suggest that the stable subpopulation carries the gist of the emotional memory across time. These findings show that stable PL ensembles encode the emotional significance of auditory cues and that these representations are shaped by A1 input, providing insight into the cortical mechanisms underlying remote fear memory.

Disclosures: P.M. Ogallar: None. **M.E. Normandin:** None. **M.R. Lopez:** None. **I.A. Muzzio:** None.

Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

Location: SDCC Halls B-H

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Program #/Poster #: PSTR134.06/CC12

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant MH117791

Title: Probability-dependent scaling of fear responding requires the periaqueductal gray

Authors: *L. H. COUNSMAN[1], G. VALVO[1], A. M. DUBOIS[1], J. BOYCE[1], S. SHEN[1], A. C. FITZPATRICK[1], M. DAVID[1], M. A. MCDANNALD[2];
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Abstract: Real-world threats typically involve uncertainty. A fear response that scales to a probabilistic threat is adaptive; under-responding or over-responding is detrimental. In widely accepted accounts of the brain's fear circuitry, the periaqueductal gray functions to organize fear responding. Yet, our laboratory has shown that periaqueductal gray threat cue firing reflects threat probability, rather than fear responding. The present experiment was designed to reveal roles for the periaqueductal gray in acquiring, and scaling fear responding to probabilistic threats. Subjects (40 Long-Evans rats; 20 females) were divided into two surgical conditions. Control rats received 4, 0.5 µl infusions of a 40/60 mixture of AAV2-eSyn-EGFP-T2A-iCre-WPRE + Saline at: (AP −7.10 mm, ML ± 1.42 mm and AP −8.00 mm, ML ± 1.60 mm. Caspase-3 deletion rats received 4, 0.5 µl infusions of a 50/50 mixture of AAV2-eSyn-EGFP-T2A-iCre-WPRE + AAV-flex-taCasp3-TEVp at the same coordinates. This approach meant that Caspase-3 rats would have PAG neurons deleted along the majority of the anterior-posterior axis. Subjects in each surgical condition were further divided into two behavioral groups. All rats were shaped to nose poke for a food reward and nose poke was always available during behavioral testing. Half of the rats in each surgical condition received auditory discrimination consisting of a threat cue that predicted foot shock (0.5 mA, 0.5 s) on 30% of trials and a neutral cue that never predicted foot shock. The remaining rats received identical treatment, only the threat cue predicted shock on 10% of trials. Initial results show that caspase-3 deletions of the periaqueductal gray protected against shock-induced decreases in baseline nose poking, and reduced overall cued nose poke suppression. Ethogram analysis of extinction responding shows probability-dependent scaling of fear responding in controls (Control 30% > Control 10%), which is abolished in Caspase-3 rats (Casp3 30% = Casp3 10% = Control 10%). Complete analyses and results will be presented.

Disclosures: L.H. Counsman: None. **G. Valvo:** None. **A.M. DuBois:** None. **J. Boyce:** None. **S. Shen:** None. **A.C. Fitzpatrick:** None. **M. David:** None. **M.A. McDannald:** None.

Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

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Program #/Poster #: PSTR134.07/CC13

Topic: H.01. Fear and Aversive Learning and Memory

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NIDA DA052317
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NIDA DA060662
NIDA DA060930
NIDA DA061606
NIDA DA058450

Title: Accumbal dopamine integrates information about salient stimuli and actions to promote learning in dynamic environments

Authors: *S. CAJIGAS GABRIEL[1], S. DUNKIN[2,3], M. Z. LEONARD[4], D. GOMEZ[3], H. ELAM[4], S. EMERSON[3], M. CHEVEE[3], E. S. CALIPARI[4];
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Abstract: Cue-outcome associations are formed based on an animal's — often incomplete — understanding of relationships between cues, actions, and outcomes. Through their actions, animals acquire new information about these relationships, allowing them to update how predictive cues influence behavior. This process is particularly relevant in stress-related disorders, where inaccurate interpretations can lead to learned helplessness (behavior characterized by a failure to avoid aversive stimuli, even when escape is possible). Here, we investigated the dopamine release patterns that developed over avoidance learning and determined how neural signals differentiate animals that learn to avoid footshocks versus those that do not. The optical dopamine sensor dLight was used to monitor dopamine responses via fiber photometry in the nucleus accumbens core to a range of task parameters over time. Sample sizes ranged from 21 to 7 mice, depending on the experiment, and included both males and females. We show that dopamine release in the nucleus accumbens core enables dynamic updating of cue-outcome associations by differentially signaling the salience of outcomes, depending on whether they are encountered passively or as a consequence of an animal's actions. In a negative reinforcement task, dopamine responses to a trial termination cue predicted future avoidance learning, but only when the trial termination cue followed an operant response. This effect was not attributable to dopamine signaling reward or safety, and this dopamine signal guided the updating of future behavior across a range of conditions and via optogenetic manipulation. These findings identify a dopamine-driven mechanism for updating cue-outcome associations based on agency, revealing how learning is shaped by control over outcomes.

Disclosures: S. Cajigas Gabriel: None. **S. Dunkin:** None. **M.Z. Leonard:** None. **D. Gomez:** None. **H. Elam:** None. **S. Emerson:** None. **M. Chevee:** None. **E.S. Calipari:** None.

Poster

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR134.08/CC14

Topic: H.01. Fear and Aversive Learning and Memory

Support: NF 19-537

Title: Dopaminergic modulation of astrocytes in the anterior cingulate cortex gates innate fear induced avoidance learning.

Authors: *B. LEONARDON, L. JONKER, M. A. ACUNA, J. HUANG, N. NEVIAN, T. NEVIAN;
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Abstract: Innate-fear-driven learning is an ethologically vital mechanism that enables prey animals to recognize and avoid dangerous environments. Although key pathways for innate-fear processing in the limbic system have become increasingly known, the precise cellular sites and mechanisms by which these stimuli are converted into long-term avoidance memories remain unclear. The anterior cingulate cortex (ACC) is a central hub for emotional processing and is innervated by dopaminergic projections signaling aversive states from the ventral tegmental area (VTA).
We hypothesize that dopaminergic modulation in the ACC gates synaptic plasticity, thereby transforming innate-fear cues into avoidance memories.
We employ a novel one-day conditioned-place avoidance paradigm using the predator odor trimethylthiazoline (TMT) to study ACC function in aversive memory formation. We demonstrate that both the ACC and dopaminergic inputs from the VTA are required for conditioned avoidance learning. At the network and cellular levels, dopaminergic activation of astrocytes in the ACC emerges as a critical “gate” for learning: astrocyte-mediated calcium signaling promotes the induction of spike-timing-dependent long-term potentiation (tLTP) at afferent synapses onto layer 5 pyramidal neurons. Selective blockade of astrocytic calcium transients abolishes both tLTP and conditioned avoidance behavior.
By placing astrocytes at the intersection of neuromodulatory and glutamatergic pathways, our results uncover a glial “checkpoint” essential for synaptic potentiation and innate-fear learning in the ACC. Targeting this astrocyte-mediated gate may therefore offer novel strategies to modulate maladaptive fear responses in stress-related disorders.

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Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

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Program #/Poster #: PSTR134.09/CC15

Topic: H.01. Fear and Aversive Learning and Memory

Support: the Korea Medical Device Development Fund grant RS-2023-00253560
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the Korea Health Technology R&D Project Grant RS-2024-00443893
the National Research Foundation of Korea(NRF) grant RS-2025-00555096

Title: Neural mechanisms driving low-frequency ultrasound-induced avoidance behaviors in mice

Authors: *E. JO[1], D. AHN[1,2], J. XING[1], G. NAN[1,3], H. KIM[1], B. LU[1], U. KIM[1], Y. OH[1], M. GRACA SANTOS[1], N. KANG[1], H. KIM[1,3];
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Abstract: Avoidance behavior is crucial for survival and linked to fear, anxiety, and psychiatric disorders. Rodents emit low-frequency ultrasonic vocalizations (USVs) in the 22-28 kHz ranges as signals of negative emotional states, such as distress and fear; exposure to these USVs, in turn, elicits avoidance behaviors. Central amygdala (CeA), inferior colliculus (IC) and periaqueductal gray (PAG) are related to aversive emotional behaviors and connected from auditory cortex (ACx). Identifying ultrasound (US) frequencies to trigger avoidance, along with the neural circuits can provide a valuable framework for investigating the processing of negative emotional states. Thus, the present study investigated which US frequencies elicit avoidance behaviors in mice and examined the associated neural circuits.
The frequency ranges of US inducing flight behavior were explored using a modified place aversion test. Changes of electroencephalography (EEG) following US exposure was analyzed in anesthetized mice. Mice showed aversive behaviors upon 20~24 kHz of low-frequency ultrasound. In particular, 23 kHz US induced a pronounced avoidance response. On EEG analysis, a sudden increase of gamma wave was observed during exposure to the low-frequency US while the US induced minimal changes of theta and delta waves compared to the basal values before treatment.
The results suggest that low-frequencies US evokes alert-like states characterized by increased gamma wave activity and induces aversive behaviors in mice. It may be associated with CeA, IC and PAG, which remains to be elucidated.
This work was supported by the Korea Medical Device Development Fund grant, the National Research Foundation of Korea(NRF) Grants and the National Research Foundation of Korea(NRF) grant, funded by the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) RS-2023-00253560, RS-2023-00262398 and RS-2025-00555096. Also this research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea RS-2024-00443893

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Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

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Program #/Poster #: PSTR134.10/DD1

Topic: H.01. Fear and Aversive Learning and Memory

Title: Cortical and striatal control of foot shock avoidance

Authors: S. PARDO[1], P. A. CASTELLANOS[2], N. DELEON[1], A. GONZALEZ[1], ***J. M. WENZEL**[1];
[2]Psychological Sci., [1]Univ. of San Diego, San Diego, CA

Abstract: Positive and negative reinforcement are fundamental drivers of behavior. While the involvement of cortical and striatal regions in positive reinforcement is well-documented, these systems' role in negative reinforcement remains less understood. In the rodent laboratory footshock avoidance tasks are commonly used to study negative reinforcement. Previous research using a lever-press avoidance task demonstrated that striatal dopamine signaling is integral for learning to avoid, but once the behavior is well-learned this system is no longer required to maintain avoidance. To assess potential roles of several brain regions in learning and maintenance of foot-shock avoidance, we undertook a large study utilizing immunohistochemical identification of c-fos expression as an indicator of region activation. We trained rats on a simple lever-press avoidance task in which rats press a lever to avoid a footshock until they learned to avoid footshock on either ~50% avoidance (these rats are believed to still be "learning the task") or 80% avoidance (in these rats the task is believed to be well-learned). One hour after completing their final day of the task rats were euthanized and brains were processed for c-fos immunohistochemical staining and quantification. We examined c-fos expression in 13 brain regions shown to be involved in aversive learning and avoidance. Surprisingly we found that among all 13 regions, significant differences in c-fos expression were only observed in cortical (prelimbic cortex (PrL) and infralimbic cortex (IL)) and striatal (dorsomedial striatum (DMS) and dorsolateral striatum (DLS)) regions. Further DREADD manipulations targeting these regions showed that DREADD inhibition of the DMS attenuated lever-press avoidance early in training, but not once the behavior was well-learned. Inhibitory DREADD manipulations of PrL, IL, or DLS had no impact on lever-press avoidance. We then used these same rats to assess the involvement of these regions in a more complex platform-mediated avoidance task in which rats must choose between lever pressing for a food reward and shuttling to a platform to avoid shock. We found that DREADD inhibition of the PrL in male and female rats, but not inhibition of the other three regions, decreased latency to the platform in the platform-mediated avoidance task. Together these data show that cortical and striatal regions play an integral role in avoidance behavior, however, the role of these structures varies based on whether the task is being learned or is already well-learned and also the type of avoidance task employed.

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Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

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Program #/Poster #: PSTR134.11/DD2

Topic: H.01. Fear and Aversive Learning and Memory

Support: T32 NS126122

Title: Assessing the role of the GPe to RRF pathway during cue-evoked avoidance

Authors: *M. V. VOUNATSOS, A. H. GITTIS;
Biol. Sci., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The external segment of the globus pallidus (GPe) is involved in the modulation of the motor output and limbic components of behavior. The circuitry by which the GPe contributes to limbic components of behavior remains unknown. While many investigations have focused on the local circuitry within the basal ganglia, numerous GPe projections to target regions outside of the basal ganglia including the midbrain, thalamus, and cortex exist and remain largely unexplored. We have previously reported, by anatomical and electrophysiological means, on the projections of the GPe to the retrorubral field (RRF), a dopaminergic nucleus in the caudal midbrain, in both male and female mice. We found that the GPe targets both GABAergic and DAergic neurons in the RRF (RRF_{DA} and RRF_{GABA}). Viral-assisted circuit mapping to trace the cell-type-specific projection patterns of RRF_{DA} and RRF_{GABA} populations revealed diverging pathways. The connectivity of GPe-recipient RRF_{DA} neurons followed the traditional medial forebrain bundle path, innervating the ventral striatum and to a lesser extent the dorsal striatum. GPe-recipient RRF_{GABA} neurons, on the other hand, displayed broad projections targeting numerous brain regions involved in limbic function including the parabrachial nucleus, amygdala, and hypothalamus. These contrasting projection profiles revealed multiple nodes by which the GPe is disynaptically connected to the limbic system, representing novel access points for the GPe to modulate limbic components of behavior. Of interest to us, given the projection patters of the GPe-recipient RRF populations, was the evidence implicating both the GPe and the RRF in fear. Furthermore, several additional nuclei of the basal ganglia (STN/SNr), which are downstream of the GPe, have been shown to be critical for cue-mediated avoidance behaviors under frightful conditions. Here, we explore the calcium dynamics of the GPe and the RRF, in a cell-type specific approach, during cue-evoked avoidance in freely moving mice of both sexes with the goal of providing insight to the role of the GPe in respect the basal ganglia and the GPe to RRF pathway during cue-evoked avoidance. Using diphtheria-mediated lesions, we investigate the role of selected populations in the initial acquisition and performance of cue-mediated avoidance. Using fear discrimination we assess how signaling in these populations changes over varying degrees of threat.

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Poster

PSTR134: Neural Systems of Avoidance and Discrimination Learning

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR134.12/DD3

Topic: H.01. Fear and Aversive Learning and Memory

Support: Uexplore

Title: Outcome Devaluation Reveals the Transition to Habit in Active Avoidance

Authors: R. P. SUMNER[1], K. J. BURKE[3], ***M. BUKKASAGARAM**[1], L. BRADLEY[1], E. WEBER[1], J. SAINI[1], Z. MEHRZAD[4], P. BEDUHN[2], A. RAIKAR[1], V. D. CAMPESE[2]; [2]Psychology & Behavioral Sci., [1]Univ. of Evansville, Evansville, IN; [3]New York Univ., New York, NY; [4]Indiana Univ. Sch. of Med., Evansville, IN

Abstract: This study explores the transition to habitual avoidance using aversive Pavlovian Instrumental Transfer (PIT) in 46 rats (32 males, 14 females). Training duration and stimulus pairing during outcome devaluation were manipulated to compare avoidance (and PIT) in limited versus extended training groups with either paired or unpaired devaluation treatment of the avoidance feedback cue. Rats underwent one day of Pavlovian Threat Conditioning, 15 (Extended) or 10 (Limited) days of Unsignaled Sidman Active Avoidance (USAA) with daily 15-minute Habituation, three days of outcome devaluation (CS Paired or Unpaired), one day of PIT testing, and a freezing test five days later. During transfer tests (i.e., PIT), paired groups showed greater response increases with the CS compared to baseline (e.g., Male Extended Paired: baseline 0.8611, CS 3.0250, increase 2.1639). Males had larger increases than females (Female Extended Paired increase: 0.9375). Extended training enhanced effects in males (Male Limited Paired increase: 1.0938), but some unpaired groups showed unexpected increases (e.g., Male Extended Unpaired: 2.8750). These findings highlight confounding sex differences and training duration's role in aversive learning, along with paired versus unpaired responses.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR135.01/DD4

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH R01 DA057330
Washington State University: Alcohol and Drug Abuse Research Program
Washington State University: Maximizing Access to Research Careers Program

Title: Dorsal hippocampus CA3 to dorsolateral septum circuit regulates cocaine-memory strength

Authors: *D. SOTO, A. Y. PRUITT, S. QI, D. J. HARTMAN, A. J. TRIVEDI, R. A. FUCHS; Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA

Abstract: Retrieval of drug-associated contextual memories can trigger drug seeking in individuals with substance use disorder and in animal models of drug relapse. Interestingly, cocaine-paired memories can become destabilized upon retrieval, allowing for updating or experimental manipulation before their reconsolidation into long-term storage. Disrupting these labile memories or their reconsolidation can weaken contextual control over drug-seeking behavior. In particular, optogenetic inhibition of the dorsal hippocampus cornu ammonis region 3 (dCA3) prior to memory reconsolidation disrupts cocaine-memory strength in rats. Conversely, pharmacological inactivation of the dorsolateral septum (dlS) enhances cocaine-memory strength in a sex-dependent manner. The dlS receives monosynaptic glutamatergic inputs from the dCA3; therefore, we investigated the role of the dCA3 to dlS circuit in regulating cocaine-memory strength using an instrumental rat model. Sprague-Dawley rats received adeno-associated virus serotype 8 infusions to express hM4Di, a Gi-coupled designer receptor exclusively activated by designer drugs, into the dCA3 and guide cannulae targeting the dlS. Rats were trained to lever press for intravenous cocaine infusions in a distinct environment to form drug-associated contextual memories, then received extinction training in a different context. Rats were then re-exposed to the cocaine-predictive context to destabilize the cocaine-related memories. Immediately after this session, rats received bilateral microinfusions of the hM4D(Gi) agonist deschloroclozapine into the dlS to inhibit the circuit. Following additional extinction sessions, rats were re-exposed to the cocaine-predictive context, and lever pressing was measured to assess changes in cocaine-memory strength. Chemogenetic inhibition of the dCA3 to dlS circuit after memory destabilization reduced subsequent context-induced reinstatement of drug-seeking in male rats, with no effects in females. Control experiments are underway, but our results suggest that dCA3 input to a subset of dlS neurons is necessary for cocaine-memory maintenance in males. Together with our previous data, these findings indicate that the dlS may bidirectionally regulate cocaine-memory strength in a sex-dependent manner.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR135.02/DD5

Topic: H.08. Drugs of Abuse and Addiction

Support: Hope for Depression Research Foundation
NIMH Grant P01DA047233
F99 Grant to A.M.T.

Title: Chronic cocaine exposure alters the balance of sex-specific approach/avoidance decision-making.

Authors: *C. BLASCHKE[1], A. M. MINIER-TORIBIO[2], T. LIN[4], T. MARKOVIC[5], F. J. MARTINEZ-RIVERA[7], G. ROJAS[3], A. V. AUBRY[6], E. J. NESTLER[8];
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Abstract: Approach/avoidance (A/A) conflicts require balancing the pursuit of rewards with the potential for undesirable outcomes. Neuropsychiatric disorders, such as drug abuse, can alter the balance of A/A decision-making, leading to maladaptive behaviors such as risky approaches to drug and natural rewards. Despite the prevalence of these disruptive A/A dynamics, the mechanism underlying the interaction between drug exposure and natural reward-seeking during A/A conflict is poorly understood. Here, we employed a platform-mediated avoidance paradigm, where we conditioned mice to avoid tones paired with foot-shocks by stepping onto a platform, thereby forfeiting access to saccharine-water rewards. We then exposed them to chronic cocaine or saline injections (20mg/kg intraperitoneal) for five days. Following a 5-day drug-free period, we tested their approach and avoidance responses under extinction conditions, where mice are exposed to tones associated with foot-shock with no consequences. Our results indicate that chronic cocaine—but not saline—exposure selectively modulates A/A behavior by increasing reward-seeking and reducing avoidance during tone periods, as opposed to inter-tone periods. These findings suggest that chronic cocaine alters decision-making processes by biasing behavior toward reward-seeking. To investigate the neurobiology underlying this heightened reward-seeking that facilitates avoidance extinction, we employed a combination of brain immunolabeling and 3D-volume imaging via iDISCO+, RNAScope, and viral-mediated gene transfer. Our preliminary iDISCO+ results revealed that chronic cocaine induces widespread ΔFOSB expression, including in the nucleus accumbens (NAc) and prefrontal cortex (PFC). ΔFOSB is a transcription factor known to be a key mediator of addiction-like phenotypes. Ongoing experiments aim to dissect the circuitry by selectively manipulating levels of endogenous ΔFOSB in NAc and PFC neurons expressing dopamine D1 or D2 receptors, which are known to signal A/A decision-making differentially. Our study provides insight into the neurobiological mechanisms underlying cocaine-induced changes in key decision-making biases, shedding light on cell-autonomous mechanisms that signal these behavioral responses. Supported by the National Institute on Drug Abuse

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR135.03/DD6

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01-DA056193-03

Title: Intermittent access to cocaine disrupts sleep architecture during prolonged abstinence

Authors: *S. R. COHEN[1], I. P. ALONSO[3], P. CLARK[4], R. A. ESPAÑA[2];
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[3]Neurobio. and Anat., [4]Neurobio. & Anat., Drexel Univ., Philadelphia, PA

Abstract: Individuals who struggle with cocaine use disorder display sleep dysregulation, often marked by reductions in rapid eye movement (REM) sleep and increased REM sleep fragmentation that persist throughout abstinence. We recently demonstrated that intermittent access to cocaine, but not short access to cocaine increases dopamine uptake rate and dopamine transporter sensitivity to cocaine following a period of abstinence - despite similar total cocaine intake levels between the two schedules of reinforcement. Further, we recently demonstrated that intermittent access to cocaine promotes REM sleep disruptions early in abstinence. To date, however, it remains unclear to what extent exposure to cocaine disrupts sleep over extended periods of abstinence. In the present studies, we monitored sleep/wake activity continuously for 28 days following abstinence from intermittent and short access to cocaine. We analyzed sleep/wake behavior using a custom machine-learning algorithm for the 24-hour, 12-hour light, and 12-hour dark phases. Given the observation that intermittent access - but not short access - to cocaine increases cue-induced seeking and enhances dopamine transporter function, we predicted that only intermittent access to cocaine would elicit marked sleep disruptions. Preliminary results support this prediction, with intermittent access to cocaine leading to persistent sleep deficits throughout abstinence with little effect on sleep following short access to cocaine. These effects were more prevalent during the 12-hr light phase, when sleep typically occurs. These initial findings suggest that the binge-like pattern of cocaine intake observed with intermittent access - and not total cocaine intake - is essential for dysregulating sleep/wake architecture during abstinence. Future studies will explore how these sleep disruptions correspond with dopamine dynamics at various abstinence periods.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant K01DA054306
Brain Behavior Research Foundation

Title: Transferring extinction memories to oppose cocaine renewal and reacquisition

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Abstract: Renewal and reacquisition of drug memories after periods of abstinence contribute to relapse. While previous studies suggest that extinction training successively impacts these processes, limited information about the magnitude and resolution of extinction versus other abstinence modalities obscures its impact. Moreover, genome-wide transcriptional modifications in brain reward regions associated with extinction vs. renewal and reacquisition behaviors remain under-characterized. Here, we used a rat model of contextual cocaine self-administration (SA), where rats acquire cocaine-SA in context A, then extinguish in a different context (B) or remain in their home-cage. This is followed by re-exposure sessions in context A with and without the drug. Our findings indicate that extinction training in context B impacts cocaine renewal and reacquisition in several ways. First, rats receiving extinction training in context B significantly reduced their seeking when compared with rats experiencing home-cage withdrawal, an effect that was subsequently reflected in delaying reacquisition. Second, analyses within the extinction group revealed a consistent seeking reduction in both the number and the proportion of animals that would otherwise show a strong renewal and faster reacquisition. Ongoing transcriptomic characterizations aim to link these phenotypes to specific gene expression patterns and central molecular drivers in key regions, including the nucleus accumbens, hippocampus, and amygdala. Together, this work reveals the effectiveness of contextually transferring extinction memories to attenuate the cocaine-associated renewal and delay its reacquisition.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.05/DD8

Topic: H.08. Drugs of Abuse and Addiction

Title: Understanding brain derived neurotrophic and mood symptoms in cocaine use disorder: a starting point differing from depressive disorders

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Abstract: Background: Depression and anxiety symptoms are negatively correlated with peripheral brain-derived neurotrophic factor (BDNF) in depressive disorders. Cocaine use disorder (CUD) presents high comorbidity with mood symptoms that impair recovery and facilitate relapses. However, a description of a potential interaction between peripheral BDNF and mood in Cocaine Use Disorder (CUD) is still unknown. Method: We performed a cross-sectional study exploring the potential relationship between peripheral BDNF levels and depression and anxiety symptoms in CUD-diagnosed subjects. Serum peripheral BDNF was determined by ELISA method. Standardized Hamilton Depression (HDRS) and Anxiety (HDRS) inventories were administered, and severity of symptoms were classified according to cut-off points in normal, moderate and severe symptoms. This data belongs to baseline measurements of participants enrolled ina randomized clinical trial aiming to evaluate a non-invasive brain stimulation technique on BDNF levels and CUD-related outcomes (Clinicaltrials.gov NCT06189690). The study followed the Declaration of Helsinki and was approved by the local ethics committee. Participants gave a written informed consent. Results: Twenty-nine CUD-diagnosed participants under stable medication (Female=3) were enrolled. According to the mood severity, 34.48% of participants were classified as normal, 24.14% as moderate and 41.38% as severe depressive symptoms ($p<0.001$). Peripheral BDNF levels were equivalent among different mood severity groups ($p<0.05$). We found no correlation between BDNF and HDRS and BDNF and HARS, regardless of mood severity($p<0.05$). Conclusion: The independence between peripheral BDNF levels and mood symptoms in CUD differs to the observed in depressive disorders. Our findings may not be aligned to the neurotrophic hypothesis of depressive symptoms. Present results suggest a particular regulation of peripheral BDNF and mood that might be part of CUD-related BDNF maladaptations perhaps intricated by chronic cocaine consumption.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR135.06/DD9

Topic: H.08. Drugs of Abuse and Addiction

Title: Dynamic, time-dependent interactions between dorsal striatal dopamine and glutamate release predict cognitive flexibility and punishment resistant cocaine use

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Abstract: Cognitive inflexibility is a trait marker that predicts substance use disorder (SUD) development across species, but the mechanism of this is unknown. Glutamate (Glut) and dopamine (DA) interactions in the dorsomedial (DMS) and dorsolateral (DLS) striatum are involved in the transition of behavior from flexible to outcome-insensitive during cognitive and drug seeking tests. Thus, we hypothesized that a common mechanism within this striatal interaction could predict both cognitive inflexibility and risk for developing SUD phenotypes. We trained rats on a discrimination learning paradigm and then performed a strategy switching test. We used multi-channel fiber photometry to simultaneously measure Glut and DA release in the DMS and DLS of the same rat during both learning and strategy switching. Next, rats were trained to self-administer cocaine and then ultimately subjected to a punishment resistance test where cocaine infusions were paired with a foot shock. Finally, we used pathway-specific DREADDs to determine where measured Glut release originated and whether each was necessary for the observed effects. We performed a median split such that rats with more than 60 errors in the strategy switching test were qualified as “slow switchers” and rats with fewer than 60 errors were qualified as “fast switchers”. Slow and fast switchers did not differ in their cocaine intake, but slow switchers took more punished cocaine infusions during the punishment resistance test. Fast and slow switchers showed test epoch-specific differences in DMS and DLS Glut and DA release. Elevations in Glut release in DLS (at trial initiation) and DMS (prior to a correct choice), with reductions in DA release, predicted both fast strategy switching and punishment sensitivity, while elevations in DLS and DMS DA release predicted the opposite. Inhibition of orbital frontal cortex inputs reduced the Glut measured in both the DMS and DLS prior to a correct choice, whereas inhibition of parafasicular thalamus inputs reduced Glut measured in both regions at trial initiation. Inhibition of both projections impaired performance on the strategy switching test and increased punishment resistant cocaine use. We propose that projection-specific elevations in Glut release at specific test epochs represent a “neurochemical signature” of flexibility that predicts resilience to SUD phenotypes, whereas elevations in DA release at those same test epochs predict inflexibility and vulnerability to SUD phenotypes.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

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Program #/Poster #: PSTR135.07/DD10

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA057360

Title: Nucleus accumbens cholinergic interneurons and incubation of cue-induced cocaine craving

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Abstract: Incubation of cocaine craving describes a progressive increase in cue-induced cocaine-seeking that occurs during abstinence following cocaine self-administration (SA; 6 h/d x 10 d, 0.5 mg/kg/infusion). Previous work showed that incubation of craving is mediated in part by plasticity involving medium spiny neurons in the nucleus accumbens (NAc). However, to date no studies have tested the role of NAc cholinergic interneurons (CIN) in incubation. This is being explored in transgenic rats expressing Cre recombinase under the control of the choline acetyltransferase (ChAT) promotor. We first determined that ChAT:Cre(+) rats do not differ from Cre- or wildtype rats in cocaine SA or incubation of cocaine craving (effect of genotype: $F(1,15)=0.3$, $p>0.1$). Then we tested how chemogenetic excitation or inhibition of CIN in the NAc core affects cue-induced seeking before and after incubation has occurred. For these studies we compared rats receiving a Cre-dependent hM4Di virus, hM3Dq virus, or a control GFP virus. We first confirmed that each virus expressed with high fidelity in CIN of ChAT:Cre rats. Surprisingly, neither exciting nor inhibiting CIN late in abstinence (40+ days after SA) has an effect on seeking when compared to rats that received the control GFP virus (effect of virus: $F(2,22)=0.14$, $p>0.1$). In light of these results, we are planning to use fiber photometry to record from CIN of the NAc core during seeking tests in early (1 day after SA) and late abstinence (40+ days after SA; sample size $\geq$ 8 rats for each time point). We expect to find multiphasic activity patterns in CIN. First, to establish recording parameters, we are recording from CIN of the NAc core during food SA and seeking tests following food SA. We are using GCaMP to measure Ca^{++} responses in CIN and GRAB_DA to simultaneously measure dopamine release in the NAc. To this point we have recorded from 5 rats. Importantly, recording Ca^{++} activity in CIN, a sparse population of neurons, is feasible. These neurons respond dynamically to cue presentation and food presentation during training, and a different pattern of activity is observed during extinction training. We will perform further analysis of these data and also perform recordings from CIN during cue-induced seeking tests following cocaine SA. Together these results suggest that ChAT:Cre rats are a viable model for use with cocaine self-administration. Also, DREADD-induced inhibition or excitiation of NAc CIN has no net effect on cue-induced reinstatement in

the incubation model, and CIN respond dynamically to reward delivery and conditioned stimulus presentation.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR135.08/DD11

Topic: H.08. Drugs of Abuse and Addiction

Support: NRF Grant RS-2025-00517214

Title: Non-invasive stimulation of parabrachial nucleus suppresses cocaine-seeking behavior

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Abstract: Maladaptive drug-seeking behavior remains a major obstacle in the treatment of substance use disorders. While existing pharmacological and behavioral therapies can be effective, their efficacy is often limited by high relapse rates and lack of circuit specificity. As a result, there is growing interest in neuromodulatory approaches that directly target the neural circuits underlying compulsive reward seeking. Stimulation of the parabrachial nucleus (PBN), particularly its subpopulation of neurons expressing calcitonin gene-related peptide (CGRP), suppresses addictive behavior through affective aversion signaling without evoking nocifensive responses. Here, we tested whether non-invasive transcranial focused ultrasound stimulation (tFUS) of the PBN could similarly reduce cocaine-seeking behavior. Mice were trained to self-administer cocaine (0.2 mg/kg/infusion) across 14 days under escalating fixed-ratio schedules (FR1-FR5). Starting on day 15, tFUS was delivered in real time, contingent upon each lever press. This closed-loop stimulation significantly suppressed cocaine-seeking behavior, with effects persisting for at least two weeks following the final stimulation session. This closed-loop intervention significantly reduced cocaine self-administration, and the suppressive effects persisted for at least two weeks after the final stimulation session. Importantly, tFUS did not induce observable nocifensive behaviors, indicating that the behavioral suppression was not attributable to physical discomfort. These findings demonstrate that non-invasive PBN stimulation using tFUS can produce lasting reductions in compulsive drug-seeking and may represent a promising neuromodulatory strategy for addiction treatment.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

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RISE Program: NIH-NIGMS #2R25GM082406, NIH-G-RISE Program #T32GM144896

Title: The impact of cocaine on the estrous cycle in female rats during conditioned place preference

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Abstract: Research has shown that women may experience a more rapid escalation in substance use, heightened cravings, and increased difficulty in cessation compared to men, potentially influenced by estradiol, a key female hormone. A clinical study indicated that cocaine-dependent women exhibited lower salivary estradiol levels throughout their menstrual cycles relative to controls, although the underlying relationship and its implications for addiction remain largely unexplored. This project investigates the effects of cocaine-seeking behavior in female rats. We hypothesized that exposure to cocaine will lead to alterations in estrous cycles and estradiol levels, thereby impacting cocaine-seeking behavior. To test this hypothesis, we employed a cocaine-conditioned place preference (CPP) paradigm utilizing female Long Evans rats, which received alternating injections of 10mg cocaine and saline over twelve days. Following a fifteen-day extinction period, two reinstatement sessions were conducted with 5 mg and 10 mg doses of cocaine. Throughout the experiment, vaginal smears were conducted to assess the estrous cycle of the animals. Blood and brain samples were collected to measure estradiol levels using an enzyme-linked immunosorbent assay (ELISA). Our findings revealed significant differences in the number of changes in estrous stages within the cocaine CPP group, while no such differenced were observed in the saline group across the entire cycle. Additionally, distinct transitions between estrous stages were noted among the cocaine group within the same day compared to controls. Moreover, rats in the estrus and metestrus stages that received a 10mg dose of cocaine exhibited a significantly greater preference in the CPP test compared to those in proestrus. Notably, cocaine-exposed rats exhibited lower brain estradiol levels, while serum estradiol levels remained unchanged. A positive correlation was found between the second reinstatement and serum estradiol levels, suggesting that higher concentrations of estradiol are associated with

greater preference for the cocaine-associated chamber. Our results highlight the complex and differential effects of cocaine on estradiol concentrations in the brain versus serum. Elevated serum estradiol levels may enhance the motivational aspects of cocaine use. Understanding the hormonal states that affects cocaine's effects could inform hormone replacement therapy and cycle-aware drug rehabilitation, supporting the development of sex-and hormone-specific treatments for substance use disorders.

Disclosures: A. Sanabria Ponce de Leon: None. **L.J. Godoy-Muñoz:** None. **M.T. Sepulveda-Orengo:** None.

Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Sex differences in delay discounting behavior in mice with a history of repeated cocaine exposure

Authors: *D. R. ZUELKE, C. MAYSONET, R. SALAZAR, N. ISMAYILZADA, A. LEE-VARAN, J. YEISLEY, E. F. GALLO;
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Abstract: Studies in humans and rodents have shown that chronic cocaine exposure induces lasting increases in impulsive choice, reflecting a preference for short-term rewards over delayed rewards. Further, females exhibit higher drug-taking, faster progression to cocaine dependence, and higher relapse rates across species, but how prior cocaine history impacts impulsive choice in females remains poorly understood. To address this critical gap, we first exposed male and female C57BL6/J mice to cocaine (30 mg/kg i.p.) or saline daily for 14 days, which led to a robust and sustained increase in locomotor activity in cocaine-treated mice, independent of sex. One-to-three weeks later, mice were trained on a delay discounting task that measures the choice between pressing a lever for a small, immediate reward or pressing another lever for a three times larger reward, presented after increasing delays. We first assessed the % “large” lever choices in the absence of delays over 14 days. Large lever preference increased with training, with no significant differences between conditions. Once delays to the large reward were introduced, both treatment groups showed discounting, but no overall effect of cocaine. In sex-disaggregated data, we found that among saline-treated mice, males had a higher preference for large rewards across delays than females, consistent with greater impulsive choice. Moreover, in females, cocaine significantly reduced the % large preference even at short delays compared to saline. Hyperbolic discounting function fitting showed that cocaine-treated females had a significantly smaller area-under-the-curve (AUC) and a higher *k* discounting factor, reflecting

increased impulsive choice relative to saline. While we found no significant treatment effect in males, cocaine-treated males showed a trend towards decreased impulsive choice. To further determine whether cocaine history has a specific impact on delay sensitivity, we modified our discounting task to only vary delay, but not the size, of one of the rewards. While we found no effect of cocaine in males in this task, a 2-way ANOVA showed a significant main effect of drug in females. Cocaine-treated females showed steeper discounting than their saline counterparts, recapitulating the effects seen in the classic paradigm. Our data suggest that prior cocaine exposure results in increased impulsive choice behavior specifically in females by reducing their sensitivity to reward size and by increasing their sensitivity to delays. These findings reveal sex differences in cocaine-induced impulsive behavior in mice and highlight the importance of studying the lasting effects of cocaine in both sexes.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

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NIH-NIDA #1F31DA053793
The Hispanic Alliance for Clinical and Translational Research (Alliance)
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Title: The impact of chronic stress prior to cocaine exposure on the motivation to seek cocaine

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Abstract: Stress has been identified as a significant factor in the onset of substance use disorders and plays a crucial role in relapse among individuals with drug addiction. Research highlights sex-based differences in stress responses and the incidence of addiction, often attributed to biological distinctions. These differences underscore the importance of investigating how stress affects brain function differently in males and females. This study aims to examine whether sex differences influence sensitivity to the rewarding properties of cocaine. We hypothesized that stress exposure in both sexes would lead to increased cocaine intake and a heightened drive to obtain the drug in females compared to their male counterparts. To test this hypothesis, we subjected rats to inescapable footshock as a form of chronic stress over 5 days. Following this stress exposure, the rats underwent extended-access cocaine self-administration for 10 days, with each session lasting 6 hours. Afterward, we implemented a 2-hour progressive ratio or dose-response protocol in both male and female rats to assess their motivation and sensitivity to obtaining cocaine. The results indicated that chronic stress prior to extended access to cocaine self-administration did not increase motivation for cocaine seeking in either the male or female treatment groups, leading us to reject our initial hypothesis. Interestingly, preliminary data from the dose-response protocol showed that stressed males consumed less cocaine and demonstrated lower motivation to seek it compared to non-stressed males across all doses. This finding suggests that stressed males may be more sensitive to the reinforcing effects of cocaine. We will conduct a study with female rats to assess their behavioral responses and explore potential sex-based differences.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

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Title: Acute Selective Antagonism of Progesterone Receptors Does Not Alter Cocaine-Related Behaviors in Female and Male Wistar Rats

Authors: *E. A. SNEDDON, K. BAI, S. L. PLASIL, S. CHONWATTANAGUL, S. BONNET-ZAHEDI, J. RAMBORGER, B. SICHEL, A. R. MARTINEZ, A. MORGAN, O. GEORGE; Psychiatry, UC San Diego, San Diego, CA

Abstract: Cocaine use remains a significant public health issue in the United States, with approximately 2.2 million regular users. Females represent an understudied population in both clinical and preclinical addiction research, despite exhibiting sex-specific vulnerabilities and progression patterns. Accumulating evidence suggests that hormonal fluctuations modulate drug-taking behaviors in females. However, it remains unknown whether acute disruptions in progesterone signaling influence cocaine-related behaviors. This study tested the hypothesis that acute selective antagonism of progesterone receptors using ulipristal acetate, an FDA-approved emergency contraceptive, would increase cocaine self-administration in female but not male rats. Male and female Wistar rats were assessed in three experiments. In Experiment 1, rats with intravenous catheters self-administered cocaine (0.5 mg/kg) under short or long access conditions. Following escalation, rodents received ulipristal acetate (vehicle, 0.3, 1, or 3 mg/kg) before long access sessions. Motivation for cocaine was assessed via progressive ratio testing, and tissue and plasma were collected at the end of testing. In Experiment 2, chronic ulipristal acetate administration was evaluated for locomotor effects. In Experiment 3, mRNA levels of the progesterone (*Pgr) receptor* gene were measured in addiction-relevant brain regions 24 hours after treatment with 3 mg/kg ulipristal acetate or vehicle. Acute antagonism of progesterone receptors did not alter cocaine self-administration or progressive ratio responding in either sex. Chronic treatment did not alter locomotor activity. Furthermore, a single ulipristal acetate injection did not affect *Pgr* mRNA levels in relevant brain regions. Additional plasma-based assays are in progress to confirm treatment efficacy. These findings demonstrate that acute progesterone receptor antagonism does not influence cocaine-related behaviors in male or female rats. Given the known interaction between hormonal fluctuations, prevalence of hormonal contraceptive use, and substance use in females, future studies should explore the effects of chronic hormonal contraceptive exposure on drug-related outcomes.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

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Title: Characterizing dynorphin activity on the kappa-opioid receptor during cocaine self-administration

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Abstract: Previous research has suggested that Dynorphin, the endogenous opioid peptide, signals through KOR (Kappa Opioid Receptor) binding and causes negative affective states like anxiety, dysphoria, and stress that ultimately instigate drug-seeking behaviors. Previous research has shown that Dopamine levels fluctuate throughout drug escalation and that Dynorphin plays a modulatory role in this. This project aims to clarify the functional dynamics of Dyn/KOR signaling in the prefrontal-accumbal circuitry during cocaine self-administration, escalation, and post-escalation phases.
The current project focused on characterizing Dyn-KOR signaling during Cocaine Self-Administration using in-vivo Fiber Photometry recording. Sprague-Dawley rats (N=28) underwent cranial surgery a kLight sensor was injected in the Prelimbic Cortex and the Nucleus Accumbens. Chronic IV (intravenous) catheters were inserted into the right jugular vein and then threaded through the right shoulder into a pedestal implanted between the shoulder blades. Rats were attached to IV lines that allowed for infusions of 5mg/mL cocaine. Following training, rats would undergo five days of Short Access in the operant chamber for an hour. Following Short Access, rats would go through two weeks of Long Access where they are run in the operant chambers for six hours each day. Fiber Photometry recordings were taken on the last two days of the Short Access week and Long Access weeks. Animals were put through a thirty-day incubation period where, once over, were injected with KOR agonist U-50,488 (10mg/kg) and recorded. Animals were also injected with 1.5cc of saline on alternating days to the U-50 injection.
Despite a lot of the project's data being preliminary, there are a lot of promising results that will be achieved with further data collection. We are currently finalizing a GUI (Graphic User Interface) through Cursor to extract our photometry data, this is a very exciting addition to our analysis and will aid in future research. We have replicated previous findings inasmuch that the female rats overall took more Cocaine infusions than the male rats. Additionally, we generally had more non-escalators than escalators in the cumulated cohorts. With further data collection, we hope to gather a larger N to use for photometry analysis. We have validated that our photometry recordings were picking up Dynorphin activity by administration of KOR agonist U-50,488. Further data collection in the coming months have a lot of potential for better insight into Dynorphin's activity during cocaine self-administration in real time.

Disclosures: M.L. Melavic: A. Employment/Salary (full or part-time): University of Washington.

Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

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Title: Striatal enkephalin gates cocaine-induced GABA plasticity and excitability of the ventral pallidum.

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Abstract: Prior research suggests that abstinence from cocaine inhibits GABA release from striatal D2 receptor-expressing medium spiny neurons (D2-MSN) to the ventral pallidum (VP). This suppression is reversed by mu- or delta-opioid receptor antagonists, implying that GABA is suppressed by cocaine-induced increased tone of an opioid peptide. However, in these experiments, basal GABA suppression was only inferred by the inability of high frequency stimulation to induce long-term depression. Moreover, the identity and source of the opioid peptide responsible remains unknown. We previously showed that abstinence from long-term cocaine increases striatal level of *Penk*, a gene encoding an opioid peptide precursor highly expressed in D2-MSNs. We hypothesized that cocaine abstinence increases striatal enkephalin, which acts via opioid receptors in D2-MSNs to inhibit GABA release onto VP neurons. Further, we predicted this would disinhibit the VP. To test this, we directly examined basal GABA release in mice lacking *Penk* from D2-MSNs (D2-PenkKO) by recording asynchronous GABA release following optogenetic stimulation of D2-MSNs through *ex vivo* electrophysiology. We found that cocaine abstinence inhibited GABA release from D2-MSNs to the VP in controls, but not in D2-PenkKOs. Enkephalin application also inhibited GABA release, except in cocaine-abstinent controls, indicating enkephalin is sufficient to suppress D2-MSN GABA transmission to VP but that GABA was already suppressed in cocaine-abstinent mice. Optogenetically-evoked GABA release from D2-MSNs inhibited VP excitability in saline-treated controls and D2-PenkKOs but not in cocaine-abstinent controls. Additionally, we found that cocaine abstinence suppressed spontaneous firing in controls, potentially due to adaptive depolarization of action potential threshold in VP neurons. Our data strongly implicate cocaine-heightened striatal enkephalin as a key mechanism gating GABA plasticity within this striatopallidal circuit to affect VP neuron excitability. Moreover, since inhibition of D2-MSN-VP circuit increases cue-induced cocaine seeking, our future studies will investigate how striatal enkephalin acts within this circuit to influence cocaine seeking and taking.

Disclosures: K. Matsumura: None. **L.K. Dobbs:** None.

Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.15/EE2

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant R01DA054329

Title: Abstinence from cocaine does not influence GABA release within intrastriatal axon collaterals

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Abstract: Prior studies indicate that optogenetic inhibition of GABA release from D2 receptor containing medium spiny neurons (D2-MSN) to the ventral pallidum drives cocaine seeking. Moreover, published work and our preliminary findings indicate that forced abstinence from long-term cocaine exposure inhibits GABA release in this circuit. This appears to be regulated by cocaine-enhanced enkephalin acting on opioid receptors expressed in D2-MSNs. In addition to their long-range projections to the ventral pallidum, though, D2-MSNs also have intrastriatal projections onto D1 receptor containing MSNs (D1-MSNs). We previously showed that dysregulation of intrastriatal GABA release mediates the locomotor response to cocaine and is associated with cocaine reward. Here, we tested how forced abstinence from prolonged cocaine affects the intrastriatal GABA release and the subsequent excitability of D1-MSNs. We hypothesized that cocaine abstinence would inhibit GABA release from D2-MSNs onto D1-MSN via heightened enkephalin from D2-MSNs acting on presynaptic μ-opioid receptors (MOR). We further predicted this would disinhibit D1-MSN action potential firing. To directly measure basal GABA release, we performed *ex vivo* electrophysiology in mice lacking enkephalin from D2-MSNs (D2-PenkKO) and *Adora2a-Cre* controls and recorded asynchronous GABA release following optogenetic stimulation of D2-MSNs. We found, surprisingly, that basal GABA release was not inhibited in either genotype following 14 days of abstinence from long-term (10 days) cocaine compared to saline-treated mice. Additionally, the MOR antagonist CTAP increased GABA release in cocaine-abstinent controls and D2-PenkKOs, suggesting cocaine abstinence enhances the tone of an opioid peptide other than striatal enkephalin. Current-clamp recordings of D1-MSNs revealed that cocaine abstinence did not affect D1-MSN excitability for either genotype; however, CTAP decreased D1-MSN firing in cocaine-treated controls. This is consistent with our asynchronous GABA findings and suggests enhanced GABAergic input onto D1-MSNs restrains their activity. In contrast, CTAP increased D1-MSN firing in D2-PenkKOs. Taken with our other plasticity findings in the ventral pallidum, it appears cocaine has synapse-specific effects to suppress GABA from D2-MSNs. Further, our data suggest that enkephalin released from D2-MSNs does not contribute to cocaine-induced intrastriatal GABA plasticity. Collectively, these data shed light on how distinct striatal circuits contribute to cocaine seeking.

Disclosures: P.N. Lyuboslavsky: None. **L.K. Dobbs:** None.

Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR135.16/EE3

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA054329
Fred M. Jones and Homer L. Bruce Endowed Graduate Fellowship in Addiction Biology

Title: C57 and DBA mouse strains express distinct cocaine avoidance phenotypes in an operant runway independent of differences in striatal enkephalin-dynorphin balance

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Abstract: In addition to its rewarding effects, cocaine can induce a negative affective state shortly after use or during the cocaine "crash" associated with withdrawal. This may decrease cocaine use or lead to the co-use with opioids to alleviate the aversion, and indeed rats show less avoidance to self-administer a heroin-cocaine combination than cocaine alone. Yet, understanding of the neurobiological mechanisms driving cocaine-induced negative affect is limited. Within the striatum, the opioid peptides enkephalin and dynorphin promote cocaine reward and aversion, respectively. Here, we investigated how the striatal enkephalin-dynorphin balance influences the development of cocaine avoidance in a self-administration runway task. We adapted this task from rats for use in mice to show the development of cocaine avoidance. Cocaine avoidance was assessed in two inbred mouse strains (C57BL/6J and DBA/2J) known to have opposing striatal dynorphin/enkephalin milieus and in D2-*Penk*KO mice, which lack enkephalin selectively from striatal medium spiny neurons. We hypothesized that DBA/2J and D2-*Penk*KO mice, which with higher relative dynorphin to enkephalin would show more cocaine avoidance. Surprisingly, both inbred strains developed cocaine avoidance, though they expressed it differently: C57Bl/6J mice primarily developed retreats away from the cocaine-paired goal box, and DBA/2J mice primarily took longer to reach the goal box. Additionally, D2-*Penk*KOs developed similar cocaine avoidance compared to littermate controls. Next, we tested whether a priming injection of morphine would alleviate cocaine's negative affect state and attenuate cocaine avoidance. Although acute morphine prime did not reduce cocaine avoidance, DBA/2J mice showed reduced retreats on the following day. We suspect this was due to an updated value of the goal box since subjects would have had morphine on board when cocaine was delivered upon reaching the goal box. Together, our data show mice develop avoidance to self-administer cocaine in the runway, similar to rats, across a range of strains. Pre-existing differences in the striatal dynorphin/enkephalin balance, however, do not alter development of cocaine avoidance, and striatal enkephalin is not necessary for cocaine avoidance. Additionally, while morphine does not appear to acutely alleviate cocaine aversion, it may mitigate cocaine avoidance by enhancing its rewarding effects.

Disclosures: B. Remmers: None. **K. Matsumura:** None. **L.K. Dobbs:** None.

Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR135.17/EE4

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA046457

Title: Dorsolateral striatum inhibition via AMPAR antagonism, but not DREADDs, enhances sensitivity to punishment of cocaine seeking in rats

Authors: *E. BRILL[1], K. ALROBAIRE[2], B. JONES[1], R. J. SMITH[3];
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Abstract: In an animal model of compulsive drug use, a subset of rats continue to self-administer cocaine despite footshock punishment and are thus considered punishment resistant. Punishment resistance has been theorized to be related to habitual drug-seeking and the dorsolateral striatum (DLS). In support of this, preliminary data from our lab found that pre-training lesions of DLS enhanced punishment sensitivity. Here, we wanted to test the effects of temporary manipulation of DLS instead, using DREADDs or AMPAR antagonism. For the DREADDs experiment, male rats were injected in DLS with AAV driving expression of hM3D (Gq), hM4D (Gi), or GFP (control). For the AMPAR antagonism experiment, male rats were implanted with guide cannulae targeting the DLS. Rats were trained to self-administer intravenous cocaine on a seeking-taking chained schedule of reinforcement and then exposed to two to four days of punishment testing in which footshock was delivered on 1/3 of trials after seeking. Prior to punishment testing each day, rats were injected with either DCZ (DREADD ligand, 0.01 mg/kg, i.p.) or NBQX (AMPAR antagonist, 5 mM, intra-DLS). We found no significant differences in punishment sensitivity after Gq-DREADD stimulation or Gi-DREADD inhibition of DLS, as compared to control. However, we observed enhanced punishment sensitivity after intra-DLS injections of NBQX, as compared to vehicle injections. Therefore, we observed enhanced punishment sensitivity following DLS lesions or temporary inactivation via NBQX, but not DREADD manipulation. This latter result may indicate that DREADDs are not effective in DLS, particularly when expressed nonspecifically in all neurons. Overall, these findings indicate that DLS is involved in punishment resistance for cocaine seeking. Further work is necessary to fully understand the relationship between DLS, habits, and punishment resistance.

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Poster

PSTR135: Cocaine: Reinforcement, Seeking, Reinstatement, and Other Behavioral Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR135.18/EE5

Topic: H.08. Drugs of Abuse and Addiction

Support: NIMES UNIVERSITY GRANT

Title: Food Motivation Exceeds Cocaine: Low cAMP Activity and Structural Nerve Changes Without 5-HT4 Receptors.

Authors: *V. COMPAN[1], S. CHOQUART[2];
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Abstract: In the nucleus accumbens, the activation of a cAMP signaling pathway plays a crucial role in transforming the immediate reduction of drugs' rewarding effects into lasting dependence. This process involves the recruitment of the cAMP-response element binding protein (CREB)-binding protein, leading to the phosphorylation of CREB (pCREB), which promotes the expression of certain genes (such as FosB and ΔFosB) while suppressing others (like the histone methyltransferase G9a), resulting in changes in neuronal morphology. Serotonin (5-HT, 5-hydroxytryptamine) volume transmission through various receptors influences this cAMP signaling and modulates the activity of reward neural pathways. In this study, we explore how the absence of one serotonin receptor subtype, the Gs-coupled serotonin 4 receptors (5-HT4Rs), impacts the morpho-functional effects of cocaine. In 5-HT4R knockout (KO) mice, cocaine failed to elevate levels of both cAMP and pCREB in the nucleus accumbens, leading to a reduced expression of FosB and ΔFosB. Additionally, under basal conditions, mRNA levels of G9a were higher in the mutants compared to wild-type animals. We also observed a decrease in the number of dendritic spines in the nucleus accumbens of the mutants. While these mutants exhibited lower motivation to self-administer cocaine, they showed increased motivation to consume food following chronic restriction. Thus, a high vulnerability to overeating and low cocaine dependence appear to be associated with reduced activity of the cAMP-dependent pathway and fewer dendritic spines in the nucleus accumbens in the absence of 5-HT4 receptors.

Disclosures: V. Compan: None. **S. Choquart:** None.

Poster

PSTR136: Orbitofrontal Cortex

Location: SDCC Halls B-H

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Program #/Poster #: PSTR136.01/EE6

Topic: I.03. Decision Making

Support: STI2030-Major Projects (2021ZD0203703)
CAS Strategic Priority Research Program (XDB1010201)
National Natural Science Foundation of China (32171030)

Title: The anterior cingulate cortex-orbitofrontal cortex circuit regulates interhemispheric transfer of visual learning

Authors: *J. REN[1,2], L. DECHEN[1], H. YAO[1];
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Abstract: *Objective:* Interhemispheric interactions shape cognitive and perceptual behaviors, but their role in mediating the transfer of visual learning across eyes remains unclear. *Methods:* We trained mice on a monocular visual Go/No-Go task. After performance plateaued, the stimulus was switched to the other eye. To investigate the mechanisms underlying initial learning and post-switch performance, we combined behavioral assays with calcium imaging, unilateral lesions, and circuit-specific manipulation. *Results:* Switching the visual stimulus to the other eye impaired performance and learning (left-to-right: n=12, p=0.011 comparing final 4 days pre- vs. post-switch, p=0.65 post-switch; right-to-left: n=12, p=0.013 comparing final 4 days pre- vs. post-switch, p=0.09 post-switch; two-way repeated measures ANOVA). Widefield imaging of cortical activity revealed increased interhemispheric asymmetry in the anterior cingulate cortex (ACC) after the eye switch (n=12, p=0.0015, one-way ANOVA). Lesioning either ACC hemisphere before initial training preserved or quickly restored performance after the eye switch, whereas inhibiting callosal projection neurons in the trained ACC hemisphere post-switch had no effect. Additional lesion experiments revealed that the orbitofrontal cortex (OFC) was required for performance recovery after the eye switch. One-photon calcium imaging of OFC-projecting ACC neurons (ACC^{OFC} neurons) identified two populations encoding licking motivation and prediction error. Impaired learning following the eye switch was associated with an increased fraction of motivation-related and a decreased fraction of error-related ACC^{OFC} neurons (motivation-related: n=2567, $p=5.3\times10^{-10}$; error-related: n=995, $p=1.4\times10^{-16}$, one-way ANOVA). We are now testing how these ACC^{OFC} populations contribute to learning when the other ACC hemisphere is lesioned prior to training.

Disclosures: J. Ren: None. **L. Dechen:** None. **H. Yao:** None.

Poster

PSTR136: Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR136.02/EE7

Topic: I.03. Decision Making

Support: 1R01MH137276

Title: Spatial generalization on a continuous spatial bandit task for rats

Authors: *S. GUPTA[1], C. CUETO[3], A. REBOLLAR[2], F. ABZUN ERAZO[2], S. MANSUR[2], A. LOK YUNG YONG[2], A. M. WIKENHEISER[1];
[1]Psychology, [2]UCLA, Los Angeles, CA; [3]California State University, San Bernardino, San Bernardino, CA

Abstract: Decision making is ubiquitous across our everyday lives. Sometimes, we choose between readily available options like items in a grocery store. Other times, however, we choose between spatially distinct options like restaurants in different parts of the city that require navigation to the chosen option. Moreover, we seldom make the same comparisons serially and repeatedly akin to how they are typically studied in laboratory paradigms. In real life, novel comparisons rely on the outcomes of similar past comparisons to guide the decision. Here, we investigated value generalization during decision making within a spatial context using a novel behavioral paradigm in which the probability of reward varies across space in a structured—but uncued—way. Rats (n = 11; 5 female) approached and paused at visual stimuli projected on the floor of an open field arena; reward was delivered probabilistically based on the location of the stimulus rats chose following a latent probability map that assigned higher and lower reward probabilities to distinct locations in the arena. Preliminary data shows rats' decisions were driven by the underlying reward-probability map; as the difference in value between stimuli increased, rats favored the higher-probability option. In trials with no difference in value between the two options, rats generalized value from previous choices and selected the stimulus that was relatively closer to the high probability zone. Value-sensitivity on trials with a value difference was significantly correlated with value generalization on trials with no value difference. We tested rats' ability to adapt to changes in the underlying probability map by systematically rotating the map by 45, 90, 135 or 180 degrees. The extent of impairment in performance following a rotation was positively correlated with the degree of rotation in the underlying map. Electrophysiological recordings from lateral orbitofrontal cortex (OFC)—a brain region important for value representations and reward processing—indicate that a significant proportion of individual neurons encoded the value of the chosen stimulus and outcome delivery as rats performed this task.

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Poster

PSTR136: Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR136.03/EE8

Topic: I.03. Decision Making

Title: The role of efferent ventral pallidal neural pathways in default mode network regulation

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Abstract: Shifting between internally oriented focus and externally guided attention is fundamental to daily routines. These transitions depend on the modulation of the Default Mode Network (DMN), a group of brain regions linked with introspective processing. The DMN is traditionally considered a cortical network; however recent evidence shows that the basal

forebrain, specifically the ventral pallidum (VP), plays a key role in DMN regulation. Here, we silence different VP efferent pathways and examine their contribution in task switching between execution of well-learned, automatized behaviors and engagement with an auditory discrimination task. We found that optogenetic inhibition of the VP projection to lateral habenula (LHb) confers a learning advantage early during task acquisition, while silencing the VP projections to mediodorsal thalamus (MD) facilitates performance during the late stage of the same task. Interestingly, the downregulation of the cholinergic population of VP improved performance during both early and late stages. We posit that this learning advantage signifies an 'escape' from the DMN brain state, supporting more effective discrimination and attention toward external auditory stimuli. We propose that these pathways govern distinct roles, whereby LHb-projecting VP neurons trigger DMN activity, MD-targeting VP neurons contribute to the DMN states maintenance, while cholinergic neurons in VP are involved in both processes.

Disclosures: E.A. Makedona: None. **M.A. Harvey:** None. **G. Rainer:** None.

Poster

PSTR136: Orbitofrontal Cortex

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Program #/Poster #: PSTR136.04/FF1

Topic: I.03. Decision Making

Support: CIHR grant (PJT-186219)

Title: Sex and brain region dependent modulation of cost/benefit decision making and motivation by CRF1 and 2 receptors

Authors: *A. MAHREZ[1], M. ZHAO[2], G. L. DALTON[1], S. B. FLORESCO[1];
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Abstract: Acute stress can exert differential effects on mnemonic and cognitive functions depending on a myriad of factors. Stress can alter different forms of cost/benefit decision-making, particularly those involving physical effort. For example, stress reduces preference for larger rewards associated with a greater effort cost and alters other measures of motivation; effects that are driven by increased corticotropin-releasing factor (CRF). However, the specific brain regions and receptor mechanisms through which increased CRF activity may perturb these functions remains to be fully explored. We examined how increased activation of CRF1 and 2 receptors contributes to stress-induced alterations of cost/benefit decision-making in three key brain regions known to regulate these types of decisions: the medial prefrontal cortex (mPFC), the basolateral amygdala (BLA) and ventral tegmental area (VTA). Male and female rats were well-trained on an effort discounting task, requiring them to choose between a low effort/low reward lever (LR; 2 pellets after one press) and a high effort/high reward lever (HR; 4 pellets). The effort required to obtain the HR increased progressively across four trial blocks within each session (1, 5, 10 and 20 presses). Intra-mPFC infusion of the CRF1 agonist Stressin did not

affect effort-related choice or decision latencies, and actually enhanced response vigor (rates of responding on the HR lever) in both sexes. Conversely, CRF1 agonist treatments in the VTA reduced response vigor across sexes in the VTA, and selectively reduced response rates in males when infused into the BLA. In contrast, stimulation of mPFC CRF2 receptors with Urocortin3 reduced HR choice in blocks where males and females displayed a preference for this option under control conditions. CRF2 stimulation in the BLA reduced preference for larger, high cost rewards in females in the higher-effort blocks, while having minimal effects in the VTA. These findings highlight that CRF1 and 2 receptor activity within distinct nodes of prefrontal cortical-amygdala and dopaminergic circuitry can exert differential, and sometimes opposing effects on cost/benefit decision making and reward-related motivation. Prefrontal vs subcortical CRF1 receptors modulate response vigor in opposing ways, whereas excessive activation of CRF2 receptors can reduce preference to pursue larger rewards associated with a greater effort cost in a sex and region dependent manner. This latter effect suggests that increased CRF2 activity may contribute to motivational impairments and abnormal decision-making associated with stress-related psychiatric disorders such as depression.

Disclosures: A. Mahrez: None. **M. Zhao:** None. **G.L. Dalton:** None. **S.B. Floresco:** None.

Poster

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Topic: I.03. Decision Making

Support: CIHR grant (PJT-162444)

Title: Complementary yet dissociable influences of medial and lateral orbitofrontal cortex over cue-guided decisions involving reward value and uncertainty

Authors: *P. ZHOU[1], J. D. SCHUMACHER[2], M. VAN HOLSTEIN[2], S. B. FLORESCO[3]; [2]Psychology, [1]Univ. of British Columbia, Vancouver, BC, Canada; [3]Univ. British Columbia, Vancouver, BC, Canada

Abstract: Converging evidence has shown that subregions of the orbitofrontal cortex (OFC) play distinct roles in decision making across a variety of tasks. Real-world cost/benefit decisions often rely on both information from the environment (externally guided) and knowledge from past experience (internally guided). Human studies have implicated both medial and lateral subdivisions of OFC (mOFC, lOFC) in externally and internally guided choice, yet rodent studies have primarily focused internally guided decisions. To address this gap, we examined the contribution of these OFC subregions to cue-guided, probabilistic decision making using a "Blackjack" task. Male rats chose between a certain, 1-pellet small reward and larger, 4-pellet reward delivered with varying probability that was signalled trail-to-trial with explicit auditory stimuli indicating the odds of receiving the larger reward were good (50%) or poor (12.5%).

Inactivation of the mOFC or lOFC induced generalized decreases or increases in large/risky choice, respectively, irrespective of trial odds, that were accompanied by opposite changes in loss (but not win) sensitivity and the likelihood of making consecutive choices of small/certain option. Additional studies examined whether these effects reflected broader impairments in cue processing or reward valuation. A cue-guided reward magnitude task was similar in structure to the Blackjack task, except here, auditory cues signaled which lever would yield a larger, 4-pellet reward, whereas incorrect choices resulted in a smaller, 1-pellet reward. Both mOFC and lOFC inactivation of reduced choice of the more valuable option. However, in a simpler, auditory conditional discrimination task, rats used the auditory cues to select a correct option delivering a deterministic 2-pellet reward, with incorrect choices yielding no reward. Here, mOFC and lOFC inactivation had no effect on performance. These findings demonstrate that the OFC is not required for implementing conditional rules and using discriminative stimuli to guide choices when rewards are delivered deterministically (i.e.; choosing between something vs nothing). However, when all actions are rewarded but vary in magnitude of payoff, the OFC plays a general role in integrating information from external cues to guide actions towards valuable rewards (choosing between something good vs something better). Importantly, when decisions involve probabilistic outcomes and larger rewards may or may not be received, , the mOFC and lOFC exert opposing influences on choice biases and sensitivity to non-rewarded actions to modulate risk-seeking and risk-avoidant behavior.

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Poster

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Shanghai Pilot Program for Basic Research – Chinese Academy of Science, Shanghai Branch Grant No. JCYJ-SHFY-2022-011;

Title: The role of orbitofrontal-striatal pathway in reward-based flexible decision-making

Authors: *H. SHI[1], S. TANG[2], N. XU[3];
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Abstract: Adaptive behavior, which reflects cognitive flexibility, is essential for animal survival and reproduction. Previous studies have implicated both the orbitofrontal cortex (OFC) and the striatum are involved in flexible action selection. Emerging findings also suggested that disruptions in this pathway may underlie cognitive inflexibility observed in disorders such as obsessive-compulsive disorder. However, the causal role and information flow of the OFC-striatum pathway in adaptive behavior remain poorly understood. In this study, we employed a reward-based flexible decision-making task, where mice are required to adapt their choices in response to dynamically changing reward probabilities. Optogenetic inhibition of the OFC-striatum pathway selectively impaired switching behavior in expert mice, suggesting that this pathway is crucial for maintaining flexibility. Furthermore, neural population recordings of OFC axonal activity in the striatum revealed persistent contralateral choice preference modulated by state identity during inter-trial interval, indicating that state-related information may be encoded within the OFC-striatum circuit. These findings highlight a critical role for the OFC-striatum pathway in adaptive decision-making.

Disclosures: H. Shi: None. **S. Tang:** None. **N. Xu:** None.

Poster

PSTR136: Orbitofrontal Cortex

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Program #/Poster #: PSTR136.07/FF4

Topic: I.03. Decision Making

Support: DFG OT562/2-1

Title: Persistent neural tuning dynamics across two decision-making tasks in rat orbitofrontal cortex

Authors: *G. KNOLL[1], A. J. CHRISTENSEN[2], A. KEPECS[3], T. OTT[4];
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Abstract: Decision-making depends on the integration of information from multiple sensory modalities and internal states. Single neurons in the orbitofrontal cortex (OFC) commonly represent critical decision-making variables, such as sensory uncertainty and subjective value. Yet, it remains uncertain whether such neural tuning is unique to specific behavioral settings. We examined the consistency of tuning patterns in the firing rates of OFC neurons across different scenarios—or whether they remain tied to particular contexts—by analyzing chronic Neuropixels recordings from successive sessions in which rats engaged in two related, but distinct, decision-making paradigms. In both tasks, rats discriminated the number of auditory clicks presented to each ear and received a water reward for selecting the side (left or right) with the larger number of clicks. In the first task, reward magnitude varied across blocks of trials, allowing us to assess

how sensory and reward cues were integrated. In the second task, rats invested time to receive randomly delayed rewards, thereby offering a behavioral indication of confidence. Across both tasks, neuronal tuning clustered into consistent categories, including encoding for confidence, time investment, or trial outcome. These categories remained largely stable across tasks, despite differences in timing and task-relevant variables. By tracking identical single units across sessions, we observed that many neurons remained in the same categories. However, some neurons adjusted their tuning profiles between tasks, demonstrating adaptability when previously encoded information became irrelevant. In addition, the single-neuron temporal dynamics were highly preserved across tasks and were often restricted to specific task epochs. These findings imply that OFC neural populations form functional modules with canonical tuning motifs that persist across behavioral contexts, have the capacity for flexible tuning when task demands evolve, and which can be recruited in a compositional manner to support adaptive decision-making.

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Poster

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Program #/Poster #: PSTR136.08/FF5

Topic: I.03. Decision Making

Support: NIH IRP

Title: Alterations in parvalbumin cell distribution patterns within ventrolateral prefrontal cortex area 12 after long standing crossed disconnection lesions of the amygdala and medial prefrontal cortex in macaque monkeys.

Authors: *M. K. BALDWIN[1,2], H. MCARDLE[3,2], J. D. FLORES[4,2], C. LO[3,2], E. A. MURRAY[5,2];
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Abstract: Lesion studies are an essential tool for assessing the contributions of brain regions to behavior and cognition. Lesion studies also provide an opportunity to identify network-related changes associated with brain damage. Understanding the full breadth of changes to the brain can provide valuable insights for therapeutic strategies involving patients with brain damage or disease. Here we assessed changes to area 12 in the ventrolateral prefrontal cortex after long standing lesions (~10 years) of the amygdala and medial prefrontal cortex (mPFC) placed during adulthood. Brains of rhesus monkeys (N=2) that had selective excitotoxic lesions of the amygdala in one hemisphere and aspiration lesions of the mPFC (areas 24 and 32) in the opposite hemisphere were compared with the brains of control monkeys (N=2). Brains were cut

coronally on a freezing microtome at a thickness of 40 microns. Sections were saved in a series of 10 with one series processed for parvalbumin, which is a calcium binding protein found in inhibitory interneurons within the cortex. Another series was processed for Nissl to aid in the delineation of cortical areal borders and layers. The number of positively stained parvalbumin expressing cells (PV+) was assessed in area 12. Relative to controls, monkeys with lesions showed a robust decrease in the quantity of PV+ cells across all layers of area 12 on the side ipsilateral to the amygdala lesion. In some regions this decrease was over 90% in comparison to controls. This reduction in PV+ cells was most pronounced in areas 12o and 12l. A reduction in this population of cells suggests an alteration in neuronal activity within area 12 after longstanding damage to the ipsilateral amygdala and/or contralateral mPFC.

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Poster

PSTR136: Orbitofrontal Cortex

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Program #/Poster #: PSTR136.09/FF6

Topic: I.03. Decision Making

Support: JST CREST JPMJCR24T5
AMED 25wm0625213h0002
KAKENHI 24K22085

Title: Optogenetic manipulation of VTA-OFC circuit underlying imbalance of reward prediction error in risk-return decision-making

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Abstract: Gambling between high risk-high return (HH) and low risk-low return (LL) choices is crucial in many situations in our daily life. Recent study showed optogenetical manipulation of the mesofrontal circuits changed HH or LL preference in primates (Sasaki et al., Science 2024). In this study, we tried to identify how the neural dynamics changed with the risk preference modulation. We hypothesized that asymmetric scaling of positive and negative reward prediction error (RPE) modulated risk preference by biasing neural representation of HH options compared to that of LL options when their expected values are the same. To test whether this hypothesis is followed in the lived brain, we trained macaque monkeys to choose between HH or LL options (HH-LL task). We then optogenetically activated the ventral tegmental area (VTA) input to the specific areas of orbitofrontal cortex (OFC) during decision-making period. This activation led the monkeys' behavior to show a stronger preference for HH options. We next asked where and

how the neural pathway accomplishes these behavioral changes. We recorded single unit activities from VTA and OFC simultaneously along with the OFC photostimulation. We observed that the unit activities were enhanced during the photostimulation in single neuron level in each recorded area. This implies that the neural property (sensitivity) and/or the neural network property (readout weights) might be changed by photostimulation. Thus we first measured the sensitivity for each neuron by computing coefficients of multiple regression for HH-LL and expected value (EV). We found VTA neurons showed the mixed-selectivity and their sensitivity were enhanced to either HHLL or EV axis by the stimulation. To investigate how this single neural modulation affects to the population coding, we next computed the canonical correlation and measured the associations among two sets of variables, coefficients (HHLL/EV) and stimulus conditions (on/off). The sensitivity to HHLL in population was increased with maintaining its correlation to EV, while their readout weights from classification decoding were unchanged. Finally we measured neural modulation to RPE. We found the photostimulation enhanced neural response to positive RPE, as a result imbalance of positive and negative RPE was increased. These findings suggest that the balancing risk-return attitude could be caused by the long term modulation of the neural sensitivity to HHLL in population driven by an increased imbalance of RPE via mesofrontal pathways.

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Poster

PSTR136: Orbitofrontal Cortex

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Topic: I.03. Decision Making

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Title: The role of hippocampus and prefrontal cortex in planning

Authors: *E. SHIN[1], M.-Y. PARK[1], M. OEMISCH[1], H. LIANG[1], B. VAN OPHEUSDEN[2], W. MA[3], D. LEE[1];
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Abstract: To achieve optimal outcomes in a dynamic environment, humans and animals need to plan adaptively. Previous studies have implicated the prefrontal cortex and hippocampus as key regions for complex and sequential planning, but whether and how these areas might interact and contribute uniquely to adaptive planning remains poorly understood. To investigate this, we trained two monkeys on a ‘Four-in-a-Row’ task. Each game began when the computer opponent placed its first stone on a 4 × 9 board shown on a computer screen. The monkey then selected the position of its stone by controlling a joystick to bring its feedback cursor onto an empty position on the same board. This exchange was repeated until either the computer or the monkey placed

four stones in a row (horizontally, vertically, or diagonally). Animals received a juice reward only when they completed the four in a row first. Therefore, they were encouraged to monitor the evolving state of the board and adjust their plans. We recorded the activity of single neurons simultaneously in the hippocampus (HPC) and dorsolateral prefrontal cortex (dlPFC) of one monkey using two 64-channel silicone probes. We used a linear regression model to investigate the frequency and time course of signals related to the choice of each player and the maximum number of stones connected by their latest choices (connection length). We found the signals related to the position of the stone chosen by the animal in both HPC and dlPFC. By contrast, only the neurons in the dlPFC encoded the information about the position of the computer's stone. We also found that neuron in both HPC and dlPFC often modulated their activity according to the connection length of the animal. However, neurons in the dlPFC encoded this information persistently throughout the game, whereas HPC neurons encode the same information more transiently after the computer's choice is revealed. Finally, signals related to the outcome of each game appeared more strongly in the dlPFC than in HPC. These results suggest that dlPFC and HPC might play distinct roles in sequential planning and learning.

Disclosures: E. Shin: None. **M. Park:** None. **M. Oemisch:** None. **H. Liang:** None. **B. Van Opheusden:** None. **W. Ma:** None. **D. Lee:** None.

Poster

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Topic: I.03. Decision Making

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Title: Local field potentials in the prefrontal cortex and hippocampus during adaptive planning

Authors: *N. H. LAM[1], E. SHIN[1], M.-Y. PARK[1], M. OEMISCH[1], H. LIANG[1], B. VAN OPHEUSDEN[2], W. MA[3], D. LEE[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Princeton Univ., Princeton, NJ; [3]New York Univ., New York, NY

Abstract: Adaptive planning often involves mental simulation on the outcomes of sequential choices, and requires adjustment in response to changes in the environment. To study the role of the prefrontal cortex and hippocampus in adaptive planning, we trained two monkeys to play a competitive strategy game (four-in-a-row) against a computer opponent. In each game, the computer first placed its stone on a 4 × 9 board shown on a computer screen. The monkey then selected the position of its stone on any unoccupied site on the board, using a joystick to control the feedback cursor. This exchange continued until either the computer or the monkey placed four stones in a row (horizontally, vertically, or diagonally). Animals were allowed to shift their gaze freely during the task and received a juice reward only when they completed the four-in-a-

row first. We analyzed local field potentials (LFP) recorded simultaneously from the hippocampus (HPC) and the dorsolateral prefrontal cortex (dlPFC), which showed the largest power in the theta (~10 Hz) and beta (~18 Hz) frequency bands, respectively, suggesting these two rhythms might serve as separate channels of communication. To better understand the roles of oscillatory activity during planning, we examined how the LFP power in theta (HPC) and beta (dlPFC) frequency bands at the time of each saccade changed according to the ordinal position of the saccade (relative to the animal's choice) and the maximum number of stones connected by the latest choice of each player (referred to as connection length). We found that the LFP power of the theta-frequency oscillation in HPC decreased with the number of stones on the board, monkey's connection length, and the ordinal position of saccade. Similar changes were observed in the LFP power of the beta-frequency oscillation in the dlPFC. These results suggest that oscillatory activity in the prefrontal cortex and HPC might reflect progress towards a behavioral goal in two distinct communication channels.

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Poster

PSTR136: Orbitofrontal Cortex

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Topic: I.03. Decision Making

Support: Wellcome Trust 224432/Z/21/Z to ACR
Hughes Hall Cambridge Edwin Leong Scholarship

Title: Strategic decision making in response to changes in reward expectation: function and connectivity of lateral orbitofrontal cortex

Authors: *X. ZHANG, S. J. SAWIAK, C. M. WOOD, A. C. ROBERTS;
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Abstract: The negative feelings people can get due to unexpected reward loss relates to the major symptom of sadness and is a core feature of depression. Previous studies have suggested that the lateral orbitofrontal cortex (latOFC) is activated by reward loss or more generally by violations of expectations. Consequently, we determined whether altered activity in primate latOFC contributes to their sensitivity selectively to unexpected reward loss or also unexpected reward gain to assess the selectivity of any effects. Using an approach-avoidance task marmoset monkeys' decision-making behaviour was assessed in response to their receipt of lower or higher amounts of reward to their expectations. In this task, variable interval reward schedules are imposed on two identical stimuli on a touchscreen with weekly probe sessions increasing or decreasing the interval of one of them to determine sensitivity to unexpected reward loss or gain, respectively. The latOFC is cannulated bilaterally to investigate whether inactivation of this

region alters marmoset's strategy during probe sessions. Since latOFC (A47L/M/O) is a large heterogenous area in primates, two pairs of cannulae targeted both the anterior A47M and the posterior A47O to assess possible functional specialisation. Results from 6 marmosets show that latOFC inactivation produces an increase in their sensitivity to both unexpected loss and gain of reward. This was reflected by marmosets showing greater bias away from the response side leading to unexpected reward loss, and towards the response side leading to unexpected reward gain. No difference was seen between animals cannulated in anterior or posterior latOFC. These findings appear inconsistent with human imaging studies implicating activity in this region with enhanced sensitivity to reward loss. Instead they suggest a more general role of latOFC in guiding responding upon violations in expectations. For translation to the human brain we used imaging to identify analogous areas to marmoset latOFC based on imaging connectivity. Building on methods used in macaques which evaluated functional connectivity with a pre-selected set of regions to calculate fingerprints that can be matched across species, our data-driven pipeline eliminates the need for manual region selection, instead identifying target regions based on their discriminative power in parcellating each brain area. Preliminary results identified targets for distinguishing latOFC subregions and comparison of these to structural connectivity show high correspondence.

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Poster

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Topic: I.03. Decision Making

Support: NIH IRP

Title: Alterations in parvalbumin cell distribution patterns within orbital prefrontal cortex area 11 after long standing crossed disconnection lesions of the amygdala and medial prefrontal cortex in macaque monkeys.

Authors: *J. D. FLORES[1], M. K. BALDWIN[2], H. MCARDLE[3], E. A. MURRAY[4];
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Abstract: Lesion studies are an essential tool for assessing the contributions of brain regions to behavior and cognition. Lesion studies also provide an opportunity to identify network-related changes associated with brain damage and could reveal potential targets for therapeutic interventions in patient populations. As part of a larger study to understand the full breadth of changes to the brain following selective lesions, we assessed the distribution of parvalbumin expressing interneurons in area 11 of the orbital prefrontal cortex after long standing lesions of

the amygdala and medial prefrontal cortex (mPFC) placed during adulthood. Brains of rhesus monkeys (*Macaca mulatta*) (N=2) that had selective excitotoxic lesions of the amygdala in one hemisphere and aspiration lesions of the mPFC (areas 24 and 32) in the opposite hemisphere ~10 years earlier were compared with the brains of control monkeys (N=2). Brains were cut coronally on a freezing microtome at a thickness of 40 microns. Sections were saved in a series of 10 with one series processed for parvalbumin, which is a calcium binding protein found in inhibitory interneurons within the cortex. Another series was processed for Nissl to aid in the delineation of cortical areal borders and layers. The number of positively stained parvalbumin expressing cells (PV+) was assessed within area 11. Our preliminary results reveal that, relative to controls, monkeys with lesions showed a decrease in the quantity of PV+ cells of over 30% within area 11 in the hemisphere with the amygdala lesion. Such a reduction in PV+ cells suggests an alteration in neuronal activity in area 11 after longstanding damage to the ipsilateral amygdala and/or contralateral mPFC.

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Poster

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Topic: I.03. Decision Making

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Title: Network Inference Analysis of a Decision Circuit in the Primate Orbitofrontal Cortex

Authors: *Y. KANAZAWA, K. ZHANG, T. G. CRIMMINS, M. KHOSHKHOU, H. L. SCHOKNECHT, G. TAVONI, C. PADOA-SCHIOPPA;
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Abstract: Economic choice entails assigning subjective values to the available options; a decision is then made by comparing values. Lesion and microsimulation studies indicate that these operations rely on the orbitofrontal cortex (OFC). Concurrently, neurophysiology work identified in OFC different groups of neurons representing the input (offer values) and the output (chosen good, chosen value) of the decision process. We hypothesized that these cell groups constitute the building blocks of a circuit in which economic decisions are formed. However, the organization of this decision circuit is poorly understood. To shed light on this fundamental question, we recorded from large populations of cells while monkeys performed a juice choice

task (Padoa-Schioppa and Assad, 2006). We then used network inference analysis (Schneidman et al., 2006; Cocco et al., 2017, Tavoni et al., 2017) to reconstruct the circuit connectivity. Our data set included 85 sessions from 3 animals and 50-150 cells/session (4784 cells total). Each neuron was classified for the encoded variable using standard procedures. For each session, the connectivity network was inferred by fitting an Ising (maximum entropy) model, with a 5 ms bin size. Ising couplings were generally stable over trials and across time windows, and they decreased with the distance between cells. For each neuron and each time bin, we computed the spiking probability predicted from the inferred network and the activity of other cells recorded simultaneously. This prediction vastly outperformed those derived from competing benchmarks. Montecarlo simulations demonstrated that inferred networks have attractor dynamics (see twin abstract by Zhang et al.). Next, averaging across cell pairs and sessions, we computed an effective 9x9 network, where nodes corresponded to variables offer value A+, offer value A-, offer value B+, offer value B-, chosen value+, chosen value-, chosen juice A, chosen juice B, and untuned (where A and B are different juice types, and +/- indicate positive/negative encoding). This effective network is analogous to published decision models (Bogacz et al., 2006; Rustichini and Padoa-Schioppa, 2015), except that its structure is entirely data-driven. Simulation of the effective network confirmed the presence of attractor dynamics.

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Poster

PSTR136: Orbitofrontal Cortex

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Program #/Poster #: PSTR136.15/FF12

Topic: I.03. Decision Making

Title: Dynamics of planning in the macaque orbitofrontal cortex.

Authors: *E. HU, J. D. WALLIS;
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Abstract: The best choices that we make often don’t yield immediate gratification but instead set us up to do well in the future. Therefore, when we make decisions, we must evaluate how good each potential action is in the long run. Simple learning algorithms evaluate the future based on the past, by looking backwards in time to recent actions and increasing the value associated with actions that led to a reward. However, humans and animals can make decisions in novel environments or contexts. We can imagine the consequences of actions, even if we have never performed those exact actions before. This mental simulation allows us to formulate plans, so that we can prospectively estimate the value associated with different actions. The orbitofrontal cortex (OFC) is necessary for flexible decision-making and may play a critical role in planning. Lesions to the OFC and nearby medial prefrontal areas impairs performance in goal-directed behaviors (Gallagher et al 1999, Camille et al 2011), and single neurons in the OFC

represent variables necessary for planning, dynamically tracking value of available options as they are considered (Hunt et al., 2018; McGinty and Lumpkin, 2023). The goal of this study is to describe how flexible valuation processes in OFC support planning behavior. We recorded the activity of OFC neurons from two macaques while they performed a multi-step navigation task. The subjects solved the task by performing a series of actions to navigate from a starting node on a 2-dimensional 4x4 grid to a goal node. Both subjects naturally interleaved action sequences with planning behaviors, during which they attended to locations that they intend to reach in the future. We find that the OFC tracks these behaviors, alternating between two distinct neural states for actions and plans. Furthermore, the OFC population encodes value during planning and choice on orthogonal axes in the neural state space.

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Poster

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Title: Neural dynamics of updating taste reward expectations

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Abstract: Expectations of reward play a critical role in cognition and decision-making, allowing us to predict the outcomes of certain actions, and influencing which actions we take. Expectations also inform how we interpret sensory input. However, when our expectations are wrong, the ability to flexibly shift our behavior in response to unanticipated circumstances is critical for our well-being. For example, recognizing that the milk in the fridge that you thought was still good has actually spoiled protects you from an unfortunate episode of food poisoning. In order to better understand the neural dynamics involved in these processes, we recorded neurons from the orbitofrontal cortex and the gustatory cortex while monkeys performed a task in which different image cues predicted the taste of a fluid bolus (from sweet to bitter). Each trial could be either forced-choice (where only one image was presented for selection) or free-choice (where a choice between two images was presented). In order to select an image, the monkey was required to fixate the image and release a touch-sensitive bar, which was followed by an initial bolus of fluid. Following image selection, there was a four-second period during which the

monkey could tap the touch-sensitive bar to receive additional small deliveries of the same fluid. Monkeys consistently chose sweeter options, and tapped more for them. Once associations were well established, a small percentage of trials became “mismatch” trials, in which the fluid delivered did not match the cue image. On these trials, tapping behavior initially reflected the expected outcome, but shifted over the four-second window in accordance with the actual fluid received. Preliminary data from chronic electrophysiological recordings suggest that the activity of the orbitofrontal cortex is flexibly modulated by expectations of taste. Simultaneous recordings from the orbitofrontal cortex and the gustatory cortex will allow us to further probe the neural dynamics of expectation in taste perception and behavior.

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Poster

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Title: Distinct Value & Choice Information Across Putative Subtypes of Primate Orbitofrontal Neurons

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Abstract: The primate orbitofrontal cortex (OFC) plays a key role in economic decision-making by encoding economic value and other decision-related variables, but how these computations emerge from the underlying microcircuitry is unknown. It has been proposed that different subtypes of OFC neurons may have distinct encoding properties corresponding to specific decision functions. For example, in rodents, inhibitory interneurons exhibit choice selectivity, consistent with a mutual inhibition mechanism (Najafi et al., 2020). However, in primates, there is little evidence for differentiation in neuronal subtypes. In this study, we addressed this knowledge gap by identifying putative neuron subtypes in primate OFC and analyzing their coding properties during decision-making.We recorded from the OFC of two monkeys performing a two-alternative value-based decision-making task. In this task, monkeys used self-directed eye movements to view two stimuli (on the left and right side of a display) and then indicated their choice by pressing the left or right lever. We assessed the neural encoding of three task variables: the values of the stimuli (value), the monkey’s gaze location when viewing the

stimuli (spatial attention), and whether the left or right stimulus was chosen (chosen action). We then compared the encoding across different neuronal subtypes classified using their extracellular waveform (Lee et al., 2021).We identified broad- and narrow-spiking neurons corresponding to putative excitatory and inhibitory neurons, respectively. These subtypes of neurons exhibited distinct task-related coding patterns when compared to the population average. For example, one narrow-spiking subtype showed strong spatial attention encoding but weak value encoding and a rapid increase in chosen action encoding around the moment of choice. In contrast, a broad-spiking subtype closely resembled the average encoding profile across all neurons yet had reliable, choice-predictive signals that were not present in the population average.This study demonstrates subtype-specific encoding of value and choice signals in primate OFC, suggesting distinct computational roles for excitatory and inhibitory neurons. While further evidence is necessary, these findings suggest a functional dissociation in which OFC excitatory neurons mainly drive value encoding, while inhibitory interneurons modulate this value encoding based on spatial attention. Future work will examine population-level dynamics and potential circuit mechanisms across these subtypes.

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Poster

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Title: Attractor Dynamics in the Orbitofrontal Cortex Underlie Economic Decisions

Authors: *K. ZHANG, Y. KANAZAWA, T. CRIMMINS, C. PADOA-SCHIOPPA, G. TAVONI;
Dept. of Neurosci., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Economic choice entails computing and comparing the subjective values of two options. An established literature links these operations to the orbitofrontal cortex (OFC). In particular, neurophysiology studies identified in OFC neurons that preferentially encode individual offer values, the binary choice outcome (chosen good), and the chosen value. These variables capture both the input and the output of the decision process (Padoa-Schioppa and Conen, 2017). However, the circuit organization and the decision mechanisms remain unclear.

To address these questions, we combined (1) large-scale recordings of neuronal populations, (2) network inference analyses (Schneidman et al., 2006; Cocco et al., 2017), and (3) theoretical analyses focused on the circuit dynamics. Simultaneous recordings of 50-150 cells were conducted in 3 monkeys performing a juice choice task (Padoa-Schioppa and Assad, 2006). For each of 85 sessions, we inferred an Ising model (a.k.a. Hopfield model) using Adaptive Cluster Expansion (Barton et al., 2016; Tavoni et al., 2017) (see twin abstract by Kanazawa et al.). We then simulated the inferred network using various localized external inputs to represent different offers. In these simulations, we computed each neuron's susceptibility to the external stimulation (Tavoni et al., 2016). Coincident susceptibility peaks indicated the presence of attractor (avalanche) dynamics - i.e., multiple neurons co-activating in response to stimulation due to reciprocal interactions. We report the following results. (1) Stimulating offer value cells associated with one particular good (A or B) induced avalanche dynamics leading to the co-activation of other cell groups. Co-activated cells predominantly encoded the corresponding choice outcome (A or B). (2) Compared to randomly generated networks, inferred Ising networks exhibited stronger avalanche effects and a greater bias toward choosing the higher-value offer. (3) Avalanches, which reflected the circuit's transformation of offer values into a binary choice, arose primarily through direct couplings between offer value cells and chosen good cells associated with the same good, and to a lesser extent via indirect connections involving other cells. These results shed light on the input-output transformation performed by OFC and suggest that this area functions as an attractor network. In ongoing work, we conduct "lesion experiments" on the inferred networks to precisely identify the connections involved in this computation and to determine the timescale over which avalanches materialize.

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Poster

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Title: Mixed-selective, distributed coding in orbitofrontal cortex supports optimal value-based decisions

Authors: *T. CRIMMINS, Y. KANAZAWA, G. TAVONI, C. PADOA-SCHIOPPA; Neurosci., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Orbitofrontal cortex (OFC) is causally involved in the computation and comparison of subjective values underlying economic choices (Ballesta et al., 2020; Ballesta et al., 2022). Both the values of good offers and the chosen good are represented by neurons in this area. However, it remains unclear if and how tuning functions in OFC and the circuit organization are optimal for choice. Previous research focused on network models with categorically tuned cells in which only a subset of recorded neurons and their connections participate in the decision. In particular, one study proposed that the representation of offer values is optimal if it leads to maximizing the expected payoff (Rustichini et al., 2017). In the framework of a simple decision model, this normative principle successfully predicted certain tuning properties of neurons in OFC. However, the model also made specific predictions about the strength of aggregate synaptic connections between cells encoding the offer value and other groups of neurons - predictions that we found to be inconsistent with connectivity estimates inferred from neural data (see abstract by Kanazawa et al.). Here we propose an alternative approach, where neuronal tuning functions and interaction couplings are fitted at the same time. This network model also operates under a maximum-payoff normative principle, but relaxes the assumption of categorical tuning. Cells possess tuning weights for multiple decision variables and linearly integrate external offer-value inputs with internal responses from across the network. The tuning weights and pairwise interaction parameters for each cell are fitted to neural data from neurophysiological recordings in macaques performing a juice choice task. In each trial, a choice and its associated payoff are computed from a weighted average of cell responses across the entire network. Each cell's response is weighted by the strength (positive or negative) of its tuning for one choice versus the other. We found that networks fitted to neural data are near-optimal, as they achieve close-to-maximum payoff. Within this new framework, we also derived a payoff-maximizing, normative prediction linking neurons' pairwise interactions to their tuning weights. Parameters fitted to neuronal data show significant alignment with this prediction. Furthermore, both key features of our model - i.e., the cells' mixed selectivity and the distributed encoding of choices across the network - are necessary to predict the neural data. These results indicate that these features work in tandem to maximize expected payoff during economic choices.

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Poster

PSTR136: Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR136.20/GG5

Topic: I.03. Decision Making

Support: NIH IRP

Title: Alterations in parvalbumin cell distribution patterns within the amygdala after long standing crossed disconnection lesions of the amygdala and medial prefrontal cortex in macaque monkeys

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Abstract: Lesion studies are an essential tool for assessing the contributions of brain regions to behavior and cognition. Lesion studies also provide an opportunity to identify network-related changes associated with brain damage. Understanding the full breadth of changes to the brain can provide valuable insights for therapeutic strategies involving patients with brain damage or disease. Here we assessed changes to the amygdala in rhesus monkeys (*Macaca mulatta*) that had sustained crossed disconnection lesions of the amygdala and medial prefrontal cortex as adults ~10 years earlier. Specifically, we assessed changes in the distribution of parvalbumin positive (PV+) cells in the amygdala in hemispheres with aspiration lesions of the medial prefrontal cortex (areas 24 and 32) and contralateral to hemispheres with excitotoxic lesions of the amygdala. Lesioned brains (N=2) were compared to neurologic controls (N=2). Each brain was cut coronally on a freezing microtome at a thickness of 40 microns. Sections were saved in a series of 10 with one series processed for parvalbumin, which is a calcium binding protein found in inhibitory interneurons within the amygdala. A second series was processed for Nissl, which was used to reveal borders of nuclei within the amygdala. Total numbers of PV+ cells within the lateral (LA), basal (magnocellular (Bm), intermediate (Bi), and parvocellular (Bp) divisions), and accessory basal (AB) nuclei of the amygdala were determined across all PV-stained sections through the amygdala. We determined cell numbers using both manual counts and computer assisted cell identification strategies. Consistent results were obtained across the two methods. Our preliminary data found that the total number of PV+ cells in the amygdala of monkeys with lesions is decreased relative to controls, with a drop of over 25%. The distribution of PV+ cells across the different nuclei between lesion animals and controls also differed. For instance, relative to controls, the percentages of PV+ cells within the basal amygdala and parvocellular division of the basal nucleus relative to the whole amygdala decreased in lesion animals, while the percentages of PV+ cells within the magnocellular and intermediate divisions of the amygdala increased. Overall, our results indicate that lesions of the medial prefrontal cortex and/or contralateral amygdala have a marked influence on PV+ cell populations within the amygdala.

Disclosures: C. Lo: None. **M.K. Baldwin:** None. **S. Williams:** None. **H. McArdle:** None. **J.D. Flores:** None. **E.A. Murray:** None.

Poster

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Program #/Poster #: PSTR136.21/GG6

Topic: I.03. Decision Making

Support: NIH grant K01-DA-036659-01
Whitehall Foundation Fellowship

Title: Value-related working memory signals during economic decisions in macaque OFC

Authors: *D. SHARMA[1], S. LUPKIN[2], V. B. MCGINTY[3];
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Abstract: When deciding between two items, we are sometimes required to consider each item sequentially. To choose optimally in these settings requires working memory (WM) — remembering the value of one item while considering the other. While much research has examined how physical stimulus features such as color or shape are maintained in WM, less is known about how non-physical information, like stimulus value, is sustained during the decision processes. One area that may be important for value WM is the orbitofrontal cortex (OFC), a prefrontal region with a critical role in representing value signals in decision-making. We recently found that gamma-range local field potentials (LFPs) in OFC are strongly modulated by the remembered value of a decision item in a sequential decision-making task. Such band-limited LFP signals are key features of an attractor-based WM model proposed by Lundqvist et al. (2011). Therefore, we asked whether the neural mechanisms underlying value maintenance in sequential decisions align with predictions from this WM model. We recorded OFC spiking and LFP activity in monkeys performing a decision-making task involving the sequential viewing of two stimuli. We found several features of the LFPs consistent with the WM model: Following the viewing of the decision stimuli, beta (10-30 Hz) and gamma (50-150 Hz) power were inversely related over time—gamma activity increased during active encoding and decreased during silent, non-encoding epochs, while beta showed the reverse pattern. At the single-trial level, gamma manifested as brief, band-limited "bursts" (60 ms duration and 28 Hz band width on average), and spikes at gamma-modulated sites were more likely to encode target values, consistent with the model predictions. However, we also found LFP patterns that defied the model's predictions. In particular, the model predicts that gamma power should increase as items are added to WM. In contrast, we found a decrease in gamma power after viewing the second stimulus. Interestingly, we also found that gamma power increases with task difficulty (defined based on the value of the first-viewed stimulus); this indicates that factors other than the number of WM items influence gamma dynamics during decision-making. In summary, our finding suggests that while attractor-based WM mechanisms may be conserved across different prefrontal circuits, further refinement is needed to extend the model's applicability to various WM types involved in different cognitive abilities, such as decision making.

Disclosures: D. Sharma: None. **S. Lupkin:** None. **V.B. McGinty:** None.

Poster

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Program #/Poster #: PSTR136.22/GG7

Topic: I.03. Decision Making

Support: ZIA DA000642

Title: Expected Outcome Representations in Orbitofrontal Cortex Drive Goal-Directed Actions

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Abstract: A critical aspect of cognition is the ability to pursue specific goals and map them to the actions which can bring them about. However, little is known about the neural mechanisms which connect goal representations in the brain to specific causal actions. We address this gap using functional neuroimaging and a novel behavioral task which isolates neural activity induced by goal-pursuit for specific rewards. We trained hungry human participants (N=20) to associate visual cues with specific rewards (desirable food odors) via Pavlovian conditioning. Participants then learned how to obtain the same rewards in an instrumental foraging game, in which they sought to maximize the number of collected rewards. During the test session participants played the foraging game, but were unexpectedly presented with Pavlovian cues at the beginning of each trial. Behavioral responses showed a preference to pursue food odors matching those predicted by the Pavlovian cues ($p<0.001$) and that these rewards were foraged more vigorously ($p<0.01$). Critically, the strength of cue-induced reward expectations in orbitofrontal cortex (OFC) predicted which reward the participants chose to pursue and correlated with the strength of the corresponding action representations in motor cortex. These results directly link specific reward expectations in the OFC to instrumental actions, advancing our understanding of how prefrontal cortex transforms goal representations into selection of appropriate behaviors.

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Poster

PSTR136: Orbitofrontal Cortex

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Topic: I.03. Decision Making

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University of Central Florida College of Medicine FIRE Fund

Title: Visualizing the Effect of Adverse Childhood Experiences (ACEs) on Ambiguous Decision Making using fNIRS

Authors: *S. TUN[1], S. SOARES[2], N. R. LIGHTHALL[2];
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Abstract: Introduction:
Adverse Childhood Experiences (ACEs) encompass abuse, neglect, and trauma before age 17, disrupting brain development and increasing the risk of psychiatric disorders such as PTSD, substance use, and depression. Neuroimaging studies highlight the prefrontal cortex (PFC) as critical for decision-making under uncertainty. This study hypothesizes that ACE exposure alters PFC activation patterns, leading to changes in neuromodulation during decision-making.
Methods:
Forty-five participants (ages 18-21) completed an ACE survey and a card-deck gambling task involving ambiguous (unknown probabilities) and risky (known probabilities) decisions. Functional near-infrared spectroscopy (fNIRS) measured cortical activity, with oxyhemoglobin (HbO) as a proxy for neural activation. Data preprocessing and first-level analyses were conducted using the SPM for fNIRS toolbox. Group-level multiple regression analyses included ACE exposure, sex, and handedness as predictors, with cluster thresholds determined using AFNI's 3dClustSim ($p<0.05$, $\alpha=0.05$).
Results:
Significant activation clusters in the right PFC were observed during ambiguous decision-making vs risky decision-making, correlating with ACE exposure ($T(41) = 2.12$, partial $R^2 = 0.125$). No significant activation was found during rest or risky decision-making, suggesting unique engagement of PFC pathways in ambiguity-related decision making.
Conclusions:
This study highlights right PFC hyperactivation during ambiguity as a potential neural marker of early life trauma. The right PFC plays a critical role in controlling impulsive behaviors, evaluating risks and rewards, and facilitating rational decision-making under uncertainty, which may be disrupted in individuals exposed to ACEs. These findings contribute to understanding the neuropathology of childhood trauma and may guide future research directions in exploring its long-term effects on brain function and behavior.

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Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

Location: SDCC Halls B-H

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Program #/Poster #: PSTR137.01/GG8

Topic: I.04. Executive Functions

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Freedom Together Foundation
The Picower Institute for Learning and Memory

Title: Oscillatory Control of Cortical Space as a Computational Dimension

Authors: *Z. CHEN[1], S. L. BRINCAT[2], E. K. MILLER[2];
[2]The Picower Inst. for Learning and Memory, [1]MIT, Cambridge, MA

Abstract: Flexible cognition depends on the ability to represent and apply context, allowing the brain to interpret sensory input and guide behavior in a context-dependent manner. Recent work has proposed Spatial Computing as a mechanism for this flexibility. It suggests that top-down control signals reflecting context are conveyed via spatial patterns of alpha/beta oscillations across the cortical surface. These act as "inhibitory stencils" that constrain where information (the "content" of cognition) can be expressed in spiking activity. Here, we provide a comprehensive empirical test of Spatial Computing Theory using multi-electrode recordings from the lateral prefrontal cortex in non-human primates performing a range of cognitive tasks (object working memory, sequency working memory, categorization). We found that alpha/beta oscillations encoded contextual information, reorganized their spatial patterns with contexts and task demands, and spatially gated the expression of content-related spiking activity. Furthermore, we found that alpha/beta oscillations reflected misattributions of task context and correlated with subjects' trial-by-trial decisions. These findings validate core predictions of Spatial Computing by showing that oscillatory dynamics not only gate information in time, but also spatially shape where in the cortex cognitive content is represented. This framework offers a unifying principle for understanding how the brain flexibly coordinates cognition through structured population dynamics.

Disclosures: Z. Chen: None. **S.L. Brincat:** None. **E.K. Miller:** None.

Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Topic: I.04. Executive Functions

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The JPB Foundation

Title: Coordinated cross-hemisphere active and inactive states in working memory

Authors: *T. BATABYAL[1], S. L. BRINCAT[2], E. K. MILLER[3];
[2]Picower Inst., [3]The Picower Inst. for Learning and Memory, [1]MIT, Cambridge, MA

Abstract: Working memory was traditionally thought to rely on persistent spiking, but recent evidence suggests information is maintained by intermittent bursts of activity. Here we show evidence that, on individual trials, working memory-related spiking activity alternates between

active and inactive states. The state statistics change over time and with disruption, and states are coordinated across both hemispheres of lateral prefrontal cortex (PFC). We examined spiking activity in both PFC hemispheres of non-human primates performing a working memory task with a disruption during the memory delay period, caused by an instructed saccade. We used a linear classifier to decode the information held in working memory at each time point through each trial. Within individual trials, classifier posterior probability alternated over time between high-confidence ("On") and low-confidence ("Off") states. This was best accounted for by a two-state mixture model, confirming the binary structure of activity during working memory. The dynamics of On and Off states changed dynamically through the memory delay period and with disruption. Over the course of the delay period, average duration of, and spike rate within, On states decreased, while both increased for Off states. Alignment of On states between PFC hemispheres and subregions (ventrolateral and dorsolateral) initially was below chance levels during the sample presentation and early delay. Toward the end of the delay, these became more aligned than expected by chance, suggesting large-scale coordination of neural activity. Disruption appeared to enhance both the state duration and coordination effects. Post-disruption On/Off state statistics correlated with behavioral performance. Average On state (but not Off state) duration was decreased in error trials. This was also reflected in decreased decoding accuracy. This suggests that errors might relate to a failure to activate active memory states. These results suggest that successful working memory maintenance relies on On/Off states whose temporal and spatial structure dynamically changes over the course of memory maintenance.

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Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Title: Similar destabilization of neural dynamics under different general anesthetics

Authors: *A. J. EISEN[1], A. BARDON[1], J. J. BALLESTEROS[6], A. BASTOS[7], J. A. DONOGHUE[8], M. K. MAHNKE[1], S. L. BRINCAT[2], J. E. ROY[3], Y. ISHIZAWA[9], E. N. BROWN[10], I. R. FIETE[4], E. K. MILLER[5];

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Abstract: Different classes of anesthetics can induce unconsciousness despite acting through distinct biological mechanisms. This raises the possibility that they produce common effects that emerge at the level of neural dynamics—how brain states evolve over time. To explore this, we analyzed intracortical electrophysiology during infusions of propofol, ketamine, and dexmedetomidine, using a rigorous method to estimate dynamical stability. We found that all three anesthetics similarly destabilize cortical dynamics, despite their molecular differences. This destabilization matched the slower recovery from sensory perturbations and longer stimulus-induced autocorrelation times observed during the anesthetic infusions. The destabilization was also reflected predominantly in lower-frequency ranges, linking it to the well-known increase in low-frequency power during anesthesia. Finally, destabilization closely tracked real-time fluctuations in consciousness. Together, these findings suggest that cortical destabilization may be a shared neural correlate of anesthetic-induced unconsciousness, offering a mechanistic explanation for low-frequency oscillations observed during anesthesia.

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Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Program #/Poster #: PSTR137.04/GG11

Topic: I.04. Executive Functions

Support: EY012135

Title: Dynamic timescales of neural fluctuations across tasks in the prefrontal cortex

Authors: *J. PARK, L. H. SNYDER;
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Abstract: Neuronal activity in many brain regions may differ depending on the task being performed. This is easily explained when tasks involve different stimuli or responses. However, in some regions, differences persist even when the stimuli and responses are held constant and

only the task changes (Mirabella et al. 2007; Mante et al. 2013). For example, we and others have observed that baseline activity in the prefrontal cortex (PFC) is modulated even before trial onset, when no stimulus has been shown and no specific response can be planned (Warden & Miller 2010; Park et al. 2025). We hypothesized that this baseline activity modulation may indicate that neuronal circuits reconfigure their dynamical properties in preparation for specific tasks. This reconfiguration of neural dynamics might help implement task set (Sakai 2008). To test such a dynamical reconfiguration, we asked whether task context might modulate the intrinsic timescale of PFC activity prior to trial onset (Murray et al. 2014). We predicted that the intrinsic timescale might scale with the short-term memory load of a task (c.f. Roman et al. 2021). An alternative prediction is that the timescale might scale with the requirement to access long-term memory. To test these predictions, we trained two rhesus monkeys on four different tasks: a memory-guided saccade task, two non-match-to-sample tasks, and a cue-target association task. The memory task required "recall" of one target; the non-match tasks required "recognition" of two targets; and the association task required retrieval of a long-term association with no short-term memory component. We recorded the spiking activity of 596 visually responsive PFC neurons as one monkey performed interleaved 16-trial blocks of each task. We estimated the timescale of neural fluctuations as the time constant of an exponential fit to the autocorrelation of activity during the initial fixations. The overall timescale was 197 ms, close to the previously reported range of 127-195 ms (Murray et al. 2014). When split up by task, the timescale was longest for memory (292 ms), shorter for non-match (230 and 232 ms), and shortest for association (191 ms). The difference was significant between memory and association. Timescales were slightly shorter (21 ms) on failure compared to success trials, but not significantly. No systematic difference was found between frontal eye field and dorsolateral PFC. Our preliminary findings suggest that the intrinsic timescales of PFC neurons may vary depending on the task being performed (increasing with short-term memory demands) and support the idea that neural connectivity may be dynamically reconfigured to prepare for an upcoming task.

Disclosures: J. Park: None. **L.H. Snyder:** None.

Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Topic: I.04. Executive Functions

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Title: Functional roles of neural circuits linking monkey prefrontal cortex and mediodorsal thalamus in cognitive flexibility

Authors: *K. OYAMA[1], Y. NAGAI[2], Y. HORI[2], Y. HORI[2], H. IWAOKI[2], T. HIRABAYASHI[2], J. HIROKAWA[2], T. BANNO[2], K.-I. INOUE[3], M. TAKADA[3], M. HIGUCHI[2], T. MINAMIMOTO[2];
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Abstract: Animals must flexibly adapt to novel environments and optimize their behavior in a dynamically changing world. The prefrontal cortex (PFC) and the mediodorsal thalamus (MD) are known to support such adaptive behavior through their reciprocal connectivity and via the PFC-basal ganglia-thalamus-PFC loop. However, the specific contribution of these circuits to cognitive flexibility in primates remain unclear. To address this, we performed large-scale neuronal recordings using Neuropixels probes in a macaque monkey engaged in a modified version of the Wisconsin Card Sorting Test (WCST). Recordings targeted the dorsolateral PFC (dlPFC), along with two of its major projection sites: the parvocellular nucleus of the mediodorsal thalamus (MDpc) and the head of the dorsal caudate nucleus (dCDh). In the WCST, the monkey was required to adapt to flexible switch between rules (based on the color or shape of a sample stimulus) and maintain the current rule to categorize subsequent stimuli, providing a robust measure of behavioral flexibility. We found that neuronal population across all three regions encoded various task-related information, including the current rule, with particularly strong rule representation observed in MD neurons. To examine the causal roles, we employed multiplexed chemogenetic manipulations. Inhibitory Designer Receptors Exclusively Activated by Designer Drugs (hM4Di) and Pharmacologically Selective Actuator Modules (PSAM4-GlyR) were virally expressed in the dlPFC and MDpc, and neural activity was reversibly silenced via systemic administration of their respective agonists, deschloroclozapine and uPSEM817. Silencing the dlPFC significantly impaired WCST performance immediately after rule switches—when adaptation to a new rule was required—and concurrently reduced rule-related signals in MDpc neurons, but not in dCDh. In contrast, silencing the MDpc impaired performance during rule maintenance (i.e., after successful rule acquisition), without affecting rule representations in either dCDh or dlPFC. These findings demonstrate distinct yet complementary roles for the dlPFC and MDpc in supporting rule-based flexible behavior. Especially, they underscore the importance of direct projections dlPFC-MD projections as a key neural substrate for cognitive flexibility in primates.

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Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.06/GG13

Topic: I.04. Executive Functions

Support: R01-MH137085

Title: Proactive and reactive control mechanisms in non-human primates performing stop-signal and self-control tasks

Authors: J. G. ELSEY[1], ***V. STUPHORN**[2];
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Abstract: In daily life, we often encounter situations that require behavioral flexibility. Adaptive behavior hinges upon a balance of proactively anticipating the upcoming task at hand and reactively adjusting behavior in response to abrupt change. Proactive control is used to select and maintain task-relevant information to optimally shape goal-directed perceptual and actionable behavior. Reactive control is a late-correction mechanism used to rapidly detect new task-related information and adjust behavior appropriately on-the-fly. To better understand the generalizability of these mechanisms in the brain, we utilized stop-signal and self-control tasks that evoke both proactive and reactive forms of control. Response inhibition is the ability to deliberately stop a prepared motor response. Self-control is the ability to inhibit self-defeating behavior in the face of temptation. Prior studies in humans have identified several regions in prefrontal cortex that are active during response inhibition and self-control tasks, however it is unknown whether the proactive and reactive control mechanisms that determine the success or failure of response inhibition or self-control are shared or distinct. To address this, we recorded single-unit neurons using linear vector arrays (194 acute penetrations) from the Frontal Eye Field (FEF: n = 476), Supplementary Eye Field (SEF: n = 529), Dorsolateral Prefrontal Cortex (DLPFC: n = 752), and Ventrolateral Prefrontal Cortex (VLPFC: n = 317). We trained two macaque monkeys to perform saccade stop-signal (countermanding) and self-control tasks that were presented in a block-wise fashion. Both tasks provide specific criteria within discrete epochs that neural activity must satisfy to be causally linked to either mechanism of behavioral control. Using a Poisson GLM modeling approach, task-invariant proactive control signals biasing performance were found in all four regions. Specifically, subsets of neurons in all four regions encoded the likelihood of successful motor inhibition in the stop-signal task and successful commitment to the initial choice in the face of suboptimal temptation in the self-control task. Reactive control signals sufficient for inhibiting a planned saccade to the target (stop-signal task) or temptation cue (self-control task) were only found in FEF. In summary, we find that motor-related activity in prefrontal regions can be modulated by the animal's level of self-control, suggesting that motor and motivational control may share a common neural circuit.

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Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Topic: I.04. Executive Functions

Support: R01MH129641

Title: Cognitive Engagement Changes Co-Modulation of Glutamate, GABA, Acetylcholine, and Dopamine in Prefrontal Cortex and Striatum

Authors: *S. SHEHREEN[1], S.-A. HASSANI[4], S. LENDOR[5], A. NEUMANN[2], J. PAWLISZYN[6], T. WOMELSDORF[3];
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Abstract: Dopaminergic (DA) and acetylcholinergic (ACh) neuromodulation gate circuit functions in the prefrontal cortex (PFC) and the striatum, supporting cognitive control and learning functions. Studies in rodents suggest that DA and ACh actions influence each other and dependent on the local excitatory and inhibitory tone. But how DA and ACh co-modulate and relate to the levels of glutamate and GABA during cognition has remained elusive. Understanding how the neurochemical profiles in PFC and striatum support cognition and adaptive behavior is of highest clinical importance. Here, we tested how the concentrations of neurochemicals change within the PFC and striatum when nonhuman primates (NHPs) engage in a cognitively demanding set-shifting task. We sampled the extracellular concentrations of multiple chemicals simultaneously with 200 um wide fibers optimized for Solid-Phase Microextraction (SPME) of glutamate (Glu), GABA, ACh, choline (Ch), DA, and serotonin (5-HT) within 20min time windows. SPME device structure, coating chemistry and sampling procedures were developed during the project. Samples were taken while NHPs were either at rest or engaged in a set-shifting task that required learning which of multiple features shown across three objects was the designated rewarded target feature in blocks of ~35 trials. The task involved trial-and-error reinforcement learning and feature-based attention to engage the prefrontal-striatal network. We found that neurotransmitter concentrations of Glu, GABA, ACh/Ch and 5-HT (in PFC) and Glu, GABA, ACh/Ch, DA and 5-HT (in striatum) were reliably sampled in both, rest and task states. While individual neurochemical concentrations showed subtle variations between rest and task state, prominent changes were evident in their co-modulation. In the PFC, when NHPs engaged in the task compared to rest, the positive correlations of Glu with GABA, ACh/Ch and 5-HT were reduced and GABA levels de-correlated with ACh levels. In the striatum, the opposite pattern was observed with the task- versus rest- state increasing the correlation of Glu with DA and GABA. These findings were similarly evident in two animals. Taken together, these findings show that SPME micro-fibers allow quantifying neurochemical profiles of task-engaged states in the PFC and striatum of NHP. In PFC, the results suggest that extracellular Glu is depleted when ACh and GABA levels rise during active states, while in the striatum, task engagement may increase Glu activation of GABAergic neurons and concomitant DA release. These scenarios illustrate the versatility of SPME to measure neurochemical profiles of active cognitive states in the NHP.

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Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Carney Institute for Brain Science Innovation Award (T.M.D.)

Title: Homologous human and macaque monkey prefrontal regions subserving abstract sequence monitoring identified via cross-species fMRI correlation

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Abstract: When turning left at a Baltimore stoplight, after the light turns red, two vehicles will run the red light before you should turn. Because this rule applies to any two “vehicles” (e.g., car, van, dirt-bike), this sequence is governed by an abstract rule. Monitoring abstract sequences is critical to navigating complex environments, but how the brain supports this executive function across species is unclear. Previous studies in humans indicate that the rostrolateral prefrontal cortex (RLPFC) is necessary for performing abstract sequences and is typically engaged with a BOLD dynamic where activity increases (ramps) over the course of each sequence. FMRI in rhesus macaque monkeys recently identified a dorsolateral prefrontal cortex region (area 46) sensitive to abstract rules when monitoring visual sequences during a no-report task that also shows ramping dynamics and is potentially homologous to human RLPFC. The same no-report abstract sequence monitoring task was conducted in humans during fMRI to directly correlate monkey and human BOLD responses. Participants (monkey $n = 3$; human $n = 28$) fixated during a series of fractal images comprising “habituation” sequences of four images following an abstract rule (e.g., same-same-same-different) and “deviant” sequences that differed from the habituated. Correlations across species were performed with t values from general linear models. Monkey-to-human correlations of onset t values revealed that monkey area 46 significantly correlated with the human right dorsolateral prefrontal cortex (DLPFC, Brodmann area, BA 9), an area that also responds to changes in abstract rules in humans. Monkey-to-human correlations of ramping t values showed that monkey left area 46 was significantly correlated with the human left RLPFC (BA 10). In humans in this no-report task, ramping activation during

deviants was localized to a cluster on the border of posterior RLPFC and anterior DLPFC. Human-to-monkey correlations showed that this region correlated with monkey left area 46 with ramping dynamics and with monkey right area 46 with onset dynamics. These findings are consistent with prior research correlating macaque and human frontal cortices using resting state fMRI and diffusion weighted imaging, and they contribute to a growing literature implicating homologous lateral prefrontal cortex and BOLD ramping dynamics in abstract sequence monitoring across species.

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Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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NIH-NIGMS Grant COBRE P20GM103645 (T.M.D)

Title: Differentiating medial and lateral frontal cortex contributions to no-report visual abstract sequence tracking in humans

Authors: *M. V. RIVERA NÚÑEZ[1], H. DOYLE[1], B. W. STEWART[1], D. BASU[3], T. M. DESROCHERS[2];
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Abstract: When taking a taxi home, you may internally track house, house, house, store (same, same, same, different building) until you arrive at your building. Such sequences are considered “abstract” because they follow stimulus-independent structural rules (e.g., AAAB) and are not governed by motor actions. Comparative evidence across species implicates both lateral and medial prefrontal cortices (e.g., inferior frontal gyrus (IFG) and medial prefrontal cortex) as key hubs in the general monitoring of abstract sequence deviations (e.g., detecting ‘AAAA’ when ‘AAAB’ is expected). Further, previous work from our lab has identified the rostrolateral prefrontal cortex (RLPFC) as necessary for tracking non-motor sequential information, characterized by ramping activity as sequences unfold. While these findings highlight the role of the RLPFC in monitoring the progression of abstract sequences, how this process interacts with the broader prefrontal network—particularly in the absence of overt behavioral responses—remains unclear. To address this gap, we acquired BOLD fMRI data from 28 human participants engaged in a no-report abstract sequence monitoring task. Participants viewed a series of fractal images arranged into four-item abstract sequences and rare “deviants” from those sequences. Areas of increased activation to deviant sequences were highly similar to those found in a

previous auditory version of the task from another group and to responses in monkeys, suggesting these responses may be modality-general across species. Specifically, human frontal cortex onset responses to sequence deviants, regardless of the type of deviant, localized to both medial and lateral regions: superior frontal gyrus/pre-supplementary motor area (pre-SMA), precentral gyrus, middle and inferior frontal gyri. In contrast, when assessing ramping activation, responses were localized to the lateral frontal cortex, primarily in the RLPFC and dorsolateral prefrontal cortex (DLPFC). Together, our findings suggests that while a broad mediolateral network may support the detection of abstract sequence deviations, lateral prefrontal regions may play a more specialized role by dynamically tracking progress through the sequence in addition to signaling sequence deviants.

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Poster

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Topic: I.04. Executive Functions

Support: NIH Grant RO1 MH133550

Title: Intracranial EEG Correlates of Concurrent Demands on Cognitive Stability and Flexibility

Authors: *J. ZHANG[1], E. BURNS[1], A. EARLE-RICHARDSON[2], R. M. GEDDERT[1], N. LIDDLE[1], B. FRAUSCHER[1], D. G. SOUTHWELL[3], T. EGNER[4], G. B. COGAN[5]; [2]Neurosurg., [3]Neurosurg. and Neurobio., [4]Psychology & Neurosci., [5]Dept. of Neurosurg., [1]Duke Univ., Durham, NC

Abstract: Two core capacities of cognitive control are *cognitive stability,* the ability to focus attention on task-relevant stimuli while ignoring distracters, and *cognitive flexibility*, the ability to shift between different rule-sets to guide behavior. Whether these capacities arise from distinct or overlapping neural mechanisms remains unclear as prior studies investigated them in isolation and used only macroscale neural data (fMRI, scalp EEG) that lack the temporal/spatial resolution to elucidate neural mechanisms. Here, we obtained mesoscale neural data (iEEG) from 17 subjects (mean age=31, 7 females) undergoing inpatient monitoring for surgical treatment of epilepsy, as they completed a local/global Navon letter task. The task independently varied demands on stability (congruent vs. incongruent stimuli) and flexibility (repeating vs. switching tasks between trials), allowing us to analyze neural activity associated with congruency, task switching, and their interaction. Subjects demonstrated robust behavioral congruency effects and switch costs. Prior work suggests the lateral prefrontal cortex (LPFC) is a primary neural substrate for cognitive stability and flexibility. We examined high-frequency (70-150 Hz) neural activity within individual LPFC electrodes (N=267), focusing on the electrodes that had

significant task-related activity (N=47/267). The majority of these task-sensitive electrodes were sensitive to at least one effect of interest (N=29/47), mostly emerging ~500ms post-stimulus-onset. Some effect-sensitive electrodes displayed exclusive effects of congruency or task switching (N=20/29), while others exhibited additive or interactive effects (N=10/29). Additionally, a linear-discriminant classifier could significantly decode both congruency (mean accuracy = 60%) and task switching (mean accuracy = 64%) information from the population of task-sensitive LPFC electrodes (N=47). Thus, despite some sites showing process-specific effects, the LPFC at a population level may employ shared neural substrates to represent both stability and flexibility. Taken together, these results suggest concurrent demands on cognitive stability and flexibility have both distinct and overlapping mesoscale neural substrates in LPFC.

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Topic: I.04. Executive Functions

Support: NIH Intramural Research Program

Title: What is the brain cooking up while cooking? exploring the role of executive functioning in an observed cooking task

Authors: *S. M. LAWLER[1], R. HINGST[2], S. M. DEGENHARD[1], S. ZAMORA[1], S. WILDRIDGE[1], D. HOOKS[1], D.-S. DERVIL[1], V. L. DARCEY[3], N. FARMER[4], L. BARDIN[2]; [1]Natl. Inst. of Health, Clin. Ctr., Bethesda, MD; [2]NIH, Bethesda, MD; [3]Interdisc. Program in Neurosci., NIDDK, Bethesda, MD; [4]Natl. Inst. of Hlth. (NIH), Bethesda, MD

Abstract: Eating involves a sensory experience linked to neurobiological mechanisms, relatedly the preparation of food through cooking may have similar mechanism involvement. Cooking is a complex, goal-directed behavior that engages executive functions and may influence neurobiological outcomes, yet few studies have examined these mechanisms directly. Cognitive flexibility, the ability to shift attention and adjust strategies in response to changing demands, is a core executive function supported by the prefrontal cortex. We examined whether cognitive flexibility is associated with motor and process cooking skills in adults. Twenty-six adults (mean age = 59; n = 21 females) enrolled in a longitudinal dietary behavior intervention in which process skills were hypothesized to increase. Participants completed the Wisconsin Card Sorting Task (WCST), a measure of cognitive flexibility, and the Assessment of Motor and Process Skills (AMPS) at baseline, 6 and 12 weeks. The AMPS is an observer-rated real-time measure of motor (e.g., posture, object handling) and process (e.g., sequencing, planning) performance

skills. Home cooking behavior was assessed by frequency and confidence. Pearson correlation and repeated measures analysis of variance (ANOVA) were used for statistical testing, with significance set at $p < 0.05$. At baseline, WCST scores were significantly correlated with AMPS motor scores ($r = 0.40$, $p = 0.04$), but not with process scores ($p = 0.94$), and neither were associated with baseline home cooking behavior (p's > 0.45). Among 18 participants with complete longitudinal data (mean age = 62.5 years; n = 15 female), AMPS motor scores increased significantly over time ($p = 0.003$), while process scores did not ($p = 0.66$). WCST scores were not significantly associated with AMPS motor scores at 6 weeks ($r = 0.30$, $p = 0.23$) or 12 weeks ($r = 0.09$, $p = 0.72$). However, at 12 weeks, AMPS process scores were inversely correlated with WCST scores ($r = -0.47$, $p = 0.05$), suggesting a dynamic relationship between cognitive flexibility and process skills (e.g., sequencing and planning) used in cooking. The goal of this work is to identify executive function domains linked to cooking tasks which can guide future neuroimaging-based task development to better understand the neuroscience of cooking behavior. These results suggest that cognitive flexibility may play a role in cooking with differing associations between process and motor skills. Future research should compare cooking with other goal-directed behaviors. These data may be useful for exploring the use of cognitive flexibility tasks during the development of functional neuroimaging protocols involving cooking tasks.

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Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Program #/Poster #: PSTR137.12/HH4

Topic: I.04. Executive Functions

Title: Executive functions in adolescence: A longitudinal study comparing evaluations before and after the COVID-19 pandemic.

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Abstract: In this study we explored the cognitive performance in adolescents at two moments of time, before and after the COVID-19 pandemic restrictions, specifically on Executive Functions (EFs) tasks. We evaluated a group of 22 students, 13 male and 9 female (ages of 12.18 ± 0.50 and 14.45 ± 0.59) using the Neuropsychological Battery of Executive Functions and Frontal Lobes (BANFE-2), which evaluates four cognitive indices corresponding to specific cognitive functions and associated prefrontal areas: Orbitofrontal Cortex (OCI), Anterior Prefrontal Cortex

(APCI), Dorsolateral Prefrontal Cortex (DCI), and Prefrontal cortex as an index of global EFs (EFI). The results were also analyzed by sex. The results after an ANOVA analysis to compare evaluations before and after revealed that the OCI post-pandemic performance was impaired in boys (pre and post mean score = 96.61 vs. 66.53), but not in girls (pre and post mean score = 93.55 vs. 95.0). No significant differences were revealed in pre-post-pandemic performances in any other BANFE-2 index or by sex. Our findings are thus compatible with the idea that the change in the educational model derived from the COVID-19 pandemic might have an impact on cognitive development, particularly on Executive Functions (EFs), and indicate a different vulnerability to changes in the educational model between sexes. They also reveal which specific EFs may have been affected during the pandemic.

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Poster

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Topic: I.04. Executive Functions

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Title: Probing the dynamics of rule switching in humans

Authors: *M. FREUND, D. BADRE;
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Abstract: Human decision-making is highly flexible: *contextual rules*, held in working memory, determine which sensory features (*targets*) will guide choices, and which will be ignored (*distractors*). Understanding the neural dynamics of transitioning between contextual rules is a key goal in cognitive neuroscience. Computational models conceptualize switching rules as transitioning between stable states within attractor neural networks. Some models predict this process follows inertial dynamics, wherein decision circuitry becomes transiently susceptible to previously-relevant, but now-distracting, input. We tested this prediction with a novel psychophysical task that temporally decouples target and distractor inputs to assess their interaction with high temporal fidelity, as a function of task preparation and switching. Human participants (N=22) categorized a dynamic stimulus based on one of two orthogonal features (color or orientation). On each trial, a task cue indicated the target feature, rendering the other feature a distractor. After variable intervals, we briefly pulsed the sensory evidence for the target and the distractor, independently. Using non-parametric modeling (generalized additive models), we estimated the separate impact that target and distractor perturbations have on performance at each moment in time following the rule cue. As expected, switch costs were evident in slower,

less accurate responses. But, these costs were ameliorated with a longer preparation interval (i.e., time since the rule cue). Independently, distractors were most disruptive when pulsed ~150 ms before the target. This performance cost was also mitigated by preparation. Most critically, we found a time-varying interaction between distractor influence and switching: switching tasks magnified the impact of distractor perturbations, but only during the early stages of preparation (0-500 ms). These results provide tentative initial evidence for inertial models of switching, and more generally highlight the utility of sensory perturbation methods for characterizing the dynamics of cognitive flexibility. Future work will extend these findings with drift-diffusion modeling and EEG decoding.

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Poster

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Topic: I.04. Executive Functions

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Title: How Perceptual and Attentional Processes Interact with a Hierarchical Representation Structure

Authors: *S. LEACH[1], K. HWANG[2];
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Abstract: To enable flexible and goal-directed behavior, task-relevant information is often organized hierarchically to optimally balances flexibility and stability (Kleinsorge and Heuer, 1999). Grouping abstract rules under overarching contexts allows for reduced interference when switching across contexts. However, perceptual and attentional processes also influence measures of behavioral flexibility, such as response time (RT) switch cost and neural dissimilarity. It remains unclear how perceptual and attention processes interact with hierarchical cognitive control. To address this question, we utilized a cued task switch design where the cue object had an embedded hierarchical structure. To assess the underlying hierarchical structure while controlling for perceptual and attentional processes we ran two mixed effects models, one predicting z-scored RTs and the other predicting trial-to-trial neural distance estimates. In order to measure trial-by-trial change in neural representation patterns, we estimated trial-wise voxel patterns using GLMsingle (Prince, 2022), and calculated trial-to-trial multivariate distance. The results of the zRT model suggested that, although perceptual and attentional processes significantly impacted zRTs, the expected RT switch costs associated with a hierarchical structure still existed above and beyond perceptual and attentional effects. To better compare RT switch costs and neural distance estimates, we used this same model to predict the trial-to-trial

changes neural activity patterns. The results of this neural model found that, for a context switch, there was a greater change in neural activity patterns in the right middle frontal gyrus (MFG), a region previously found to encode contextual information (Badre and Nee, 2018). However, no regions showed a greater change in neural activity patterns for a within-context representation switch. Interestingly, an interaction between how many cue object features changed and the no-switch condition revealed distributed clusters in frontal, parietal, and occipital regions where there was a greater change in neural activity patterns on no-switch trials when more cue features changed. Finally, when repeating both task and response, there was a smaller change in neural activity patterns in occipital and parietal regions. In summary, our results suggest that hierarchical task representations include both abstract rule structures as well as perceptual representations, and these representations are encoded in a distributed fashion beyond the lateral frontal cortex

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Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Topic: I.04. Executive Functions

Support: NIH Grant MH126161

Title: Causal role of lateral prefrontal delta oscillations for processing abstract rules

Authors: *W. LI[1], J. RIDDLE[1], M. PAGNOTTA[2];
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Abstract: Adaptive behavior relies on hierarchical cognitive control—the ability to select lower-level stimulus-response mappings according to higher-order contextual rules. Based on functional MRI (fMRI) evidence, the mid-dorsolateral prefrontal cortex (mid-dlPFC) shows increased activation as rule abstraction increases, and is theorized to be at the apex of the cognitive control hierarchy. Electroencephalography (EEG) studies further link delta-band (2-4 Hz) oscillations to rule abstraction. Yet, causal evidence remains limited. While a prior study delivered delta modulated electrical stimulation and found a change in abstract rule processing, this previous study did not focally target specific subregions of the lateral prefrontal cortex. Here, rhythmic transcranial magnetic stimulation (rTMS) was delivered at delta frequency (2.2 Hz) to right mid-dlPFC as participants performed a hierarchical cognitive control task. The task manipulated hierarchical rule-selection by either requiring contextual cues to signal an abstract policy (high abstraction) or required only simple stimulus-response rules (low abstraction). Using a full factorial counter-balanced design, 24 participants received online TMS in either delta frequency, an active control frequency (theta), or in an arrhythmic pattern during processing of the task stimuli. In addition, TMS was delivered to dorsal premotor (PMd), a

region lower in the lateral prefrontal hierarchy, to control for the site-specificity of TMS. Three-way repeated-measures ANOVA (difficulty by abstraction by TMS frequency) on response time revealed a significant interaction between task abstraction and TMS frequency ($F(2,46) = 4.01$, $p = 0.02$, eta = .15). Post-hoc t-tests revealed that delta-rTMS selectively impaired performance under high-abstraction demands; i.e., response times were slower after delta versus arrhythmic stimulation ($t(23) = 2.50$, $p = 0.02$, $d = .51$). There was no change in behavior following delta-rTMS to PMd. These findings provide causal evidence that delta oscillations in mid-dlPFC support the processing of abstract rule, but future analysis is needed to elucidate what information is encoded in delta oscillatory activity.

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Poster

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Topic: I.04. Executive Functions

Title: Electrophysiological Signatures of Generalized Distributed Neural Activity in Human Cognition

Authors: *J. F. ZOU[1], A. C. PAULK[2], S. S. CASH[3];
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Abstract: Generalized activity - the response of individual brain region to multiple cognitive functions - is a core property in the functional organization of cognition. Evidence of generalized activity has broadly been supported by the Multiple Demand Network in fMRI in humans and as mixed selectivity in electrophysiological recordings in non-human primates. However, the extent to which and the electrophysiological signatures of generalized activity in human cognition remain unclear. Here, we used intracranial stereo-electroencephalography (sEEG) electrodes implanted in patient participants (n = 11) with medically intractable epilepsy to record Local Field Potentials (LFPs) during numerous cognitive tasks which probed visual processing, selective attention, interference, and social cognition. We time-locked the LFP to the stimulus onset and response time to examine the role of Event-Related Potentials (ERPs) and oscillatory power (theta, alpha, beta, low gamma, and high gamma) in encoding task-relevant information of sensory stimuli, task demand, and motor responses for each task. Through a channel level analysis (n = 1536 channels), task-relevant contrasts were compared using one-sample permutation tests ($p < 0.05$) on the ERP and Kruskal-Wallis tests ($p < 0.05$) on the oscillatory power to identify whether that channel encodes task-relevant information. We found that 53.7% of channels encoded task-relevant information for multiple cognitive tasks. The channels with multiple roles were distributed broadly across the prefrontal cortex, precentral gyrus, temporal cortex, as well as the hippocampus, amygdala, caudate, and putamen. We characterized how

individual brain regions represented diverse task information through a representational similarity analysis on the ERP and oscillatory envelopes across the task-space. The dimensionality of the multi-task representations was calculated as the participation ratio of the eigenvalue spectra. Channels exhibiting generalized activity showed a lower dimensionality than channels recruited for only one task ($p = 0.02$, Kruskal Wallis Test). This aligns with the idea that lower-dimensional representations (i.e. more abstract) would be useful for generalization because abstract representations could more easily be utilized in many contexts. These results provide valuable insight into the distributed nature of generalized activation and the role of lower-dimensional representations and suggests a fundamental neural strategy in which generalized activity in a distributed set of brain regions are essential in enabling the robust and flexible nature of human cognition.

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Title: Single neuron dynamics of cognitive control in prefrontal cortex of children

Authors: *D. BONDA[1], C. P. MOSHER[2], N. DEVULAPALLI[2], A. MAMELAK[1], U. RUTISHAUSER[3];
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Abstract: A major open question in human neuroscience is how the neural mechanisms of executive function and cognitive control develop from childhood through adolescence. While it is well appreciated that these capacities do not fully mature until early adulthood, little is known about the specific neural mechanisms that mediate the maturation process. In adults, intracranial recordings have significantly expanded our understanding of the neural mechanisms for cognitive control, revealing single-neuron substrates of error monitoring and conflict detection in the medial prefrontal cortex. Despite the routine clinical use of intracranial recordings for invasive epilepsy monitoring in the pediatric population, this neural substrate has so far not been studied in children. We have successfully established a new program to obtain reliable, high quality, single neuron recordings and correlated behavioral responses in pediatric epilepsy patients undergoing invasive epilepsy monitoring. Here, we report on the successful development of a child-friendly and engaging version of a countermanding task and the very first single neuron recordings during this task in children. Subjects are instructed to rapidly initiate movement in response to a cue that is infrequently interrupted by a “change” signal, which calls

for active suppression and redirection of the ongoing motor activity (cognitive control). This capacity is measured by reaction time and change-signal reaction time, which is derived from a mathematical race model, and which varies with developmental stage and neurocognitive pathology. Across two patients (age range 10-15), we isolated 72 high-quality single neurons from the anterior cingulate cortex (ACC), pre-supplementary motor area (pre-SMA), and orbitofrontal cortex (OFC) during task performance. Of the isolated neurons in the ACC, 10% responded to change signals (conflict), 7% to errors, and 35% to movement initiation. 35% of pre-SMA and 20% of OFC neurons responded to movement initiation. These data reveal evidence for these much-studied neurons for the first time in the brains of children and represent the first reported single neuron assessment of cognitive control in the pediatric population. We show that important questions relating to the development and maturation of neurocognitive phenomena can be addressed in this population at the cellular level and that doing so is safe and feasible.

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Title: Mixed coding of target and distractor information in human medial frontal cortex supports the emergence of abstract conflict and error signals

Authors: *J. GAVENAS[1], Z. FU[3], C. REED[1], A. MAMELAK[1], U. RUTISHAUSER[2]; [2]Dept. of Neurosurgery, AHSP #6432, [1]Cedars-Sinai Med. Ctr., Los Angeles, CA; [3]Neurolog. Surgery, UT Southwestern Med. Ctr., Dallas, TX

Abstract: The capacity to flexibly monitor and control one's actions is crucial for intelligent, goal-directed action. It is largely agreed that medial frontal cortex (MFC) utilizes abstract signals such as conflict and error when updating control parameters to regulate behavior. However, how these abstract signals are computed from more basic stimulus and response representations remains debated. In particular, it is unclear whether MFC (1) simultaneously maintains representations of correct and distractor responses or (2) selectively amplifies and suppresses information based on task relevance. In the present study, we test the encoding and representational structure of color (target) and word (distractor) information in a human single-neuron 3-option Stroop dataset. We find that individual MFC neurons (N=1259 from 32 patients) exhibit nonlinear mixed selectivity for color and word (21.8% exhibit significant interactions).

At the population level, however, both color and word meaning are encoded in the presupplementary motor cortex (preSMA; decoding accuracy 89.5% and 85.4% respectively, $p < 0.05$ both). Color and word representations exhibited an 'inverted' geometric structure, such that decoders anti-generalized across color and word contexts (cross-condition generalization accuracy 21.6% and 23.7%, $p < 0.01$ both). This way of encoding allowed for the emergence of conflict as an abstract signal. This representational structure is incompatible with classic network models of the Stroop task but can be explained by the presence of targeted lateral inhibition allowing color and word nodes to inhibit each other. The inverted geometry was also present on error trials. Also, feedforward neural networks trained to perform error detection also developed the same representation, suggesting that the geometry's primary functional relevance is for error monitoring rather than immediate control implementation. Supporting this view, information about the actual response was also decodeable in preSMA (accuracy 55.6%, $p = 0.003$), which could be combined with color decoders to predict whether an error occurred (accuracy 52.8%, $p < 0.001$). These results indicate that preSMA encodes all information needed to generate an error signal (target response and actual response) from a local mismatch computation. They thereby support a model of performance monitoring we recently proposed, wherein MFC utilizes forward models to compute the distractor and target responses and utilizes these in concert with actual response information to compute abstract conflict and error signals.

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NIMH Grant R01MH110831

Title: Neural Correlates of Performance Monitoring in Human Medial Frontal Cortex and Medial Temporal Lobe

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Abstract: Humans can flexibly adapt their behavior to achieve desired goals based on self-monitored experiences and outcomes. Previous research has established the central role of the human medial frontal cortex (MFC) —particularly the dorsal anterior cingulate cortex (dACC) and pre-supplementary motor area (pre-SMA)—in encoding conflict and error signals essential

for guiding cognitive control. These signals facilitate behavioral adjustments such as error detection, conflict resolution, and fast or slow response, enabling individuals to rapidly adapt their performance during ongoing tasks. However, performance monitoring also depends critically on memory domains, and the roles of medial temporal lobe (MTL) structures—especially the hippocampus and amygdala—in these processes remain poorly understood. To bridge this gap, we recorded a total of 2455 single neurons from both MFC and MTL regions in human subjects engaged in Stroop and Multi-Source Interference Tasks. We identified neurons in the hippocampus and amygdala (13% and 15%, respectively, compared to 22% in dACC and 30% in pre-SMA) that represent self-monitoring of errors. Decoding analyses revealed a clear hierarchical temporal pattern, where error signals appeared first in pre-SMA (half-peak at -0.05 s relative to button press), then subsequently in dACC (0.08 s), and finally in MTL regions (0.3 s). These error signals could be read out with more than 90% accuracy in MFC and 80% in MTL regions. Further, temporal generalization analyses revealed asymmetric error representations in both MFC and MTL, reflecting an evolving balance between transient and persistent error signals, as well as the propagation of monitoring dynamics from medial frontal to temporal areas. These findings demonstrate direct MTL involvement in error monitoring and suggest a network mechanism where self-evaluated outcomes are relayed for further processing, potentially related to learning from experienced conflicts or errors and the formation of performance monitoring memory.

Disclosures: Z. Geng: None. **C. Reed:** None. **A. Mamelak:** None. **U. Rutishauser:** None. **Z. Fu:** None.

Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.20/HH12

Topic: I.04. Executive Functions

Support: NINDS R01NS120987

Title: Diverse activity in prefrontal projections promotes temporal control of action

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Abstract: Prefrontal neurons can have diverse activity during cognitive functions like working memory, attention, and timing; however, the importance of this heterogeneity is unclear. Our goal was to better understand the diversity of prefrontal activity through connectivity. We harnessed circuit-specific tools to capture activity within prefrontal projections during interval timing, an elementary cognitive process that requires working memory for temporal rules and

attention to the passage of time to estimate a temporal interval of several seconds. We used human electroencephalography and single neuronal recordings in mice to capture prefrontal activity during interval timing, with major patterns characterized by time-dependent ramping (monotonic changes) over a temporal interval. We then leveraged retrograde viruses to interrogate prefrontal cortex (PFC) projections to the mediodorsal thalamus (PFC-MD) and to the dorsomedial striatum (PFC-DMS). We report three novel results. First, circuit-specific calcium fiber photometry revealed that PFC-MD and PFC-DMS activity encoded distinct temporal signals, with PFC-MD projections ramping down and PFC-DMS ramping up to interval timing response times. Second, circuit-specific inactivation revealed that PFC-DMS inactivation disrupted animals' internal estimates of time. Third, circuit-specific single-nucleus RNA sequencing of prefrontal projections revealed distinct transcriptomic profiles between PFC-MD and PFC-DMS projections, with enriched genes for cortical layers and neuromodulators as well as genes such as *Cux2, Camk2n1, Htr4,* and *Foxp2*. These data suggest differences in gene expression and connectivity give rise to the diversity of prefrontal activity during interval timing. These findings advance our fundamental understanding of prefrontal function and dysfunction in human disease.

Disclosures: X. Ding: None. **M.A. Weber:** None. **T. Butler:** None. **A. Bova:** None. **S. Guerrero:** None. **N.S. Narayanan:** None.

Poster

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Topic: I.04. Executive Functions

Support: Connected Minds Master's Scholarship
Christine Mohrmann Fellowship, Radboud University
Canada Research Chair Program

Title: Medial frontal neuronal activities during repeated rule switches in rats

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Abstract: Cognitive flexibility - the brain's ability to adapt to the changing environment - is disrupted in several neuropsychiatric disorders. It is an important subconstruct of Cognitive Control in the NIH RDoC matrix. Compared to simpler forms of flexibility, such as reversal learning and set-shifting, switching between abstract rules is difficult to study in rodent models. We developed a novel abstract rule-switching task for rats, in which they maintained nose-fixation for one second before responding in the left or right nose-poke ports. Under the Stay rule, the correct side, remained the same for every trial in the block. Under the Shift rule, rats must alternate their choices from trial to trial. We conducted single-unit recordings from the

medial frontal cortex (MFC) while they learned to switch from the Shift to the Stay rule, which they did on the first or second training day. Over 16 days of rule switch training, they progressed through Stages, from Beginner to Expert. To identify factors that contributed to performance, we evaluated 16 multilinear regression models using Akaike Information Criterion (AIC). Response accuracy was best predicted by the model with Training Stage, Rule, post-switch Trial Position, and Rule-Side interaction. Reaction time was best predicted by Training Stage as the sole factor. Expert animals committed much less perseverative errors and relatively more regressive errors than Beginner animals. Additionally, for each MFC neuron, we evaluated 100 multi-linear models. Each model contained from 1 to all 5 of the factors (Rule, Side, Accuracy, Reaction Time and Epoch), either with or without an additional interaction factor. The model with Side of choice, Accuracy and the interaction between them reached significance and achieved the lowest AIC for 11% of MFC neurons. The second most successful model was Accuracy alone, which optimally explained activity of 6.6% of all neurons. Our novel task is well suited for the analysis of the single-neuron, population and network-level mechanisms that support this training-related improvement in cognitive flexibility.

Disclosures: R.P. Nathaniel: None. **L. Ma:** None.

Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.22/HH13

Topic: I.04. Executive Functions

Support: NIH Grant

Title: Prefrontal cortex dopamine tracks task-related events during behavioral flexibility task

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Abstract: Cognitive flexibility, the ability to adapt behavioral strategies in response to environmental demands, is essential for goal-directed behavior and is significantly impaired in psychiatric disorders such as schizophrenia. Dopamine (DA) in the prefrontal cortex (PFC) plays a key role in flexible behaviors. However, the dynamics of PFC DA have yet to be characterized during flexibility tasks on a timescale relevant for fast behavioural events. Determining whether these signals evolve as animals update their behavior and exactly how they enable learning is a critical next step for understanding the role of DA in behavioral flexibility. Previous work from our lab demonstrated that the activity patterns of DA inputs to the PFC during a rule shift task influence whether mice maintain or update learned cue-reward associations. In this study, we used the genetically encoded DA sensor dLight3.8 to monitor DA fluctuations in the medial PFC of mice engaged in the rule-shift task, where mice choose between bowls with distinct digging

mediums and odors to find hidden food rewards. Using fiber photometry to measure dLight3.8 fluorescence in the medial PFC, we observed clear, temporally precise DA signals. These signals dynamically tracked key task events, including trial initiation, decision-making periods, and both correct and error outcomes. Furthermore, our results indicate that prefrontal DA is sensitive to shifts in reward contingencies and, more broadly, deviations from expected outcomes. Ongoing studies are aimed at probing these dynamics through projection- and receptor-specific manipulations of PFC DA signaling.

Disclosures: M.O. Nesbit: None. **V.S. Sohal:** None.

Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Program #/Poster #: PSTR137.23/HH14

Topic: I.04. Executive Functions

Support: VA Merit I01 BX005209-01

Title: Impact of psilocin pro-drug 4-Aco-DMT on probabilistic reversal learning in rats

Authors: S. BARNES[1], M. TRANTER[3], A. L. HALBERSTADT[2], ***S. B. POWELL**[4], M. SIKKINK[2], E. PHILLIPS[5];
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Abstract: Psilocybin has shown efficacy in treating end of life anxiety, major depressive disorder, treatment-resistant depression, and substance use disorders. Cognitive flexibility is a known deficit in humans with schizophrenia, depression, PTSD, and other mental illness. It can be measured with experimental animals using the probabilistic-reversal learning (PRL) task. These tasks require the subject to learn a reward contingency and adjust their responding when a change in reward contingencies has been detected, i.e., that the response previously associated with reward is now associated with non-reward and vice versa. Hallucinogens are previously cited to have therapeutic effects in promotion of learning and cognitive flexibility. In this experiment, the effects of the hallucinogen 4-Aco-DMT were tested using a homologous task in Sprague Dawley rats. 4-AcO-DMT is an unscheduled tryptamine that, like psilocybin, is rapidly metabolized to psilocin and thus acts as a psilocin pro-drug. Each rat was trained to perform a task consisting of 240 trials. After 80 trials the contingencies were switched (e.g. the target lever switched from left to right), then after another 80 trials the levers were switched once more (e.g. the target lever was switched from right to left). In the 70/10 PRL task, the target lever was rewarded 70% of trials and the non-target lever was rewarded 10% of trials. Rats were trained for a period of 10 days until they performed consistently for three consecutive days. During these three days, saline was injected to acclimate the rats to injections. On the following day, vehicle or one of two doses of 4-AcO-DMT (0.3, 1.0 mg/kg) was administered 20 min prior to PRL

testing. 4-AcO-DMT increased non-target lose shift responding, indicating an enhanced ability to adapt behavior and switch after an incorrect response that delivered negative feedback. No effects of 4-AcO-DMT were evident on overall accuracy. These studies suggest that behavioral flexibility is increased under active treatment, as seen in humans. However, it is unclear if and how long these effects might be maintained and what receptor signaling mechanisms are required.

Disclosures: S. Barnes: None. **M. Tranter:** None. **A.L. Halberstadt:** None. **S.B. Powell:** None. **M. Sikkink:** None. **E. Phillips:** None.

Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.24/HH15

Topic: I.04. Executive Functions

Support: R21AA031415

Title: Investigating the impact of perineuronal nets on behavioral flexibility and functional connectivity

Authors: *S. D. GARRISON[1,2], G. E. KIRKPATRICK[2], H. TREVATHAN[2], E. D. K. SULLIVAN[2], M. H. MCFARLAND[2], J. BETHEA[2], T. BALDWIN[2], Y.-Y. I. SHIH[2,3], D. L. ROBINSON[2,4];
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Abstract: Behavioral flexibility, the ability to adapt to change and switch behavioral responses when needed, can be impacted by factors like substance use and genetics. The orbitofrontal cortex (OFC) plays a key role in regulating aspects of behavioral flexibility, such as reversal learning. The Attentional Set Shifting Task (ASST) assesses behavioral flexibility in animals by training them on a stimulus-response task, followed by a series of reacquisitions (testing memory) and reversals (shifting attentional set). Findings from our lab show adult rats with adolescent ethanol exposure have task impairments during reversals. These impairments have correlated with reduced functional connectivity in frontostriatal circuits using functional magnetic resonance imaging (fMRI). Understanding the neurobiology of inflexibility and connectivity is critical to uncover how substance use or psychiatric disorders impair behavioral flexibility. We recently found increased perineuronal nets (PNNs) around PV+ cells in the OFC and other prefrontal areas in adult male Sprague-Dawley rats after adolescent ethanol exposure. PNNs are extracellular matrix structures that encapsulate the soma and dendrites of some neurons, such as fast spiking parvalbumin-positive (PV+) interneurons, and help regulate synaptic plasticity. As PNNs envelop cells, they restrict synaptic inputs, leading to a reduction in plasticity and, perhaps, behavioral flexibility. Before examining how adolescent ethanol

exposure affects PNNs and behavior, we must first understand their role in behavioral flexibility in typical rats, the goal of this study. **We hypothesized that enzymatic degradation of PNN glycosaminoglycan side chains in the OFC using chondroitinase ABC (ChABC) will open a window of plasticity, improving ASST performance and enhancing OFC functional connectivity.** This study is ongoing. Our initial data (n=2 rats per time point) show that PNNs in the OFC are fully degraded 4 days following an infusion of ChABC, and they begin to reform by day 6 and return to near-control levels by day 8, based on PNN counts and matrix density (matrics/mm^2). Additionally, preliminary data (n=2 ChABC rats, n=2 vehicle rats) suggest that this degradation impacts ASST performance, supporting our hypothesis that OFC PNN integrity influences behavioral flexibility. A separate cohort of rats (n=9 ChABC rats, n=9 vehicle rats) underwent MRI scans to assess functional connectivity between the OFC and cortical and subcortical brain regions on day 4 after ChABC or vehicle (MRI analysis will occur upon completion). Together, these data will enhance our understanding of PNNs in behavior and brain circuits.

Disclosures: S.D. Garrison: None. **G.E. Kirkpatrick:** None. **H. Trevathan:** None. **E.D.K. Sullivan:** None. **M.H. McFarland:** None. **J. Bethea:** None. **T. Baldwin:** None. **Y.I. Shih:** None. **D.L. Robinson:** None.

Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.25/II1

Topic: I.04. Executive Functions

Title: Complementary contributions of mouse prefrontal and thalamic neuronal populations to cognitive set shifting

Authors: *X. WANG[1,2], D. HÄHNKE[1], A. RANGANATH[1], T. W. BERNKLAU[1,2], S. AYASREH FIERRO[2], S. N. JACOB[1];
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Abstract: Cognitive flexibility requires dynamically shifting between cognitive sets, i.e. internal representations of task demands. Prior studies of the cellular and circuit mechanisms of cognitive flexibility have mainly focused on choices between competing response options, but not on choices between cognitive sets. Here, we developed a two-alternative forced-choice task for mice with predictive and non-informative auditory contexts, requiring the animals to shift their cognitive set (plan for a movement or defer planning) on a trial-by-trial basis. Mice adopted a default-overwrite strategy, favoring one response direction unless contextually prompted to prepare for the alternative or withhold a plan. Submovement decomposition of continuous motor output revealed subliminal, context-sensitive preparatory movements that aligned with

underlying neuronal dynamics. Large-scale unit recordings from the prelimbic cortex (PL) and mediodorsal thalamus (MD) showed distinct roles in preparatory and executive phases of decision-making: PL encoded abstract task structure and showed generalizable preparatory signals, while MD responses were more phasic and instruction tied. Sparse-component analysis and Granger-causal connectivity revealed a dissociation between context-modulated PL circuits and instruction-sensitive MD circuits. These findings suggest that PL-MD interactions support cognitive set shifts, with PL maintaining flexible internal representations and MD shaping their translation into action. Our results underscore the importance of the prefrontal-thalamic network in supporting adaptive behavior under dynamically changing task demands.

Disclosures: X. Wang: None. **D. Hähnke:** None. **A. Ranganath:** None. **T.W. Bernklau:** None. **S. Ayasreh Fierro:** None. **S.N. Jacob:** None.

Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.26/II2

Topic: I.04. Executive Functions

Title: Distributed context representation in the mouse brain during sensory task switching

Authors: E. G. MCBRIDE[1], S. AKELLA[2], B. HARDCASTLE[2], S. D. GALE[3], H. CABASCO[2], V. LAFEHR[2], J. KUYAT[4], C. BENNETT[2], ***S. R. OLSEN**[2];
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Abstract: Animals adaptively regulate their responses to sensory stimuli based on goals and environmental context. However, it remains unclear whether this flexibility is controlled by a central brain region such as the prefrontal cortex or a distributed network of regions that maintain task context information and adjust computations to guide behavior. To address this question, we used Neuropixels probes to measure brain-wide neural activity in mice performing a context-based switching task. In the task, mice selectively responded to either visual or auditory stimuli in alternating trial blocks.
To identify brain regions representing task context, we conducted single-cell and population-level analyses across 83 cortical and subcortical regions. Using a linear encoding model, we quantified the influence of context on individual neurons beyond the effects of stimulus, motor movements, and task-related choices. We used a "drop-out score" to determine the unique contribution of context to neuronal activity by measuring the fraction of variance lost when context was excluded from the model. Our analysis revealed context encoding across many brain regions, with stronger encoding in the frontal cortex, midbrain, and striatum, and weaker encoding in primary sensory areas including the visual and auditory cortices. Importantly, context encoding was correlated with task performance. Population decoding using pre-stimulus neuronal activity confirmed this widespread context representation. Together our results argue

against a localized model of context encoding and instead suggest that a broad network of areas encode context information to support flexible behavior.

Disclosures: E.G. McBride: None. **S. Akella:** None. **B. Hardcastle:** None. **S.D. Gale:** None. **H. Cabasco:** None. **V. LaFehr:** None. **J. Kuyat:** None. **C. Bennett:** None. **S.R. Olsen:** None.

Poster

PSTR137: Prefrontal Mechanisms of Executive Functions in Humans and Animals

Location: SDCC Halls B-H

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Program #/Poster #: PSTR137.27/II3

Topic: I.04. Executive Functions

Title: Inactivation of mouse orbitofrontal cortex impairs performance in a visual-auditory switching task

Authors: *V. LAFEHR[1,3], H. CABASCO[2], A. SRIDHAR[3], S. AKELLA[3], B. HARDCASTLE[3], E. G. MCBRIDE[1], S. D. GALE[4], C. BENNETT[1], S. R. OLSEN[1];
[2]Mindscope, [1]Allen Inst., Seattle, WA; [3]Allen Inst. for Neural Dynamics, Seattle, WA; [4]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Animals flexibly switch between different cognitive goals in a context-dependent manner. To investigate the flexible linking of context information to appropriate sensorimotor transformations, we trained mice in a sensory switching task. Mice were required to respond to either visual or auditory stimuli in alternating blocks of trials. Proficient performance was characterized by robust responses to stimuli of the context-appropriate modality (e.g. visual target in visual context blocks) and suppression of responses to stimuli of the context-inappropriate modality (e.g. visual target in auditory context blocks). We measured brain-wide neural activity using Neuropixels probes while mice performed this task. Decoding analysis revealed a strong and persistent context representation in orbitofrontal cortex (ORB). Consequently, we investigated ORB's functional contribution to task performance. We reversibly and bilaterally inactivated ORB during the task using muscimol (GABA-A agonist), interleaving inactivation sessions with control sessions. Inhibiting neural activity in ORB disrupted task performance by impairing suppression of auditory target responses in visual context blocks, while mostly leaving suppression of visual target responses in auditory context blocks intact. These results suggest ORB plays a causal role in context-dependent auditory stimulus gating. The reason for the asymmetry between visual and auditory modalities remains to be determined but could reflect modality-specific processing in the subregions of ORB inactivated in our study. In future experiments, we will systematically inactivate focal subparts of ORB to test this hypothesis.

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Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

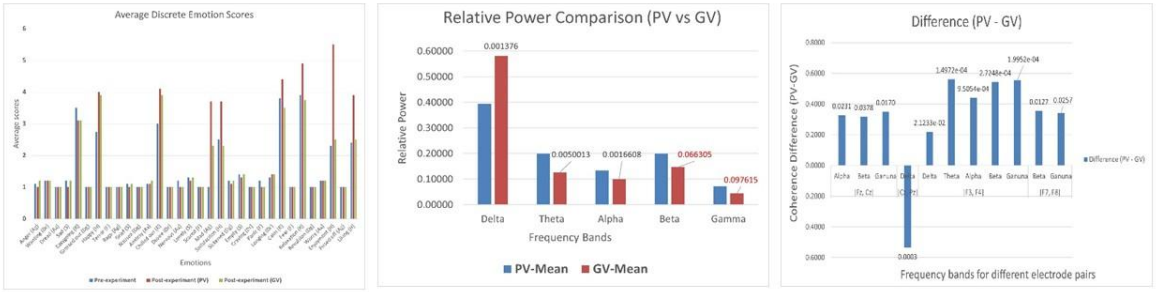
Program #/Poster #: PSTR138.01/Web Only

Topic: I.06. Social Cognition

Title: Influence of Personalized and Generalized Videos on Emotion and Brain Activity

Authors: W. LEE[1], I. NIAZI[2], ***S. SHAKIL**[1];
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Abstract: Background- Emotional responses to media are highly individualized. Algorithmically tailored short form personalized videos (PVs) can influence emotions and neural activity differently from non-tailored generalized videos (GVs). The aim of this study is to uncover how PV content influences the functional organization of brain networks underlying emotion compared to GV content.**Methods-** Twenty participants (9 females, age: 18-22 years) viewed videos while undergoing EEG recording and completed pre- and post-viewing emotion rating surveys prepared using the Discrete Emotion Questionnaire(Harmon-Jones et al., 2016). EEG data (Neuroscan SynAmps RT 128- channel Amplifier using 10-20 system) was collected during exposure to either algorithmically tailored personalized Instagram Reels or generalized (non-tailored) Instagram Reels. EEG data preprocessing included bandpass filtering and artifacts removal (powerline, DC, eye & head movements etc.). We analyze the relative power of different frequency bands (theta, alpha, beta, and gamma) and coherence between brain regions to study brain activity and connectivity, respectively. **Results-** Our results show that PVs increased happy and relaxation emotions such as enjoyment, satisfaction, calmness, and liking showing emotional arousal after PV viewing as shown in Figure 1 (a). This emotional arousal was also reflected in brain activity with the increase power in theta, alpha, beta, and gamma frequency bands, which are associated with emotional arousal (Chen et al., 2024) (Rahman et al., 2021), and in enhanced coherence between regions in frontal and temporal brain regions during PV viewing as shown in Figure 1(b) and (c), respectively. **Conclusion-** Our findings demonstrate that personalized video content elicits stronger emotional engagement and more efficient brain network dynamics, reinforcing the role of individualized digital experiences in shaping neuro-emotional states.



(a) (b) (c)

Disclosures: W. Lee: None. **I. Niazi:** None. **S. Shakil:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.02/II4

Topic: I.06. Social Cognition

Support: NIH Grant ZIAAT000036

Title: Confidence and pupil responses track learning from feedback in pain emotion recognition

Authors: Y. ZHAO[1], J. KANG[1], *L. Y. ATLAS[2];
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Abstract: Feedback improves recognition of basic emotions (Blanch-Hartigan et al., 2012) and influences measures of conscious awareness, such as confidence (Katyal et al., 2025), and physiological arousal, such as pupil responses (Harris et al., 2022). However, it remains unclear whether feedback-driven learning influences pain assessment, whether individuals have metacognitive insight on performance, and how learning and awareness relate to physiological changes. We tested whether trial-by-trial feedback facilitates learning for recognizing painful faces, and whether improvements are accompanied by changes in confidence and pupil dilation during observation.Forty-seven healthy adults viewed videos of individuals (“targets”) experiencing noxious heat of varying intensities. Participants completed two tasks (a Binary pain

vs. no pain judgment task and an Intensity rating task) in which they rated targets' pain and provided their confidence in their rating on each trial. They were randomly assigned to a Feedback Group (n = 23) or a No-Feedback Group (n = 24). The Feedback Group received the target's self-reported pain rating as feedback after each trial. Pupil size was continuously recorded. We used model selection to identify the best fitting models for pain judgment accuracy, including all main effects and interactions of Group, Block, Trial, and Confidence. Separate mixed-effects models predicted pupil size based on Group, Block, Trial, and Accuracy (correctness or rating error).The Feedback Group was more accurate in both tasks ($\beta_{\text{Pain/No Pain}} = 0.191$, $p < .05$; $\beta_{\text{Pain Intensity}} = -5.127$, $p < .001$). In the Binary pain vs. no pain task, accuracy decreased over time in the Feedback Group ($\beta = -0.047$, $p < .01$) and there was a positive association between confidence and accuracy across Groups ($\beta = 0.024$, $p < .001$). Neither Correctness nor Group predicted pupil size. In the Intensity task, higher confidence tracked improved performance (smaller rating error) in the Feedback Group ($\beta = -0.068$, $p < .01$) and decreased performance in the No-Feedback Group ($\beta = 0.076$, $p < .05$). Furthermore, in the Feedback Group, improved performance was link to larger pupil size ($\beta = -1.564$, $p < .05$) and increased pupil dilation over blocks ($\beta = -2.404$, $p < .05$).These findings show that trial-level feedback improves pain recognition and shapes learning over time. Increased confidence and pupil responses aligned with performance improvements - even before feedback - reflect emerging awareness of learning. These behavioral and physiological markers advance understanding of social learning and support the development of feedback-based training tools for pain recognition in clinical settings.

Disclosures: Y. Zhao: None. **J. Kang:** None. **L.Y. Atlas:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR138.03/II5

Topic: I.06. Social Cognition

Title: Explorating social emotions of people with moderate to severe dementia based on care records from a group home

Authors: *A. ONZO[1], T. TAKANO[2], K. MOGI[3], S. ISHIKAWA[4], S. HOTTA[5];
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Abstract: People with severe dementia often struggle with verbal expressions. Even if they have a rich inner world and experience a wide range of emotions, it becomes difficult for others to understand their feelings. Research has shown that individuals with dementia struggle with the theory of mind and cognitive empathy, making it difficult to maintain social connections. Recent studies suggest that non-verbal emotional empathy tends to remain relatively intact (Shi, et al,

2025). It is important to investigate the richness of their social emotions. At a group home for people with dementia, staff members have been recording ‘small positive events’ they notice about residents with dementia. We obtained care records over two years starting in 2023 and analyzed how individuals with moderate to severe dementia initiate interactions with others in their living environment, as well as joys these interactions bring to both the individuals themselves and those around them. Events recorded by staff included, for example, a person with dementia pulling out a chair for someone in a wheelchair who was coming to the dining table, or putting a cardigan on a tired-looking staff member. These examples showed that people with dementia were actively thinking about and taking initiative to do things that benefited the staff and the people they lived with. A wide range of events were recorded, from these that were considered to be positive because the person was able to do something that was thought to be impossible for him/her, to those that were considered positive because the person took actions that benefited everyone, such as wiping all the tables after meals. Two researchers categorized these records of ‘small positive events’ according to the classification of Levasseur et al. 2005 (1. Activities performed alone as preparation for interacting with others, such as eating or watching TV, 2. Activities where the individual is not directly in contact with others but others are around, such as going for a walk, 3. Activities involving interaction with others, such as interacting with a cashier while shopping, 4. Activities done with others, such as playing tennis or games, 5. Activities to help specific others, and 6. Activities that contribute to an organization or group). Our analysis revealed that categories 5 and 6 were commonly observed even in individuals with severe dementia. This suggests that individuals with dementia, even as their care needs increase, do not lose their social emotions and continue to actively consider and act on behalf of others. We discuss the possibility of forming robust social connections in the face of variable types of dementia and locations of brain damages.

Disclosures: A. Onzo: None. **T. Takano:** None. **K. Mogi:** None. **S. Ishikawa:** None. **S. Hotta:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.04/II6

Topic: I.06. Social Cognition

Title: Tasit-s adaptation for mexican population: preliminary findings

Authors: *S. MEZA-CAVAZOS, G. MONTES GONZÁLEZ, A. VARGAS RAMIREZ, R. GARZA SANDOVAL, K. RAMOS, P. AGUIRRE;
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Abstract: Introduction: The Awareness of Social Inference Test - Short Version (TASIT-S) is an audiovisual test that assesses social cognition through scenes requiring inferences about mental states. It includes three sections: emotional evaluation, social inference, and enriched

social inference. The aim of this study is to validate the TASIT-S and obtain normative data in a Mexican population to enhance its applicability in clinical and research settings. **Method:** An adapted version of the TASIT-S for the Mexican population was applied, following the guidelines of the International Test Commission (2017). The process included script adaptation, expert evaluation, video recording with Mexican actors, video editing, and pilot testing. A total of 94 participants from Monterrey, Nuevo León (38 men and 56 women, aged 18 to 50) were evaluated across three modalities: in-person (n = 27), Zoom (n = 26), and self-administered (n = 41). Performance was analyzed using ANOVAs and Bonferroni post hoc analyses between modalities and groups. **Results:** No significant differences were found between the three groups in Part 1 (emotion evaluation) of the test. In Parts 2 and 3 (minimal and enriched social inference), significant differences were observed in the self-administered group compared to the in-person and Zoom groups ($p < .001$). Additionally, item-by-item analyses were conducted to identify ceiling or floor effects in order to remove inadequate items. **Conclusions:** The results indicate that the self-administered group performed significantly worse compared to the in-person and Zoom groups. This suggests that the lack of supervision and immediate guidance may have affected participants' understanding, concentration, and motivation, negatively influencing their performance. Furthermore, this preliminary analysis provides a sensitive and specific version of the TASIT-S for the population of northeast Mexico.

Disclosures: S. Meza-Cavazos: None. **G. Montes González:** None. **A. Vargas Ramirez:** None. **R. Garza Sandoval:** None. **K. Ramos:** None. **P. Aguirre:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.05/II7

Topic: I.06. Social Cognition

Support: Albion College FURSCA Grant

Title: Effects of pheromones and circadian rhythms on perceptions of personal characteristics

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Abstract: The present study examines the influence of pheromones and circadian rhythms on perceptions of personal characteristics. Using only a basic resume for information, personality was measured through a modified Big 5 personality survey and participants were tasked with determining whether a hypothetical candidate was a good fit for a proposed job. Participants were divided into 4 groups: exposure to pheromone and morning condition, exposure to control/vehicle substance and morning condition, pheromone and evening condition, and control and evening condition. The study aims to contribute to the understanding of how biological rhythms and putative human pheromones combine to influence daily perceptions and possible

interactions between individuals. We hypothesized that participants who were exposed to a pheromone, androstadienone (AND), specifically in the evening, would report higher ratings of competent employee characteristics, positive physical attributes and increased skills related to hiring the individual. A total of 74 (31 Female) participants were recruited from a Psychology 101 participant pool for a morning or evening research session and were randomly assigned to either the experimental group (presence of AND) or the control group (no AND, vehicle only). Results suggested significant main effects of pheromone exposure on perceived success and physical attractiveness. There was a significant effect of perceived masculinity based on sex and presence of pheromone. There was also a significant effect on perceptions of conscientiousness based on pheromone and time of day, along with a trend toward significance on hiring decisions based on pheromone exposure and time of day.

Disclosures: T.J. Jechura: None. **R. Mitchell:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.06/II8

Topic: I.06. Social Cognition

Support: DARPA Grant N660012324016

Title: Long-term pattern in the behavior can encode personal traits

Authors: *P. RAJAEI[1], A. ZIOUZIOU[2], P. KALLAM[2], M. BRONSTEIN[3], B. GARCIA[4], A. MCINNES[4], B. BROWN[3], S. YADAV[3], M. FREEDMAN[4], M. GOODMAN KEISER[3], A. S. WIDGE[4], A. YOUSEFI[2];
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Abstract: Decoding cognitive and affective states from behavior remains a key challenge in neuroscience, as traditional metrics like average response time (RT) often lack sufficient encoding power. Ignoring behavioral temporal dynamics can obscure insights into underlying neural mechanisms. This study presents a case where long-term behavioral patterns offer strong encoding power, while average RT yields minimal cognitive information. Behavioral data came from 50 participants completing a variant of the Death Implicit Association Test (D-IAT), which assesses implicit associations with life- and death-related concepts. The D-IAT embeds implicit conflict within trials, making it useful for detecting behavioral deviations linked to traits like suicidal ideation. Participants were grouped by high or low active suicidal ideation (SI) based on ecological momentary assessment (EMA) responses collected over two weeks. During the D-IAT, participants matched stimulus words to categories ("Life + Me" or "Death + Me") using arrow keys, with mappings counterbalanced. The task induced cognitive conflict, especially with incongruent pairings like "Death + Me." Response categories alternated every 20 trials to

introduce variability. While average RTs showed no significant group differences, RT trajectories revealed a rhythmic pattern synchronized with block transitions—especially in participants with low SI. To explore this, researchers developed a hybrid framework combining state-space models and deep neural networks (SSM-DNN). The SSM extracted smoothed latent dynamics from noisy RT sequences, then analyzed by a convolutional neural network (CNN). Training both components jointly let the SSM act as a supervised feature extractor, boosting robustness and decoding performance. This model achieved 78% classification accuracy (AUC = 0.80) in distinguishing high vs. low SI participants, outperforming state-of-the-art methods like pre-trained ResNet (~58% accuracy). These results underscore two advances: first, longer-term behavioral patterns encode substantial mental health information; second, the SSM-DNN framework offers an interpretable, generalizable, scalable method for decoding such states from behavior alone. Findings from the D-IAT and modeling pipeline offer neuroscientists and clinicians a robust tool for identifying behavioral biomarkers, improving diagnostics, personalizing mental health assessments, and deepening insight into cognitive and affective processes.

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Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.07/II9

Topic: I.06. Social Cognition

Support: Swedish Research Council
Swedish Foundation for Strategic Research
Karolinska Institutet Strategic Research Area Neuroscience (StratNeuro)
Wenner-Gren Foundations
Swedish Society of Medicine
Swedish Brain Foundation
Swedish Society for Medical Research

Title: Observers Accurately Discriminate Interoceptive from Exteroceptive Attention in a Face-to-Face Dyad Experiment

Authors: *K. VERANIC[1], M. PASKIN[1], E. MANSOUR[1], O. OTTERSEN[2], M. LEKANDER[1], L. LUNDQVIST[1], A. GUTERSTAM[1];
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Abstract: Social interactions often require inferring where another person's attention is directed to improve coordinating actions, sharing information, and predicting behaviour. While prior

work shows that attending to internal bodily signals (interoception) recruits partly distinct neural pathways from attending to external sensory input (exteroception), it is unknown whether these states can be read by observers from overt behaviour. We tested this ability in 32 healthy adults (16 mixed-sex dyads, 19-46 years) who alternated roles of Attendee and Reader, while seated face-to-face, across 50 ten-second trials. While Readers' view of Attendees was restricted to the head and shoulders, Attendees fixated a central dot and (covertly) performed either (i) heartbeat tracking (interoceptive attention) or (ii) visual-target tracking of vertical orientations in a rotating Gabor patch (exteroceptive attention). Attendees reported detected events (i.e., heartbeats or visual-targets) with a handheld button press. At the end of each trial Readers identified the Attendee's task and rated confidence on a scale ranging from 1-4. Eye-tracking was used to verify Attendee's fixation. The preregistered primary outcome was Reader classification accuracy versus chance. Permutation testing (1000 iterations) showed that the mean accuracy was 52.75% (95% CI [48.55, 56.95]), significantly above 50% ($p = 0.014$), which indicates people were able to determine whether their partner was attending inwardly or outwardly. Trial-level generalized linear mixed modelling revealed that participants' accuracy did not vary reliably with trial-level confidence ($\beta = 0.01$, 95% CI [-0.17, 0.18], $p = 0.920$, OR = 1.01), suggesting that Readers' subjective certainty in their decision did not track their accuracy. This finding indicates that the 'mind reading' effect occurs at an implicit level, which was supported by many subjects' spontaneous verbal reports that they primarily relied on their 'gut feeling' for the decisions. Our results provide the first evidence that observers can discriminate when another person's attention is directed inward to their bodily signals versus outward to the external environment. This means that interoceptive and exteroceptive attention have distinguishable behavioural signatures, which are available to others during social interactions.

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Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.08/II10

Topic: I.06. Social Cognition

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Swedish Foundation for Strategic Research
Karolinska Institutet Strategic Research Area Neuroscience (StratNeuro)
Wenner-Gren Foundations
Swedish Society of Medicine
Swedish Brain Foundation
Swedish Society for Medical Research

Title: Characterizing the role of eye gaze dynamics for attributing awareness to social agents

Authors: *E. MANSOUR, L. LUNDQVIST, A. GUTERSTAM;
Karolinska Institutet, Stockholm, Sweden

Abstract: As social animals, we have a special sensitivity to each other's gaze. With the advent of humanoid robots, it has become increasingly relevant to determine what exactly signifies natural human gaze behavior. Previous research has demonstrated that people are sensitive to the precise manner in which another person's attention 'spotlight' moves across an image over time (Ziman et al. 2023 PNAS), suggesting that our brains construct a predictive internal model of how others' attention moves naturally. However, it remains unclear how others' eye movements influence our perception of that person being a conscious human agent as opposed to an artificial, robot-like agent. We hypothesized that the spatiotemporal dynamics of natural eye movements is key for attributing awareness to other agents. To test this hypothesis, we conducted a behavioral study where participants (n=39, aged 18-40) viewed short videos of another person's eyes observing an image. In each trial, subjects viewed two videos ("Agent A" and "Agent B") presented sequentially, showing a pair of eyes freely viewing an image for 3s. One of the videos was shown as recorded, the other one in time-reversed order (video presentation order was randomized across trials). Subjects were then asked to indicate which agent (A or B) was a conscious human agent (as opposed to an artificial agent) in a forced-choice task. In two separate sessions, subjects were either shown, or not shown, the looked-at image before viewing the eye videos in each trial. The results showed that subjects were significantly better than chance at determining which agent was the conscious human one, both when the looked-at image was available (average accuracy = 56%, SEM = 1%, $p<0.0001$, t-test) and unavailable (average accuracy = 54%, SEM = 1%, $p=0.0064$, t-test). Subjects' accuracy increased with the confidence level, suggesting that the effect was, at least partially, explicit. These findings demonstrate that the natural spatiotemporal dynamics of another's eyes shape our perception of that agent as being a conscious human agent. Future studies will investigate the influence of eye gaze dynamics on awareness attribution to virtual avatars, with the goal of identifying which aspects of humans' natural pattern of fixations and saccades are crucial for awareness attribution.

Disclosures: E. Mansour: None. **L. Lundqvist:** None. **A. Guterstam:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.09/II11

Topic: I.06. Social Cognition

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Karolinska Institutet Strategic Research Area Neuroscience (StratNeuro)
the Wenner-Gren Foundations
he Swedish Society of Medicine

he Swedish Brain Foundation
the Swedish Society for Medical Research

Title: Perception of other people's gaze towards the self distorted across body regions

Authors: *M. PASKIN, L. LUNDQVIST, A. GUTERSTAM;
Clin. Neurosci., Karolinska Institutet, Solna, Sweden

Abstract: The ability to accurately perceive the target of another person's gaze when directed towards one's own body can be critical in many social situations. Despite its profound behavioral relevance, the interaction between gaze, self, and body perception remains unexplored. Here we combined motion capture (Qualisys Miqus Hybrid, 8 camera setup) and wearable eye-tracking (Tobii Pro Glasses 3) to characterize people's ability to perceive others' gaze when directed towards the self or another for target points across the body. In experiment 1 (n=31), a Looker gazed at 38 points across the body surface of the participant (self) and another person (other), while the participant indicated perceived gaze target using a (trackable) reflective marker. We estimated the difference between the actual and perceived gaze target for each point, generating whole-body maps of local gaze perception error vectors. Our results revealed an unexpected and striking perceptual bias: while participants showed high accuracy for face targets, they consistently perceived gaze targets below the face as significantly lower than they actually were. This perceptual 'away-from-face' bias for targets below the face was significantly greater in self than other (-10.7cm vs -5.6cm p=0.01, t-test), suggesting that self-related gaze is processed differently than gaze toward others. In experiment 2, we repeated the other condition and compared it with two interleaved conditions, in which the other was replaced with a body-shaped object (mannequin) or blank screen. We found that the 'away-from-face' bias was significantly greater in other compared to both mannequin and blank screen (-11.2cm vs -6.2cm vs -6.9 cm; p=0.01 and p=0.04), with no significant difference between mannequin and blank screen (p=0.45), suggesting that the away-from-face bias is specific for gaze towards social agents. Subjects reported no explicit awareness of their biases in neither experiment. Together, these results demonstrate that our perceptual systems implicitly exaggerate the difference between gaze towards the face versus the rest of the body. This perceptual distortion across body regions was specific for social agents and more pronounced for self-related gaze. Our findings suggest the existence of a novel social-perceptual mechanism that may help us to swiftly determine whether another agent is attending to the face, at the cost of erroneous gaze perception for the lower body.

Disclosures: M. Paskin: None. **L. Lundqvist:** None. **A. Guterstam:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.10/II12

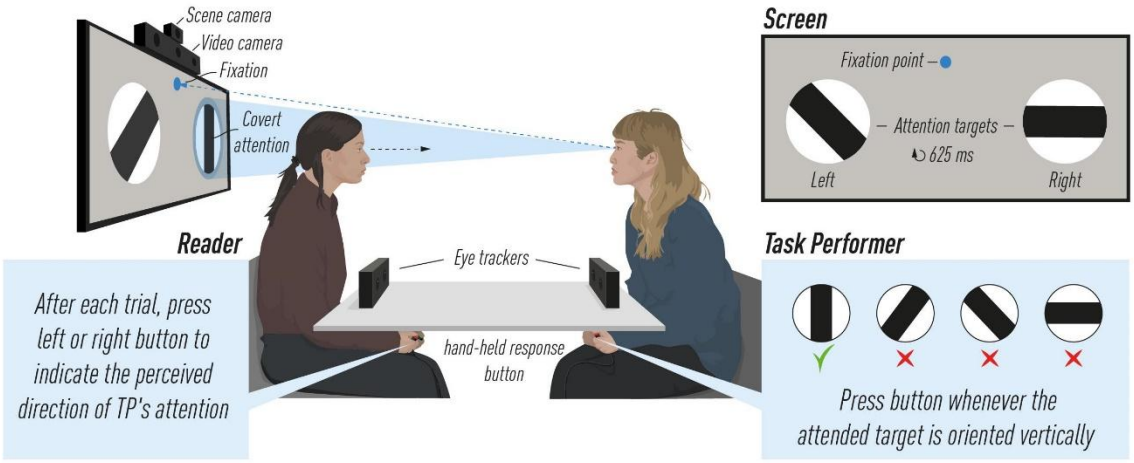
Topic: I.06. Social Cognition

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Swedish Foundation for Strategic Research
Karolinska Institutet Strategic Research Area Neuroscience (StratNeuro)
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Swedish Society of Medicine
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Swedish Society for Medical Research

Title: Social perception of other people's 'covert' attention

Authors: M. PASKIN[1], L. LUNDQVIST[2], *A. GUTERSTAM[1], M. LEKANDER[2,3], O. OTTERSEN[4];
[1]Karolinska Institutet, Solna, Sweden; [3]Dept. of Clin. Neurosci., [2]Karolinska Institutet, Stockholm, Sweden; [4]Inst. Basic Med. Sci. Univ. Oslo, N-0317 Oslo.

Abstract: Covert attention is defined in psychology textbooks as the act of orienting one's attention to a stimulus without moving one's eyes. In the absence of other overt bodily or environmental cues indicating an attention shift, the reorienting of one's covert attention is considered undetectable to outside observers. Here we tested the hypothesis that people implicitly perceive the direction of another person's covert spatial attention by processing involuntary miniature eye movements and/or subtle bodily cues associated with attention reorienting. 64 healthy adults (34 in experiment 1; 34 in experiment 2) alternated roles of Attendee and Reader, while seated face-to-face, across fifty 10-s trials. In each trial, the Attendee performed a high-load visual (exp 1) or auditory attention task (exp 2) requiring them to allocate their spatial attention to the right or left side of the Reader's head, while fixating their gaze at a central fixation dot just above the head of the Reader. The Reader, whose view was restricted to the head and shoulders of the Attendee, was tasked to identify the direction of the Attendee's attention (left or right) at the end of each trial. Results reveal that Readers were significantly better than chance at detecting the direction the Attendees visual attention (experiment 1: mean accuracy [SEM] = 53.6% [1.7%], p=0.002) and auditory attention (mean accuracy=53.5% (1.8%), p<0.001). A machine learning model trained on face-video and eye-tracking data out-performed human subjects (experiment 1, mean accuracy=63.3% [2.9%], p<0.001; experiment 2, mean accuracy=54.1% [2.9%], p=0.016). Subtle head, lip and eyebrow movements emerged as the most important features, while microsaccades data did not significantly improve model performance. Our results demonstrate that observers can discriminate the spatial direction of another person's 'covert' attention, regardless of sensory domain. Thus, covertly attending to different parts of space induces distinguishable patterns behavioural cues, which are available to others during social interactions.



Disclosures: M. Paskin: None. **L. Lundqvist:** None. **A. Guterstam:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.11/II13

Topic: I.10. Human Learning and Cognition

Title: Compromised spontaneity in social contexts: group influence on action timing

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Abstract: In everyday life, seemingly spontaneous actions by individuals are often constrained by external temporal demands, such as deadlines or implicit expectations about when an action must be completed. These time-based constraints, which partially limit individuals' temporal agency and influence the onset timing of voluntary actions, which we refer to here as spontaneity. The Libet experiment (Libet et al., 1982) is a well-known paradigm for studying the cognitive basis of voluntary action. In this experimental setup, participants are asked to report the subjective timing of internal events associated with voluntary actions by using a circular visual timer, the Libet clock. A substantial body of research has since explored the mechanisms through which subjective experiences of free will are generated (e.g., Haggard et al., 2002; Ivanof et al.,

2022). However, fewer studies have addressed the temporal dynamics of when, within a constrained time window, a spontaneous action is actually initiated.In this study, we conducted a series of experiments to measure the timing of spontaneous action initiation under temporal constraints across various social contexts. Participants were instructed to watch a 15-second video clip without narrative content and to take a single snapshot at a moment they personally preferred during the video. The task was designed to induce spontaneous behavior within a fixed time window, while varying the social setting, i.e, (1) viewing alone (Solo condition), (2) viewing simultaneously with others online (Online condition), and (3) viewing simultaneously with others onsite (Onsite condition).Previous studies that provided explicit visual cues to highlight temporal constraints observed multiple peaks in the distribution of action timing (Kodaka et al., 2024). In contrast, this experiment presented temporal constraints implicitly, resulting in trends that partially diverged from previous findings. Moreover, human behavior often reflects behavioral contagion, in which individuals unconsciously mirror the actions of others (Gallup et al., 2012; Néda et al., 2000). Comparing the Online and Onsite conditions, we observed a significant clustering of snapshot-taking within the first quarter of the time window when participants were physically co-present. This suggests that perceptual interaction influenced the timing of spontaneous actions. Based on the results, we further discuss potential causes of this temporal bias, focusing on group size and unity, and further explore the mechanisms underlying the expression of spontaneity and creativity within social groups.

Disclosures: T. Sudo: None. **S. Nozawa:** None. **K. Mogi:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.12/II14

Topic: I.06. Social Cognition

Support: Simons Foundation Autism Research Initiative #990500

Title: Feature-based modeling of visual attention in autism: a large-scale online eye-tracking study

Authors: *N. KIM[1,2], Q. WU[1], B. OUTTEN[1], L. K. PAUL[1], R. ADOLPHS[1];
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Abstract: Autism spectrum disorder (ASD) is a pervasive developmental condition whose genetic, neural and developmental causes exhibit dramatic heterogeneity. Because of this heterogeneity, it has been challenging to elucidate the cognitive and neural mechanisms underlying autistic behavior. Among various behavioral characteristics associated with ASD, atypical visual attention is one of the most consistently observed across developmental stages and diverse contexts, holding potential as a reliable phenotype that could lead to further investigation into genetic and neural underpinnings. Quantifying inter- and intra-individual

variation in this phenotype, however, requires naturalistic stimuli and large, diverse samples. Here, we leverage webcam-based eye-tracking over the Internet and feature-based computational modeling to characterize visual attention in a large sample of autistic adults. Participants watched videos of group conversations that incorporated controlled social and nonsocial features. Across a discovery study and a pre-registered replication study in over 1,300 adult participants (439 ASD, 271 women; 417 Controls, 192 women), we found that individuals with ASD showed reduced attention to speakers, increased attention to distractors, and more frequent gaze shifts. These findings could not be attributed to lower-level visual features and were not observed in psychiatric comparison groups without ASD. Notably, increased attention to distractors was context-sensitive and most pronounced in autistic women. Our study demonstrates the power of scalable online eye-tracking and modeling approaches for capturing individual differences in visual attention, providing a rich platform for future exploration of the multivariate phenotype and the underlying neural mechanisms associated with ASD.

Disclosures: N. Kim: None. **Q. Wu:** None. **B. Outten:** None. **L.K. Paul:** None. **R. Adolphs:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.13/JJ1

Topic: I.06. Social Cognition

Title: Neuropsychological Rehabilitation of Social Cognition in Autism Spectrum Disorder

Authors: *M. DEL VILLAR BASAURI, M. GARZA OLIVARES, D. ZUBIETA HINOJOSA, V. DE LA ROSA, L. ALMARAZ MACIAS, S. MEZA-CAVAZOS;
Psychology, Univ. de Monterrey, San Pedro Garza García, Mexico

Abstract: Aim: To systematically analyze the most recent scientific evidence on neuropsychological rehabilitation programs for social cognition (SC) in children with Autism Spectrum Disorder (ASD). Method: An exhaustive search of relevant databases (PubMed, Google Scholar and Consensus) was carried out using keywords related to ASD, childhood, social cognition, and neuropsychological rehabilitation.Results: 96 scientific articles were identified, considering only those intervention programs focused on the direct training of specific components of social cognition: emotion recognition, Theory of Mind (ToM), and empathy. Interventions that incorporate technology, such as software or applications, are engaging for children and may hold promise in developing specific skills such as emotion recognition. Some studies report improvements in specific tasks; however, a common challenge in the literature is the limited evidence of generalization of these improvements to everyday social contexts. It is observed that interventions that combine explicit training in social cognition with the practice of social skills, or that are implemented in naturalistic contexts, tend to show better generalization.Conclusions: While a variety of interventions targeting specific social cognition

skills have demonstrated efficacy in trained tasks, solid evidence of widespread and sustained improvement in social functioning in real-life contexts remains limited. Key challenges identified include achieving generalization of learned skills and adapting interventions to the diverse cognitive profiles and characteristics of children with ASD.

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Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.14/JJ2

Topic: I.06. Social Cognition

Support: UVA STAR (Supporting Transformative Autism Research)
UVA iTHRIV (NIH 2KL2TR003016)

Title: Divergent patterns of interpersonal neural synchrony in autistic and typically developing child-parent dyads engaged in musical interaction

Authors: *E. DING[1], A. MARZORATTI[4], K. A. PELPHREY[2], S. BOKER[3], J. CONNELLY[3], T. M. EVANS[1];
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Abstract: Interpersonal neural synchrony (INS), the temporally aligned coordination of neural activity between interacting individuals (e.g., children and parents, students and teachers), is a neurobiological indicator of social interaction dynamics. This study investigates INS during music-related tasks between children with/without autism spectrum disorder (ASD) and their parents, and its relationships to either individual's social behaviors and oxytocin receptor gene methylation (OXTRm), a biological correlate of social processing. DNA methylation of OXTR (sites 924 and 934) was measured from saliva. Child-parent dyads (ASD: n = 38; typically developing [TD]: n = 30) completed two EEG hyperscanning tasks (i.e., Music Patterns and Music Free Play) in a naturalistic setting. INS was computed using Windowed Cross-Lagged Correlation applied to dyad members' EEG signals, estimated separately per channel. Our final INS metrics were the mean (scalp-wide) and maximum (the highest single-channel) INS across electrodes. Behavioral Attunement (BA) was assessed from video-recordings of task completion, scored for behavioral markers of child-parent social engagement. Results showed that behaviorally, ASD child-parent dyads exhibited significantly lower BA than TD dyads ($F = 39.58$, $p < .001$). At the neural level, TD dyads' maximum INS was not significantly different than ASD dyads ($F=3.32$, $p=0.076$), but their global mean INS was significantly lower than ASD dyads ($F = 17.37$, $p < .001$). Task condition effects were all nonsignificant. In other words, ASD dyads showed higher average but lower peak INS, indicating a sustained but less dynamic

synchronization profile. Follow up analyses reveal that TD dyads' maximum INS was concentrated in prefrontal areas, while ASD dyads' maximum INS sources were more spread. Likewise, TD dyads' mean INS in PFC areas was significantly higher than ASD dyads' ($F=5.65$, $p=0.022$), indicating distinct neuroactivation patterns during cooperation. Additionally, maximum INS was negatively correlated with child- and self-reported parents' alexithymia symptoms (i.e., difficulty in identifying feelings) ($r = -.217$ to $-.268$), highlighting the role of parental emotional skills in neural alignment. Finally, contrary to predictions, children's OXTRm was not associated with ASD symptom severity (i.e., the extent of autism-related social and behavioral challenges), and parent OXTRm was not associated with their alexithymia. These findings support distinct INS signatures in ASD and underscore the value of jointly examining biological and behavioral indicators of social dynamics in real-world contexts.

Disclosures: E. Ding: None. **A. Marzoratti:** None. **K.A. Pelphrey:** None. **S. Boker:** None. **J. Connelly:** None. **T.M. Evans:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.15/JJ3

Topic: I.06. Social Cognition

Title: Resting-state theta activity in individuals with psychotic-like experiences: a potential marker of early vulnerability

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Abstract: Neuronal oscillations in the theta frequency band (4-7 Hz) have been widely associated with key cognitive processes, including working memory, attentional regulation, and cognitive control. These oscillations are considered particularly relevant during resting-state periods, where they may reflect the brain's intrinsic functional organization. In clinical research, alterations in theta power have been reported across various psychiatric conditions, yet findings remain inconsistent. Particularly, the role of resting-state theta activity in individuals at risk for psychosis is still not well understood. The current study explores theta band activity in individuals who report psychotic-like experiences (PLE), with the aim of identifying early neurophysiological patterns that may signal vulnerability to psychosis. PLEs refer to attenuated or subclinical symptoms resembling those observed in psychotic disorders, such as hallucination-like phenomena or unusual beliefs, and have been proposed as potential markers of risk in the general population. Material and Method: A total of 26 participants aged 14 to 30 years were recruited and assessed using the Community Assessment of Psychic Experiences - Positive scale (CAPE-P15), a validated self report measure for detecting psychotic-like experiences. Based on their scores, participants were divided into two equal groups: PLE group (n = 13), mean age of 22.3 years (SD = 5.6), and Control group (n = 13), mean age of 24.2 years (SD = 6.7).

Electroencephalographic (EEG) activity was recorded under resting-state conditions for two minutes with eyes closed using a 64-channel Biosemi ActiveTwo system. All recordings were visually inspected and preprocessed using standard artifact removal procedures. Wavelet transform was applied to extract spectral power in the theta band across all channels. Theta power was compared between groups using an independent samples t-test. The results revealed a significantly higher theta power in the PLE group compared to the control group ($p = 0.007$). This suggests that individuals with psychotic-like experiences may exhibit distinct neural dynamics even at rest, characterized by increased low-frequency activity. Conclusions: These findings support the hypothesis that resting-state theta activity may serve as a neurophysiological correlate of early vulnerability to psychosis. The increase in theta power observed in individuals with PLE could reflect alterations in self-regulation mechanisms, consistent with literature on theta activity in other psychiatric populations.

Disclosures: R. Mayol: None. **P.A. Gaspar:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.16/JJ4

Topic: I.06. Social Cognition

Title: Associations between sleep measures, cognitive function, and psychosocial wellbeing in midlife adults

Authors: *K. GARG[1], H. LAMONT[1], K. BHATTACHARYYA[2], Z. ADAHMAN[3], P. X. DIAZ MUNOZ[4], E. CANFIELD[5], T. NASKAR[6];
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Abstract: Poor sleep quality is a recognized risk factor for cognitive impairment, particularly in aging populations. Psychosocial wellbeing, specifically a strong sense of life purpose, may buffer these effects. However, few studies have characterized the relationship between sleep quality, cognitive function, and psychosocial wellbeing. We conducted a cross-sectional analysis using data from the second wave of the Midlife in the United States study (MIDUS II, 2004-2006) using self-reported sleep measures. Cognitive function was assessed using the Brief Test of Adult Cognition by Telephone (BTACT), covering global cognition, episodic memory (EM), and executive function (EF). Psychosocial wellbeing was measured using the Ryff's model. Pearson correlations were calculated between psychosocial, sleep, and cognitive variables ($n = 3,659$ for psychosocial-cognitive analysis; $n = 319$ for sleep-cognitive analysis). Higher life purpose was positively associated with global cognition ($r^2 = 0.002862$), EM ($r^2 = 0.01588$), and EF ($r^2 = 0.05382$). In the sleep subsample, greater sleep regularity and alertness were significantly

associated with better global cognition (r^2= 0.02965 and r^2= 0.01780, respectively), EM (r^2= 0.03725 and r^2= 0.02182, respectively), and EF (r^2= 0.03838 and r^2= 0.01295, respectively). These findings suggest that both sleep quality and psychosocial wellbeing independently contribute to cognitive function in midlife adults, supporting their potential as intervention targets to promote cognitive resilience during aging.

Disclosures: K. Garg: None. **H. Lamont:** None. **K. Bhattacharyya:** None. **Z. Adahman:** None. **P.X. Diaz Munoz:** None. **E. Canfield:** None. **T. Naskar:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.17/JJ5

Topic: I.06. Social Cognition

Support: JSPS KAKENHI 20K21823

Title: Individual differences in locus of control correlate with white mater microstructure assessed by diffusion tensor imaging

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Abstract: Locus of Control (LoC) refers to an individual's perceived control over life outcomes, a psychological construct that significantly influences various behavioral domains, particularly academic performance and health-related behaviors (Rotter, 1966). LoC lies on a continuum from internal to external control: individuals with a high internal LoC attribute life events primarily to their own actions and decisions, whereas those with a high external LoC perceive outcomes as driven by external factors beyond their control. Although LoC has been extensively studied in behavioral research, its neural correlates remain largely underexplored. The present study investigates the association between individual differences in LoC and white matter integrity in young adults, hypothesizing that variability in LoC is reflected in structural differences in white matter architecture. Fifty-eight healthy young adults participated in the study. Written informed consent was obtained from all participants, in accordance with the ethical guidelines approved by the internal review board of AIST. LoC was assessed using the Japanese version of the Locus of Control Questionnaire (Kamahara et al., 1982), which includes 18 items rated on a 4-point scale. Diffusion tensor imaging (DTI) data were acquired on a 3-T MR scanner (Philips Ingenia 3T) with the following parameters: TR = 18,496 ms, TE = 60 ms, flip angle = 90°, b = 1,000 s/mm², 70 axial slices with 2 mm thickness. Fractional anisotropy (FA) maps were computed as an index of white matter integrity. Correlation analysis between internal LoC scores and FA values revealed significant positive correlations in the bilateral posterior cingulate cortex (PCC) and the precuneus. These regions are known to be involved in self-referential processing and self-related mental representations (Cavanna & Trimble, 2006),

and are densely connected to the hippocampus—a region previously shown to correlate with LoC-related traits (Pruessner et al., 2005). The PCC and precuneus are central hubs of the default mode network (DMN), which supports internally directed thought processes (Buckner et al., 2008). These findings suggest that individual differences in LoC may be linked to the structural integrity of white matter tracts within the DMN, particularly in regions associated with self-referential and introspective functions.

Disclosures: S. Iwaki: None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.18/JJ6

Topic: I.06. Social Cognition

Support: NIH R01DC019653
NIH U01NS121616

Title: Neural Signatures of Semantic Processing in the Prefrontal Cortex: A Cross-Species Comparison

Authors: *S. LEE[1], I. CAPRARA[1], B. MASH[1], D. J. KELLAR[1], R. BÁEZ-MENDOZA[2], M. JAMALI[1], Z. WILLIAMS[1];
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Abstract: Semantic knowledge is essential for interpreting and interacting with the environment—not only in humans but across many animal species. The prefrontal cortex (PFC) plays a central role in high-level cognitive, emotional, and social processing, and has been implicated in semantic representation and categorization. While prior studies have highlighted broad neuroanatomical similarities across species, the fine-grained neuronal mechanisms underlying semantic representation—particularly at the single-neuron level—remain poorly understood. To address this gap, we performed single-unit and local field potential (LFP) recordings from homologous regions of the PFC in two rhesus macaques (*Macaca mulatta*) and three human participants undergoing awake neurosurgery. During the task, macaques viewed short sequences of images (2-3 per trial), while humans viewed single images or listened to semantically matched spoken words. All stimuli spanned a wide range of categories, valences, and themes and were selected to elicit semantic associations. To characterize semantic space, we used 14 behaviorally relevant attributes (sensory, motor, spatial, temporal, affective, social, and cognitive). These high-dimensional vectors were used to model neural responses and assess representational structure. Neurons in both monkeys and humans exhibited selectivity to specific semantic features, and decoding analyses confirmed that semantic information could be reliably extracted from population activity. Representational similarity analysis revealed substantial

cross-species overlap in the geometry of semantic representations, suggesting the presence of a partially shared semantic manifold. However, species-specific differences were also observed, particularly in the granularity and organization of semantic domains within neural population codes. These findings indicate that while core aspects of semantic representation may be evolutionarily conserved, they are also shaped by species-specific adaptations. This study offers new insights into the neuronal foundations of meaning, revealing how semantic information is encoded at the level of single neurons and neural populations in both humans and non-human primates.

Disclosures: S. Lee: None. **I. Caprara:** None. **B. Mash:** None. **D.J. Kellar:** None. **R. Báez-Mendoza:** None. **M. Jamali:** None. **Z. Williams:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.19/JJ7

Topic: I.06. Social Cognition

Support: Sapien Labs

Title: Correlates of cortical behavior and mental health in Tanzania: An electroencephalographic study

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Abstract: Mental health in Sub-Saharan Africa (SSA) is severely understudied. There have been few attempts to collect empirical evidence of mental health status of individuals and the mental health challenges of communities in SSA. The tools of electrophysiology (EEG) can augment the study of mental health by illuminating connections between objectively measured cortical activity and the data yielded by survey/questionnaire instruments. It is important to identify EEG metrics that have high variance across the population, because these will allow us to discriminate between brain states and find associations with socio-demographic parameters. The purpose of this study was to observe the cortical behavior of a large cohort of people living in Tanzania and to identify demographic factors that can predict differences in key features of EEG recordings. A large sample (n = 5,450) of the population of Tanzania participated in this study including subjects from communities that are difficult to access, such as hunter-gatherer tribes and nomadic people. A series of short questionnaires were used to collect sociodemographic data and confidential information about the life context, such as if a subject had experienced abuse, neglect, traumatic disease or injury, etc. Each participant also completed the Mental Health Quotient (MHQ) survey resulting in an overall score of mental health as well as scores along six subscales, including cognition, adaptability & resilience. EEG was recorded while subjects sat

quietly under four conditions: eyes open, eyes closed, while performing a pattern completion task, and while watching a short video. Data was collected between November 2023 and May 2025. Data was analyzed through various statistical modeling approaches using the following as EEG variables: spectral power across frequency bands, electrode location, signal complexity, and task type. Correlations were measured between these variables and the overall MHQ and its subscales. As well, each of the sociodemographic factors were tested for significance against these variables. This is the largest study of its kind in Sub-Saharan Africa.

Disclosures: A. Thrasher: None. **J. Vianney:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.20/JJ8

Topic: I.06. Social Cognition

Support: Grant from Jananese Society for Higher Brain Function

Title: Differential Influence of Empathy Subcomponents on Moral Judgment After Brain Injury

Authors: *M. SUGANAMI[1], K. TAKAHATA[4], Y. MIMURA[2], M. YAMAMOTO[5], T. MURAMATSU[6], M. MIMURA[3];
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Abstract: Empathy is a multifaceted construct known to influence moral judgment. However, how various empathy subcomponents interact with moral evaluation after brain injury remains unclear. This study examined how four dimensions of empathy—Empathic Concern (EC), Fantasy Scale (FS), Personal Distress (PD), and Perspective Taking (PT)—predict moral judgments in brain-injured individuals compared to healthy controls. We analyzed data from 35 individuals with acquired brain damage and 30 healthy participants who completed a five-condition moral judgment task (e.g., Responsibility, No Negligence, No Harm) and the Interpersonal Reactivity Index (IRI-J). For each condition, we calculated mean “badness” ratings and conducted separate multiple regression analyses by group. In the brain-injured group, PD significantly predicted increased blame in the No Negligence condition, and FS unexpectedly predicted stronger blame in the Responsibility condition. In the healthy group, EC was a significant predictor in the Violation of Norm and Responsibility conditions, but no other empathy subscales showed significant effects. These results suggest a structural divergence in how empathy modulates moral cognition following brain damage. While healthy individuals may rely more on normative evaluation, brain-injured individuals appear more susceptible to affective immersion or narrative overidentification. This dissociation in empathy profiles highlights the

importance of tailored rehabilitation strategies focusing on emotional processing and self-regulation mechanisms in social decision-making contexts.

Disclosures: M. Suganami: None. **K. Takahata:** None. **Y. Mimura:** None. **M. Yamamoto:** None. **T. Muramatsu:** None. **M. Mimura:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.21/JJ9

Topic: I.06. Social Cognition

Title: Shared pain histories enhance socially induced placebo analgesia

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Abstract: Social observation not only modulates placebo analgesia but may also engage empathic mechanisms. Given that individuals typically exhibit greater empathic responses toward in-group than out-group members, group membership contributes to intergroup empathy bias. However, it remains unclear whether, and how, pain-related group membership influences socially induced placebo analgesia via empathic mechanism. The aim of the current study was to investigate the influence of shared prior pain experiences on placebo analgesia. In this study, we manipulated group membership between healthy participants and confederates (i.e., fake participants) by randomly assigning individuals into either an in-group or out-group group (the participant with or without shared prior pain experiences with the confederate, respectively). An observational learning placebo paradigm was employed during functional magnetic resonance imaging scanning, in which the participant was administered the placebo and control creams and they reported their perceived pain intensity after observing the confederate receiving placebo analgesia (i.e., pain reduction in placebo versus control condition). Preliminary data showed that participants in the in-group group reported significantly stronger placebo analgesia compared to those in the out-group group. Crucially, between-group differences in empathic responses predicted the magnitude of placebo analgesia, suggesting a potential role of empathy in modulating socially induced placebo analgesia. These findings offer valuable insights into how social factors, such as group membership, modulate observational learning and empathic processes to shape placebo analgesia.

Disclosures: Z. Li: None. **H. Tsai:** None. **M. Tseng:** None.

Poster

PSTR138: Human Social Cognition: Behavioral and Neural Processes I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR138.22/JJ10

Topic: I.06. Social Cognition

Title: Implications of Frontal Lobes and Sleep Quality in University Students

Authors: *R. A. R. AVILÉS-REYES, E. ARIAS CHÁVEZ;
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Abstract: Introduction: The frontal lobes are brain areas that allow us to regulate, control, monitor, and verify behavior (Bausela, 2017), such as academic processes at the university level. Sleep quality refers to sleeping well at night and functioning well during the day (Domínguez, 2017). There is evidence that poor sleep quality is related to poor functioning of the frontal lobes (Sierra, 2012). **Aim:** To determine the relationship between frontal functioning and sleep quality in university students from public higher education institutions in the Mexico. **Method:** A non-probability convenience sampling was conducted, and 360 university students with a mean age of 21.28 (± 1.96) years were evaluated using the Frontal Systems Behavior Scale (FrSBe, 2001) and the Pittsburgh Sleep Quality Index (PSQI, 2008). A Spearman correlation was performed using SPSS. **Results:** A positive relationship was found between overall sleep quality and general frontal functioning ($rs=0.417$, $p<0.05$), as well as with executive dysfunction ($rs=0.307$, $p<0.05$), apathy ($rs=0.459$, $p<0.05$), and disinhibition ($rs=0.338$, $p<0.05$). Likewise, among the components of sleep quality and frontal systems functioning, a positive relationship was found between subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, use of hypnotic medication, and daytime dysfunction with executive dysfunction, apathy, and disinhibition. Conclusion: It was identified that poor sleep quality leads to frontal dysfunction, resulting in issues such as apathy, executive dysfunction, disinhibition, and general impairment of frontal functioning in university students. It is important to highlight that each component of sleep quality is essential to maintain proper frontal function.

Disclosures: R.A.R. Avilés-Reyes: None. **E. Arias Chávez:** None.

Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.01/JJ11

Topic: I.08. Learning and Memory

Support: NIH Grant F32NS129626
NIH Grant R01NS135850

Title: Increased processing time preserves spatial information across reference frames: The role of posterior medial cortex

Authors: *M. J. STARRETT AMBROSE[1], C. E. L. STARK[1,2], E. R. CHRASTIL[1,2]; [1]Neurobio. and Behavior, [2]Ctr. for the Neurobio. of Learning and Memory, Univ. of California Irvine, Irvine, CA

Abstract: Long-standing models of spatial processing posit that posterior medial cortex (PMC) regions such as the retrosplenial cortex (RSC) are crucial for translating spatial knowledge across viewpoint-dependent (egocentric) and observer-independent (allocentric) frames. In such models, changes to the relative utility of the egocentric or allocentric frame should result in either lower precision to maintain response speed or slower responding to maintain precision, but this prediction has not been directly tested. Inspired by previous work on task switching, we developed a novel spatial memory stay-switch paradigm where participants recalled information about spatial relationships from both a first-person (egocentric) or top-down (allocentric) frame of reference. Participants learned the layout of a 100 m x 150 m virtual town environment by navigating to eight distinct stores within the town. In the spatial memory task, participants were told they would complete randomized trials from two spatial memory tasks. First-person trials showed a viewpoint from a virtual desert with only a single target store visible in front of the participant and a text prompt for a target store; participants turned to face the target store before submitting their response. Top-down trials showed an aerial view of the virtual desert (circle) with an icon at the center of the screen indicating the participant's location relative to a store directly above it on the screen (establishing a heading comparable to the first-person trials) and a text prompt for a target store; participants rotated a pointer to the direction of the target store before submitting their response. Critically, approximately half of the trials stayed in the same format as the preceding trial (both top-down or both first-person) while the other half switched (top-down -> first-person and vice versa). Data from 27 neurotypical adults were analyzed to compare cognitive costs associated with implicit reference frame switching. Memory precision was measured as the absolute angular error between the correct target heading and the heading indicated by participants and processing time was measured using the elapsed time between trial onset and participants' responses. Results indicate that participants incurred a significant processing time cost for switch trials while memory precision did not differ across trial formats or switching. These results provide direct support for translator models of reference frame switching. Ongoing neuroimaging work is being conducted to further test whether RSC or other PMC regions indeed support reference frame switching.

Disclosures: M.J. Starrett Ambrose: None. **C.E.L. Stark:** None. **E.R. Chrastil:** None.

Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.02/JJ12

Topic: I.08. Learning and Memory

Title: Building consensus about human posterior medial cortex

Authors: *E. R. CHRASTIL[1], M. J. STARRETT AMBROSE[2], S. KOSLOV[3], E. HERRERA[6], A. D. STEEL[7], A. BARNETT[8], R. BRAGA[9], R. A. EPSTEIN[4], B. L. FOSTER[5], S. R. HEILBRONNER[10];
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Abstract: The human posterior medial cortex (PMC), also referred to as medial parietal cortex, has been implicated in a wide variety of cognitive functions including episodic memory, spatial navigation, decision making, and scene perception. PMC also overlaps with critical hubs in the default-mode network. However, the anatomical and functional boundaries of human PMC and its subregions are not well defined and vary across research domains. Moreover, PMC subregions that are well-defined in brains of other animals like rats - such as the retrosplenial cortex - do not have well-established homologs in the human brain. As a highly connected hub region in the human brain, properly characterizing PMC function requires first establishing its location with some degree of consensus in the field. To address this problem, we formed the Posteromedial Cortex Cognition Group. We developed a survey to gain insight into the degree of overlap in cognitive functions associated with PMC and the siloing of PMC research areas. A total of 41 respondents from the academic community, ranging from graduate students to full professors (with a cumulative 746 years of reported experience studying the brain). Respondents consistently rated PMC as important for internally directed cognition, episodic memory, and navigation with more uncertainty for other functions such as social processing, working memory, attention, and decision making. While there was a fair amount of consensus on the specific locus within PMC for each cognitive function, these loci overlapped considerably across functions, particularly in the ventral precuneus, posterior cingulate cortex, and retrosplenial cortex. These results highlight a need for collaboration across research disciplines to successfully characterize PMC's role in complex cognition, and provide a foundation on which researchers can come together to achieve this goal collaboratively.

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Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

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Program #/Poster #: PSTR139.03/JJ13

Topic: I.08. Learning and Memory

Support: R01 MH116914
F32 MH130027

Title: Electrophysiology of human posterior cingulate cortex during value- and memory-based decision-making

Authors: *S. R. KOSLOV[1], A. S. DOMINGUEZ ZESATI[4], H. G. REY[4], S. A. SHETH[5], K. DAVIS[2], H.-C. I. CHEN[1], J. W. KABLE[3], B. Y. HAYDEN[5], B. L. FOSTER[1];
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Abstract: Human posterior cingulate cortex (PCC) is routinely implicated across differing tasks of episodic memory. Specifically, while the dorsal subregion of PCC (dPCC) is uniquely implicated in item-recognition decisions, the ventral subregion (vPCC) is linked to the retrieval of autobiographical memories. Interestingly, neuroimaging work has also repeatedly associated similar regions of the dPCC to value-based decision-making. Together, these findings promote the view that the dPCC may support computations common to both memory- and value-based decision-making. However, there is a lack of consensus regarding the specific contributions and timing of PCC involvement to these common decision processes - whether during choice, delay, or feedback periods - as well as the degree to which mnemonic and economic information influences the region's engagement. To test this question, we obtained electrophysiological recordings of local field potentials (LFP) and single-neuron activity from the human PCC during risky value- and memory-based decision-making tasks that were matched in their temporal structure (n = 16). For both tasks, participants earned points by selecting between two options on each trial: a guaranteed, fixed low-reward option or a risky high-reward option. For the value-based task, the chance of reward was indicated by a displayed probability, while for the memory-based task, the chance of reward depended on stimulus memory, defined by exposure during a prior encoding period. Across both tasks, dPCC LFPs reliably showed an increase in broadband gamma (BBG; 70-150Hz) amplitude during the choice period, which remained elevated through the delay period until after feedback was presented. Notably, during the delay period, BBG activity in dPCC was greater for risky compared to safe decisions during value-based decisions only. In contrast, decision related responses were not reliably observed in the vPCC for either task, highlighting subregional differences in PCC engagement during decision-making. Relative to LFP responses, preliminary evidence shows that single neuron spiking in dPCC was more temporally circumscribed, with units primarily engaged during either choice, delay, or feedback periods across both tasks. This observation suggests that human dPCC is comprised of distinct functional subpopulations that may support specific stages of decision-making. Together, these findings indicate a role for dPCC in making and monitoring value- and memory-based decisions. Furthermore, these results align with a proposed role for the PCC in temporal information integration, serving as a convergence zone for mnemonic and executive processes.

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Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.04/JJ14

Topic: I.08. Learning and Memory

Support: 24KKSGR017

Title: Neural trajectories coding for time in precuneal neurons in the macaque

Authors: ***Z. JIN**[1], A. SARKAR[2], N. SU[3], J. CHENG[1], X. ZHU[1], X. ZHOU[3], M. KUSUNOKI[4], S. KWOK[1];
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Abstract: Objective Understanding how the brain encodes the temporal order of episodic memories remains a central question in neuroscience. We investigated how temporal order of episodic memory in the order of seconds is represented in the macaque precuneal neurons, focusing on population-level neural dynamics during memory retrieval in a temporal order judgement (TOJ) task. **Methods** Macaques were trained to view naturalistic videos and performed a temporal order judgement test. Each video consisted of two concatenated segments, and on each trial, monkeys judged which of two still frames had appeared earlier in a specific video, either after a 2-s or 1-min delay. We recorded spiking activity from 88 precuneus neurons across 30 sessions using chronically implanted multichannel electrodes. Trials were categorised by the temporal location of the TOJ frames within the original videos. We applied neural manifold learning via PCA to reduce the high-dimensional firing rate data into a low-dimensional memory subspace. This allowed us to visualise and quantify the neural geometry of different task phases (Cue, Watching, Delay, TOJ) and to assess how temporal information is coded during TOJ. We also examined how the coding evolved over time (short vs. long delays) and its relationship with the animals' memory performance. **Results** Firstly, memory subspace trajectories revealed clear separation among the four task phases, with within-phase clustering and a continuous progression that respected the trial's temporal structure. In both 2-s and 1-min conditions, temporal locations of TOJ frames were not differentiable during the delay period but became increasingly separable after TOJ onset as the monkeys started to retrieve memories. Trajectories corresponding to different temporal locations exhibited maximal neural distance from one another at approximately 2.3 s after TOJ onset, and this separation was systematically modulated by the age of memories (manipulated by delays). These distinctions were absent in incorrect trials, suggesting a behaviourally relevant neural correlate. Importantly, such distinctions were observable in the geometry of population dynamics in the memory subspace but not from individual neuron firing rates. We further quantified neural distances as a function of temporal locations in memory and confirmed a dynamic encoding process unique to the TOJ phase. **Conclusion** Temporal memory in the precuneal neurons is expressed through population dynamics rather than isolated neuron tuning. Neural manifold analysis reveals structured memory subspaces that code for time progression that support successful retrieval of temporal order of episodes.

Disclosures: Z. Jin: None. **A. Sarkar:** None. **N. Su:** None. **J. Cheng:** None. **X. Zhu:** None. **X. Zhou:** None. **M. Kusunoki:** None. **S. Kwok:** None.

Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

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Program #/Poster #: PSTR139.05/JJ15

Topic: I.08. Learning and Memory

Support: Neukom Institute for Computational Sciences
BBSRC BB/V003887/1

Title: Bifurcation of scene-related perception and memory processes in superior parietal cortex

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Abstract: Scene perception and memory are closely linked in cortex: each of the three scene-selective brain areas in posterior cerebral cortex (parahippocampal place area, PPA, occipital place area, OPA, and medial place area, MPA) has a paired area, situated anteriorly that selectively activates when participants recall familiar places. Recently, two labs (Kennedy et al., 2024; Yoon et al., 2025) have described a fourth scene-selective brain area situated on the posterior intraparietal gyrus that selectively activates during scene perception, referred to as PIGS. Here, we asked whether PIGS also has a paired anterior region that activates during place memory recall in two independent datasets. In Dataset 1, we localized PIGS in 12 participants by comparing fMRI activity while participants viewed static images of scenes compared with faces. In Dataset 2, we localized PIGS by comparing fMRI activity while 13 participants viewed 3-second videos of scenes, faces, objects, and bodies. In both datasets, we compared the locations of PIGS with place memory selective activity, localized by comparing activation when participants visually recalled personally familiar places compared with people. In both datasets, we found a swath of memory-selective activity immediately anterior and adjacent to PIGS, consistent with the posterior-anterior perception-memory arrangement observed for the other scene selective areas. Interestingly, memory responses anterior to PIGS followed two different trajectories. One trajectory dove down the medial wall toward precuneus and Area 23a. The second trajectory moved anteriorly along the lateral surface toward prefrontal cortex. We investigated this relationship in using resting-state functional connectivity analyses in Dataset 2. These analyses confirmed these distinct medial and lateral pathways, with PIGS situated at the bifurcation point. The medial pathway was preferentially functionally connected to areas activated during the place memory recall task, including Area 23a, the parietal-occipital sulcus, and hippocampus. The lateral pathway was functionally connected to areas that were not active during the place memory recall task, including the anterior intraparietal area, frontal eye fields,

and inferior frontal junction. These results suggest that PIGS may be an intersection or bifurcation point of visual and memory-related information related to visually-guided navigation.

Disclosures: A.D. Steel: None. **C. Scrivener:** None. **E.H. Silson:** None.

Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

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Program #/Poster #: PSTR139.06/JJ16

Topic: I.08. Learning and Memory

Support: NIH Grant GR00016004

Title: Dissociation Between The Anatomical Retrosplenial Cortex and the Retrosplenial Complex Engagement for Learning Overlapping Navigational Routes

Authors: *E. HERRERA, T. BROWN;
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Abstract: Prior work has shown that there might be functional differences between anatomical Retrosplenial Cortex (RSC) and a broader, more-posterior area known as Retrosplenial Complex (RSComplex) in scene perception tasks (Epstein, 2008). However, it is not clear whether these regions also contribute differently to processes like route learning when one route can be integrated with already familiar routes on the basis of perceptual overlap. To test this idea, we had humans navigate virtual mazes in fMRI. Importantly, half of the routes crossed paths with previously-learned ones (overlapped; OL), which increases demands on configural learning of the environment for route integration, while the other half were completely distinct routes (non-overlapping; NOL). We used machine learning to test when and where anatomical RSC and RSComplex timecourses differed along locations in these two types (OL and NOL) of routes. Overall, both ROIs had significantly similar differences in their timecourses between OL and NOL (quantified by training the classifier in one ROI and testing in the other). However, we demonstrate that RSComplex timecourses do not differentiate between OL and NOL route learning, but anatomical RSC does. This was driven by overlap/integration demands, because when we directly compare the timecourses from anatomical RSC and RSComplex, we could significantly discriminate the ROIs for OL but not for NOL. Collectively, these results suggest that the anatomical RSC might be more sensitive to integrating novel and old spatial memories.

Disclosures: E. Herrera: None. **T. Brown:** None.

Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.07/JJ17

Topic: I.08. Learning and Memory

Support: 1R01NS107357-03

Title: Differentiating contributions of the medial parietal cortex during episodic memory using iEEG

Authors: *B. C. LEGA;
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Abstract: Models of episodic memory drawn primarily from non-invasive data implicate the medial parietal cortex (MPC), as integral in episodic memory processing networks. Moreover, aging research models have characterized these MPC structures, primarily the posterior cingulate cortex and the precuneus, as changing in functional organization and performance across the lifespan, correlating with age-related deficits in automatic-binding processes in associative memory. Theta oscillations, which support processes such as inter-regional coordination, represent a key mechanism previously identified in hippocampal networks as key to memory processing, as well as medial parietal recordings in humans.
Using a data set of 68 patients with intracranial recordings who performed a verbal associative pairs paradigm, we examined neural activity of successful encoding and recollection within these regions and their related networks. Our data identified regional contributions of oscillatory power and phase network synchrony, as well as specific differences in these contributions for older adults that differentiate the posterior cingulate cortex and precuneus.
Specific to encoding, bilateral decreases in theta oscillatory activity of the posterior cingulate cortex were associated with age-invariant subsequent recollection. We demonstrated this pattern of oscillatory decrease occurred in young adults in addition to age-invariant effects with age-specific sub-analyses. Furthermore, using mixed-effects modeling, we demonstrate age-related differences in these oscillatory patterns, especially in the left posterior cingulate and left precuneus, which exhibited both a greater decrease in theta relative to younger adults and increases in relative theta power of familiar items relative to those items subsequently recollected. We interpret these data within general models of episodic processing, such as the posterior medial/anterior temporal framework and core recollection network, as well as models of age-related differences, such as the associative deficit hypothesis. Our findings represent one of the first examinations of neurophysiological processes in intracranial patients that differentiate regions within the MPC with respect to age-related changes. The temporal precision of intracranial recordings facilitates identifying regional differences connected to mnemonic processing.

Disclosures: B.C. Lega: None.

Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.08/JJ18

Topic: I.08. Learning and Memory

Support: ZIA MH002920-09

Title: Atypical place selectivity in the retrosplenial complex in individuals with autism spectrum disorder

Authors: *A. PERSICHETTI[1], T. LI[2], W. STEVENS[3], A. W. GILMORE[4], A. MARTIN[5]; [1]Moss Rehabil. Res. Inst., Philadelphia, PA; [2]Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Psychology, York Univ., Toronto, ON, Canada; [4]Psychological and Brain Sci., Univ. of Delaware, Newark, DE; [5]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: A small, but intriguing, behavioral literature on individuals with autism spectrum disorder (ASD) has shown that they are impaired when navigating using an allocentric reference frame (i.e., map-based navigation), but are not impaired when navigating using an egocentric reference frame (i.e., visually guided navigation). Meanwhile, there is some neuroimaging evidence in typically developing individuals (TD) demonstrating that the retrosplenial complex (RSC) is part of a map-based navigation system, while the occipital place area (OPA) is part of a visually-guided navigation system. The key identifying feature of the RSC and OPA (putative place-processing cortical regions) is that they respond significantly more to pictures of places compared to pictures of objects or faces (i.e., place selectivity). Therefore, we predicted that in individuals with ASD, the RSC would show significantly weaker place selectivity when compared to a TD control group, while the OPA would not show such a difference between the groups. To test our prediction, we used functional MRI (fMRI) to scan groups of ASD and TD individuals that were matched on age, IQ, in-scanner head motion, and tSNR. During the scan, participants viewed pictures of unfamiliar places, faces, and objects while performing a one-back task. We operationalized place selectivity as the difference between the brain responses to places and the average responses to faces and objects in each region. As predicted, independent-samples t-tests showed that place selectivity was significantly lower in the RSC, but not the OPA, in the ASD group compared to the TD group. Crucially, we also found a significant ROI x Group interaction in a two-way ANOVA. These results suggest that impaired map-based navigation in individuals with ASD may be due to atypical functioning in the RSC.

Disclosures: A. Persichetti: None. **T. Li:** None. **W. Stevens:** None. **A.W. Gilmore:** None. **A. Martin:** None.

Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.09/JJ19

Topic: I.08. Learning and Memory

Support: Hartmann

Title: The Salience / Parietal Memory Network Responds to Salient Transients Even When They Are New Items in an Old-New Recognition Test

Authors: *X. WEI[1], R. L. BUCKNER[2];
[1]Psychology, [2]Psychology and Ctr. for Brain Sci., Harvard Univ., Cambridge, MA

Abstract: The Salience / Parietal Memory Network (SAL/PMN) is a network that has been explored through two distinct functional perspectives. Study of the Salience Network (SAL) anchored on the dorsal anterior cingulate and anterior insula, and focused on transient responses to salient, relevant stimuli (Seeley, 2019). Study of the Parietal Memory Network (PMN) focused on posterior midline regions and mid-cingulate cortex, and noted responses to familiar items in old-new recognition tasks (Gilmore et al., 2015). Within-individual precision neuroimaging explorations have demonstrated the full set of regions is likely a single distributed network that has been explored from different perspectives, leading to the question of how detection of salient events and processes contributing to old-new recognition relate to one another (Du et al., 2024). To explore this question, we examined the network across multiple conditions in intensively scanned individuals that contrasted familiarity with saliency (N=6, each person scanned 4 times). In a standard oddball paradigm (detect an infrequent red “K”), the SAL / PMN network was activated. It was also activated by old words in a standard old-new recognition task, thus reproducing both effects that have been emphasized in the two historical lineages. In a critical oppositional contrast, old-new recognition was examined when old items were rare (10%) and the task was to detect the old items versus a second condition when new words were rare and the task was to detect the new items. The full extent of the SAL / PMN network was activated during the detection of targets even when those targets were new items and the control was old items, consistent with a response to the saliency of the targets not their mnemonic history. These findings suggest the SAL / PMN responds to salient, transient events. The finding that the network can show differential responses in old-new recognition paradigms likely reflects that such decisions are asymmetrical, and the old items are treated as the targets by the participant, as the effect can be reversed by changing the relevance of the new items.

Disclosures: X. Wei: None. **R.L. Buckner:** None.

Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

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Program #/Poster #: PSTR139.10/JJ20

Topic: I.08. Learning and Memory

Support: NIH Grant R01MH130529

Title: A voxel-level visuospatial code structures hippocampal-Default Network interactions

Authors: *P. A. ANGELI[1], A. D. STEEL[2], C. E. ROBERTSON[1];
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Abstract: Cortical hierarchy models posit that posteromedial cortex, along with the broader Default Network (DN), serves as an associative "hub" coordinating information between the hippocampus and visual networks to support mnemonic-sensory interactions. However, little is known about the coding principles that enable the hippocampus's context-dependent, allocentric codes to interface with the sensory-driven, egocentric codes of visual cortex. Our previous work has observed a latent, bivalent visuospatial code in the human hippocampus (Angeli*, Steel* et al. bioRxiv), expanding on previous work in cortex (Steel*, Silson* et al. 2024; Steel*, Angeli* et al. bioRxiv). Here, we test whether this bivalent visuospatial code structures hippocampal-cortical interactions. To do this, we leveraged densely-sampled high-resolution 7T functional MRI (Allen et al. 2022), voxel-wise visual population receptive field (pRF) modeling, and individualized resting state networks definitions. We first identified voxels in both the hippocampus and in broader cerebral cortex that were significantly well-fit by a retinotopic pRF model (i.e., with spatial-tuning for a particular location in visual space). The visuospatial tuning preferences of hippocampal voxels - specifically preferred visual field location (x,y) and response valence (positive vs. negative) - were highly stable across runs ($p < 0.05$). Next, we tested the extent to which this retinotopic code structured the co-activity of hippocampal-cortical voxels in independent resting-state data. Our results show that voxel visuospatial tuning structured hippocampal-cortical functional connectivity: spontaneous activity in negatively tuned hippocampal voxels was significantly anticorrelated with positively tuned cortical voxels and vice versa ($p < 0.01$), with the strongest anticorrelation occurring between voxels preferring matched (vs. unmatched) visual field locations ($p < 0.01$). This effect persisted specifically between the hippocampus and the DN ($p < 0.01$), which relative to other cortical networks showed the highest proportion of voxels that preferentially co-fluctuated with negative hippocampal pRFs ($p < 0.05$). This finding highlights the role of a voxel-level visuospatial code in structuring interactions between the hippocampus and posteromedial cortical networks.

Disclosures: P.A. Angeli: None. **A.D. Steel:** None. **C.E. Robertson:** None.

Poster

PSTR139: Hippocampal: Cortical Interactions in Primates and Human

Location: SDCC Halls B-H

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Program #/Poster #: PSTR139.11/JJ21

Topic: I.08. Learning and Memory

Support: NIH R01MH119099
NSF CAREER Award (Honey)

Title: Narrative representations resist interference

Authors: X. LI[1], H. LEE[3], *C. J. HONEY[2];
[1]Psychological and Brain Sci., [2]Johns Hopkins Univ., Baltimore, MD; [3]Dept. of Psychological Sci., Purdue Univ., West Lafayette, IN

Abstract: Daily tasks like reading and problem-solving are frequently interrupted. How do we maintain cognitive context in the face of such interference? We hypothesized that readers generate an interference-resistant "episodic background" representation that sustains mental context through interruptions. We used fMRI to measure neural responses as participants (N=73) listened to coherent (or incoherent) narratives (~11 minutes long) with or without 17 interruptions (each 20-30 seconds). Across all conditions, hippocampal (HC) activity transiently increased at interruption onset. Individuals with larger onset activations recalled the story better ($r=.465$, $p<.001$), consistent with the notion that HC activity reflects encoding of the preceding narrative epoch (Ben-Yakov & Dudai, 2011). To identify signatures of an "episodic background" during the interruption periods, we measured inter-subject neural pattern similarity. In the posterior-medial cortex (PMC), we observed reliable neural patterns that: (a) persisted through silent pauses in the intact story and (b) were selective to the preceding narrative content. Moreover, similar PMC patterns were detected in a separate group of participants whose interruption periods were filled with theory-of-mind tasks. Individuals with more reliable PMC patterns during interruptions exhibited post-interruption neural activations in high-level areas (e.g., angular gyrus) more closely matching continuous listening baselines ($r=.320$, $p=.015$), indicating successful restoration of narrative context. Additionally, more reliable PMC dynamics during interruption periods predicted better narrative memory ($r=.472$, $p < .001$), even though it was not related to participants' conscious thoughts about the story ($p > .1$). These stable, selective interruption PMC patterns were absent when interruptions occurred in an incoherent (scrambled) version of the narrative. These findings support an "episodic background" process in the human PMC; this process constructs and sustains mental context through interruptions, aiding long-term memory formation and the restoration of context following interruption.

Disclosures: X. Li: None. **H. Lee:** None. **C.J. Honey:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dynamic Memory Solutions.

Poster

PSTR140: Hippocampal Architecture, Representations, and Navigation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.01/JJ22

Topic: H.02. Reward and Appetitive Learning and Memory

Support: EKÖP-2024-214

Title: Synaptic and dendritic architecture of two types of hippocampal somatostatin interneurons

Authors: *Á. OROSZ[1], V. T. TAKACS[2], Z. BARDOCZI[2], P. BERKI[2], K. E. SÓS[2], H. SEBOK[2], S. KALI[2], T. F. FREUND[2], G. NYIRI[2];
[1]Inst. of Exptl. Med., Budapest, Hungary; [2]HUN-REN Inst. of Exptl. Med., Budapest, Hungary

Abstract: GABAergic inhibitory neurons fundamentally shape the activity and plasticity of cortical circuits. A major subset of these neurons contains somatostatin (SOM); these cells play crucial roles in neuroplasticity, learning and memory in many brain areas including the hippocampus, and are implicated in several neuropsychiatric diseases and neurodegenerative disorders. Two main types of SOM-containing cells in area CA1 of the hippocampus are oriens-lacunosum-moleculare (OLM) cells and hippocampo-septal cells. These cell types show many similarities in their soma-dendritic architecture, but they have different axonal targets, display different activity patterns in vivo and are thought to have distinct network functions. However, a complete understanding of the functional roles of these interneurons requires a precise description of their intrinsic computational properties and their synaptic interactions. In the current study we generated, analyzed and make available several key datasets that enable a quantitative comparison of various anatomical and physiological properties of OLM and HS cells. The dataset includes detailed scanning electron microscopy-based 3-dimensional reconstructions of OLM and HS cells along with their excitatory and inhibitory synaptic inputs. Combining this core dataset with other anatomical data, patch-clamp electrophysiology and compartmental modeling, we examined the precise morphological structure, inputs, outputs, and basic physiological properties of these cells. Our results highlight key differences between OLM and HS cells, particularly regarding the density and distribution of their synaptic inputs and mitochondria. For instance, we estimated that an OLM cell receives about 8300, whereas an HS cell about 14800 synaptic inputs, about 16% of which are GABAergic. Our data and models provide insight into the possible basis of the different functionality of OLM and HS cell types and supply essential information for more detailed functional models of these neurons and the hippocampal network.

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Poster

PSTR140: Hippocampal Architecture, Representations, and Navigation

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.02/KK1

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Inverse Reinforcement Learning Infers Parameters Driving Hippocampal Learning and Downstream Behavior

Authors: *I. RUSU[1], T. O. SHARPEE[2];
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Abstract: Investigating and predicting reward-driven behavior is crucial for understanding how learning and decision making occur in brain. The field of reinforcement learning provides an excellent framework to study such questions. In this framework the organism, otherwise known as agent, exists in an environment comprised of various states. The agent occupies a state, performs an action, allowing it to move to the next state. For this state transition, it can receive a reward. The objective of the agent is to accumulate as many rewards as possible. The agent thus learns a policy, a probability distribution of actions per state that if followed maximizes overall reward.We use a known model called Information-to-Go, which builds off classic Q-learning, and proposes an analytical solution for an agent to solve for an optimal policy. This is done by minimizing a free-energy functional via a Bellman-type recursion. The model assumes the agent exists in a fully observable Markov Decision Process (MDP). The MDP stipulates that the next state and reward is only dependent on just the current state and action pair.This model allows us to characterize each state in our environment into terms which stand for decision complexity, information gain, and overall preference for reward-seeking vs. exploration, . We show that will three main theoretic quantities can be analyzed in real organisms and provide novel insights into how neural populations encode information.We analyze a published dataset of macaques that performed a special navigation task for a reward. While each animal was navigating an X maze towards a goal, right mid-posterior hippocampus recordings were taken from 183 cells. We use the dataset of navigation paths in the maze to infer both the policy for each trial, as well as the three parameters in the Information-to-Go model. This form of inverse reinforcement learning which allowed us to infer the learned policy, gives us insight into which neural populations in the spike train correspond to parameters in the model. We analyze how spike trains in the hippocampus encode theoretic qualities, using correlation and mutual information. We study what populations of neurons firing patterns maximize the mutual information, between the firing pattern and the state transition.

Disclosures: I. Rusu: None. **T.O. Sharpee:** None.

Poster

PSTR140: Hippocampal Architecture, Representations, and Navigation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.03/KK2

Topic: I.03. Decision Making

Support: NIH R01 MH129439

Title: A vectorial code for semantics in human hippocampus

Authors: *M. FRANCH[1], K. KATLOWITZ[1], E. MICKIEWICZ[1], J. BELANGER[2], B. Y. HAYDEN[1], S. A. SHETH[3];
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Abstract: As we listen to speech, our brains actively compute the meaning (semantics) of individual words. Inspired by the success of large language models (LLMs), we hypothesized that the brain employs vectorial coding principles for semantics. Just as LLMs represent meaning using patterns of numbers, we wondered if the brain might do something similar - using patterns of activity across many neurons to represent what words mean. To test this, we recorded from hundreds of individual neurons in the human hippocampus, a brain area known to support memory and meaning, while people listened to stories. We found that groups of neurons respond differently depending on a word's meaning, especially when the meaning depends on the context of the sentence - just like how language models like BERT work. In contrast, models that ignore context, like Word2Vec, didn't match brain patterns as well. Interestingly, we also saw that when two words are very similar in meaning, the brain sometimes makes their patterns *more* different, possibly to keep them from being confused. This kind of contrastive coding may help the brain sharpen subtle differences. We also found that words with more than one meaning (like "bank") evoked a wider range of brain responses, highlighting the role of context even more. Overall, our results suggest that the human hippocampus encodes meaning using flexible, context-sensitive patterns similar to the vector-based systems used in modern AI.

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Poster

PSTR140: Hippocampal Architecture, Representations, and Navigation

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Program #/Poster #: PSTR140.04/KK3

Topic: H.04. Emotion

Support: NIH Grant R01DC019813
NARSAD Young Investigator Award
UCSF PBBR independent research award

Title: Differential encoding of odor space across hippocampal subregions

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Abstract: The hippocampus plays a crucial role in discriminating and decorrelating representations of similar inputs. Although the dentate gyrus (DG) is important for disambiguating closely related contexts, whether the DG plays a similar role in disambiguating individual sensory stimuli remains unresolved. Moreover, how distinct cell types and subregions

of the hippocampal complex contribute to this process has been scarcely explored. To better understand how stimulus information is processed and transformed across subregions of the dorsal hippocampus, we used 2-photon calcium imaging of granule (GC), hilar (HC), or CA1 cells to probe neural representations of innately neutral odor pairs that systematically varied in their chemical similarity to one another. Performance of linear classifiers trained to discriminate odor-related population activity varied across sublayers. In general, decoding accuracy between odors was inversely correlated with their chemical similarity. Consistent with a role in pattern separation, however, granule cells displayed high decoding performance when segregating similar odors. Interestingly, hilar neurons performed significantly worse than both GC and CA1 cell types, illustrating functional heterogeneity across sublayers within the DG. Population vector and dimensionality reduction analyses supported these findings, with similarity between related odor pairs lowest for GCs. Moreover, recording across multiple days of odor presentations allowed us to assess the stability of odor representations across days, as well as experience-dependent changes in representational similarity. Collectively, these results elucidate region-specific encoding properties across the dorsal hippocampus.

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Poster

PSTR140: Hippocampal Architecture, Representations, and Navigation

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.05/KK4

Topic: H.04. Emotion

Support: NIH Grant R01MH136270
NIH Grant R01MH108623

Title: Dynamic Representations of Stimulus Features in the Hippocampal-Amygdala Network

Authors: *J. A. WAGNER-CARENA[1,2,3], E. LIU[3,4], R. LELONG[4,6], J. BIANE[3,4], M. KHEIRBEK[2,3,4,5];
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Abstract: Understanding how meaning is attached to otherwise neutral cues is crucial to uncovering the neural basis of emotional and associative learning. The ventral hippocampus (vHPC) is a central hub and interface linking cognitive and emotional processing. Here, we show that vHPC robustly encodes the identity - but not valence - of salient stimuli, and maintains stable representations of stimulus cue identity even after the reversal of cue valence. This stability was unexpected, as the vHPC is reciprocally connected with the basolateral amygdala

(BLA), a region well studied for its role in valence coding. Thus, we sought to determine 1) whether employing identical stimulus parameters would reveal robust valence coding within the BLA and 2) how neural representations in the BLA adapt in tasks where the valence of a stimulus is reversed. Using in vivo two-photon calcium imaging, we recorded BLA neural responses across time and experience. Analysis of activity patterns in response to innately appetitive and aversive stimuli revealed mixed selectivity at the single-neuron level, with individual cells responding to multiple stimulus features. However, at the population level, ensembles reliably discriminated valence categories, suggesting the generalized code for valence in the BLA fundamentally differs from that of the connected vHPC. Next, we performed an associative learning experiment, where, after mice were trained to associate a specific odor cue with a positive or negative outcome (reward versus shock), the associations were reversed to determine how BLA neurons track the associated value of a conditioned stimulus (CS). Early in learning, we found that the CS was weakly represented compared to the unconditioned stimulus (US). However, with continued training, we found that CS and US became jointly represented and dynamically updated in the BLA, suggesting a flexible conjunctive encoding that supports efficient pattern separation. Notably, each CS/US pair exhibited distinct neural representations, even when cues or outcomes overlapped. Overall, our findings confirm that, unlike in vHPC, emotional valence is effectively represented within BLA ensembles and indicate that BLA supports flexible updating of associative and emotional information. Future experiments will directly manipulate vHPC-BLA projections to causally test their role in updating emotional associations, further elucidating the interaction between stable hippocampal representations and flexible amygdala-based valence encoding.

Disclosures: J.A. Wagner-Carena: None. **E. Liu:** None. **R. Lelong:** None. **J. Biane:** None. **M. Kheirbek:** None.

Poster

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Topic: H.04. Emotion

Support: NIH U01 NS117838
NIMH 1R01MH120194
R61 MH135109

Title: Neural mechanisms of incidental visual attention and subsequent memory for landmarks during real-world navigation

Authors: *A. KAZEMI[1], L. AUGUSTIN[2], U. TOPALOVIC[3], T. DAVIS[1], M. HOLLEARN[2], J. CAMPBELL[1], D. ELIASHIV[5], V. R. RAO[6], I. FRIED[7], N. HASULAK[8], S. HILLER[5], N. A. SUTHANA[4], C. S. INMAN[2];
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Abstract: Real-world navigation is a foundational behavior that demands the judicious processing of complex and continuous streams of sensory information. Given our finite cognitive resources, real-time processing and identification of the important information in our environment is crucial for efficient learning and memory encoding. For instance, the dynamics of visual exploration guided by attention mechanisms may facilitate the encoding of key landmarks while navigating through a park or mall, which in turn facilitates successful subsequent wayfinding. Despite the dynamic demands of this real-world behavior, our current understanding of the interplay between visual attention and episodic memory has been largely limited to controlled and simplified laboratory experiments on a computer screen. Using mobile eye-tracking precisely synchronized with direct hippocampal recordings, the current study examined how visual attention influences subsequent landmark memory and its neural correlates during real-world navigation.

Five participants with intractable epilepsy, implanted with NeuroPace Responsive Neurostimulators recording hippocampal local field potentials (LFPs), wore mobile eye-trackers while learning a 0.75-mile indoor-outdoor route. On Day 1, participants completed an experimenter-guided encoding walk followed by self-guided retrieval walks. On Day 2, they completed additional retrieval walks, followed by a surprise recognition task for route landmarks.

Participants demonstrated incidental encoding of landmarks along the route without explicit memory instructions after their fifth walk. Longer and more frequent fixations on landmarks predicted successful recognition, particularly during the initial, second, and final walks before the recognition test. Post-test visual attention was also modulated by landmark recognition outcomes, suggesting a top-down memory-driven guidance of attention. Critically, neural activity time-locked to the first fixation on each landmark predicted subsequent memory performance.

Overall, these findings replicate key results from laboratory settings, demonstrating that visual attention in real-world navigation is predictive of both behavioral memory performance and underlying neural activity. This approach offers a novel framework for studying the neural dynamics of naturalistic memory formation in freely moving humans.

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Poster

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Program #/Poster #: PSTR140.07/KK6

Topic: H.04. Emotion

Support: R61MH135405

Title: Introducing CAMERA: Context-Aware Multimodal Ecological Research and Assessment Platform

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Abstract: We aim to identify novel biomarkers of anxiety and memory in the human brain during naturalistic behavior, and to investigate how anxiety state influences memory. However, this has been challenging due to subjective or sparse measures of anxiety and memory state that vary with time. To address this, we developed CAMERA (Context-Aware Multimodal Ecological Research and Assessment), a multimodal platform for measuring brain-behavior interaction in hospitalized EEG patients. It synchronizes neural, physiological, behavioral and environmental data with intermittent active cognitive state assessments. To date, CAMERA has been deployed in 20 patients, including 13 scalp EEG and 7 stereo-EEG subjects.A central innovation of this work is the integration and real-time synchronization of multimodal data. Passively collected data include EEG, autonomic physiology signals from wristband sensors, smartphone linguistic features and audiovisual monitoring. It also actively delivers random, intermittent ecological momentary assessments (EMA) that include self-reported anxiety state ratings and a visual-spatial memory task ("Treasure Hunt"), triggered by an acoustic startle alert. In addition, CAMERA will use machine learning on recent data to predict subjects' anxiety and memory states, optimizing EMA timing to improve response rates.This infrastructure enables temporally precise, minimally disruptive monitoring of internal states in humans, facilitating real-time state decoding and closed-loop neuromodulation.Our current scientific goal is to identify novel biomarkers of anxiety and memory state. Preliminary analysis demonstrates associations between variations in anxiety level and theta band power (2-10 Hz) from hippocampus and amygdala. We also explored additional features potentially relevant to anxiety-memory states, including smartphone-derived linguistic features, such as sentiment valence, pronoun use, and absolutist language, vocal fundamental frequency (F0) from acoustic analysis, automated annotation of affective states using deep learning-based facial expression recognition models. These features show promise as robust, novel physiological biomarkers. Together, CAMERA and our multimodal analysis framework support developing predictive models of anxiety and memory function, and establish a rich dataset for advancing brain-behavior research.

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Poster

PSTR140: Hippocampal Architecture, Representations, and Navigation

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Program #/Poster #: PSTR140.08/KK7

Topic: I.03. Decision Making

Title: Preference Tracking in Decision Making via Hippocampal Retrieval

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Abstract: Evidence accumulation models of decision making have been found to account for many aspects of choice behavior, including response times. These models typically require the parallel tracking of dynamic preferences for all options over the course of deliberation. When considering possible neural computational mechanisms for such evidence accumulation accounts, this dynamic tracking of all options in parallel is problematic. While extremely common choice tasks, such as choosing a saccade location, can accommodate the encoding of preferences over a fixed option space, such as a retinotopic map, deliberations over novel choice options cannot be easily explained by neural inhibition between fixed patches of tissue for each option's levels of preference. It is not clear how inhibition between such patches might spontaneously configure when a novel choice problem is presented. We present an alternative account in which choice options are considered serially, represented over a common pool of neurons in frontal cortex, with competition arising from a process of adaptively increasing the likelihood of focusing upon (representing) high value options over deliberation time. This approach is inspired by the idea that abstract decision making capabilities might have coopted systems that evolved to make binary decisions during foraging, in which case the choice is between exploiting a focal resource versus exploring alternatives. From this perspective, when faced with a novel decision making task, serial deliberation involves repeatedly choosing between continued consideration of a given option versus switching focus to another option, with the likelihood of switching decreasing over time. We present results from a computational model of such serial deliberation in which the likelihood of focusing on a given option is a function of the probability of retrieving that option from a hippocampal memory system. The relative increase in probability of retrieval for high value options arises from dopamine mediated synaptic plasticity in the CA3 region of the hippocampus. We present both an abstract mathematical version of this model and a version building on past computational neuroscience models of hippocampal function. We compare the decision making behavior of model simulations with that of a standard drift diffusion model, which requires the parallel tracking of option preferences.

Disclosures: D.C. Noelle: None.

Poster

PSTR140: Hippocampal Architecture, Representations, and Navigation

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Topic: H.04. Emotion

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CFI John R. Evans Leaders Fund 38098
NARSAD Young Investigator Grant 25287

Title: Serotonergic inputs to the ventral hippocampus underlie sex differences in anxiety

Authors: *L. PIZZOCCARO[1], S. VAN DER VELDT[3], A.-S. SIMARD[1], F. HENDERSON[2], G. DUCHARME[5], B. AMILHON[4];
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Abstract: Anxiety disorders are among the most common psychiatric conditions worldwide, with women being almost twice more likely than men to be diagnosed throughout their lifetime. Serotonergic (5-HT) neurons from the raphe nuclei are heavily involved in the regulation of mood and anxiety, yet the neural substrates underlying sex-related differences in anxiety remain largely unknown. The ventral hippocampus (vHP) acts as a major modulator of anxiety and receives dense 5-HT inputs. We hypothesize that serotonin release in the vHP is crucial in controlling anxiety, and that this process is influenced by sex. All experiments were carried out on male and female SERT-Cre mice, which expresses the Cre recombinase in 5-HT neurons. A retrograde viral vector carrying the fluorescent protein eYFP was injected into the vHP, allowing us to target exclusively the raphe-vHP serotonergic neurons. vHP-projecting raphe neurons are located in various raphe sub-regions, including the interfascicular part of the dorsal raphe (DRi), median raphe (MnR) and B9. Fiber photometry recordings of vHP-projecting MnR neurons during anxiety tests revealed sex differences in population activity levels. Pathway specific optogenetic activation of 5-HT neurons projecting to the vHP was achieved using the excitatory opsin ChETA. Activating vHP-projecting 5-HT neurons robustly increased anxiety levels in a sex-dependent manner, with female mice showing increased anxiety, increased grooming and decreased risk-assessment. Local field potential recordings in the vHP showed that this sex-dependent modulation of anxiety is accompanied by female-specific alterations of vHP theta rhythm. To investigate the cellular mechanism underlying the sex-differences in anxiety behavior, we performed whole-cell patch-clamp on vHP-projecting 5-HT neurons from the DRi, MnR and B9 regions. Passive membrane properties, excitability, and firing dynamics between regions and sexes were evaluated. Strikingly, no differences were found in passive membrane properties between regions or sexes, while significant sex differences were observed in excitability. Indeed, female MnR vHP-projecting neurons exhibited a more depolarized resting membrane potential and a substantially higher firing frequency compared to their male counterparts, with firing frequency being the highest among all recorded regions. Together, these results provide a novel mechanistic insight into a previously under-investigated sexual dimorphism in the raphe-ventral hippocampus serotonergic pathway, thereby paving the way for new therapeutic avenues for the treatment of anxiety disorders in females.

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Poster

PSTR140: Hippocampal Architecture, Representations, and Navigation

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Program #/Poster #: PSTR140.10/KK9

Topic: I.03. Decision Making

Support: Return program of the Ministry of Culture and Science of the State of North Rhine-Westphalia
Federal Ministry of Education and Research (BMBF; 01GQ2402A)

Title: Cellular correlates of allocentric and egocentric memory retrieval in humans

Authors: *L. NETT[1], T. A. GUTH[1], P. K. BÜCHEL[1], M. F. KHAZALI[3], A. BRANDT[3], P. C. REINACHER[4,5], A. SCHULZE-BONHAGE[3], V. BORGER[2], R. SURGES[1], F. MORMANN[1], L. KUNZ[1];
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Abstract: To accomplish spatial navigation and spatial memory, humans represent spatial information in both world-centered (allocentric) and self-centered (egocentric) reference frames. The neural processes underlying allocentric and egocentric representations in humans remain largely unknown, however.
To identify potential cellular correlates of allocentric and egocentric spatial memory recall, we performed human single-neuron recordings in epilepsy patients engaged in a virtual navigation task. This task featured separate periods for memory encoding, allocentric memory retrieval, and egocentric memory retrieval. Specifically, during the encoding period of each trial, participants navigated a virtual environment and encountered two objects at different locations within the environment. Participants were asked to memorize the positions of these objects both relative to their starting position (egocentrically) and relative to the environment (allocentrically). After encoding, participants were asked to recall the object locations in abstract allocentric and egocentric reference frames.We recorded single-neuron activity from the medial temporal lobe of 11 epilepsy patients as they completed this task. Across 29 sessions, we recorded a total of 1,575 single units and multi-units. We observed a significant proportion of neurons responding more strongly during allocentric versus egocentric retrieval (“allocentric retrieval neurons”; 10% of all neurons), or more strongly during egocentric versus allocentric retrieval (“egocentric retrieval neurons”; 12% of all neurons). More specifically, we found significant proportions of allocentric and egocentric retrieval neurons both in the parahippocampal cortex and in the entorhinal cortex, indicating that these regions are involved in representing both spatial reference frames. Along the longitudinal axis of the hippocampus, we found evidence for an anatomical separation between allocentric and egocentric processing. Allocentric neurons were more prevalent in the posterior hippocampus, whereas egocentric neurons were more prevalent in the anterior hippocampus. These preliminary findings suggest both overlapping and distinct contributions of medial

temporal lobe regions to allocentric and egocentric memory retrieval. More broadly, they provide novel insights into the cellular processes underlying spatial memory retrieval in humans.

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Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.01/Web Only

Topic: I.08. Learning and Memory

Support: CONAHCYT 1269044

Title: Cognitive Flexibility in CD1 and C57BL/6 Mice: Evidence of Win-Stay/Lose-Shift (WSLS) and Temporal Estimation Strategies in the MSR Task

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Abstract: Cognitive flexibility enables organisms to adapt their responses to environmental changes. This study examines cognitive flexibility in CD1 and C57BL/6 mice using the Midsession Reversal Task (MSR), assessing fixed and variable reversals with 100% and 50% reinforcement probabilities. Phase one involved a fixed reversal with full reinforcement (F100), while phase two introduced a variable change with full reinforcement (V100). Phase three combined a variable reversal with partial reinforcement (50%). To evaluate prior experiences, phases 1 and 2 were swapped for half the subjects. Results indicate that both strains successfully complete the MSR, developing distinct response patterns. CD1 mice consistently outperform C57BL/6 in phases with stable reinforcement (100%), whereas both strains show similar accuracy when reinforcement is unpredictable (50%). Regardless of prior conditions, CD1 mice maintain higher response accuracy in fixed phases. Analysis reveals that both strains employ a win-stay/lose-shift (WSLS) strategy integrated with timing mechanisms to optimize performance. These findings suggest strain-specific differences in cognitive flexibility, highlighting the role of reinforcement stability and temporal estimation in adaptive learning.

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Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.02/Web Only

Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (25H01096)
JSPS KAKENHI (22K18263)

Title: Limited generalization of multiple prior distributions in timing behavior of individuals with higher autistic traits

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Abstract: To optimize timing behavior, the brain learns a prior distribution of target timing and integrating it with sensory signals. However, individuals with autism spectrum disorder or high autistic traits have been reported to be less able to acquire and/or utilize prior information. In daily tasks, we encounter multiple events with distinct statistics. Therefore, the brain should learn multiple prior distributions in daily lives. When short and long prior distributions were imposed in a timing task by a keypress, participants initially acquired a single prior by generalizing over the two distributions ("generalization", Roach et al. 2017). Then, they gradually acquired two independent priors after prolonged training. In the current study, we investigated the effects of autistic traits on learning of multiple priors in a coincidence timing task. Individuals with typical development participated in our experiments. Autism spectrum quotient (AQ) score was used to assess autistic traits for the participants. For each trial, three sequential visual stimuli (S1, S2, and S3) were presented at the center of a display. The stimulus time intervals were same between S1-S2 and S2-S3 in each trial. Based on the S1-S2 interval. participants pressed a key to coincide with the onset of S3, using their dominant index finger. Inter-stimulus time intervals were alternatively sampled from either the short (450-1050 ms) or long (1200-1800 ms) prior distributions. Each stimulus sequence was colored by orange or green, and each color was associated with one of the prior distributions. Each participant completed 640 trials of the timing task. Using participants' response timing, we evaluated the short and long priors that each participant acquired. If participants acquired a generalized prior, there should be no or little divergence between the two acquired priors. We found that the degree of divergence between the two acquired priors positively correlated with the AQ scores across participants. That is, individuals with lower autistic traits learned a generalized prior whereas those with higher autistic traits learned two independent priors. This positive correlation was statistically significant in the latter half of trials where variation across participants decreased. Our results suggest that generalization of multiple prior distributions is limited in timing behavior of individuals with higher autistic traits.

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Poster

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Topic: I.08. Learning and Memory

Support: 24KJ2146
23H00502
21H05296
JPMJCR23P2
24K15711
23K11838

Title: Temporal representation by hippocampal neurons during self-generated timing in rats

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Abstract: Hippocampal neurons are modulated by a variety of variables, including space, time, and continuous sensory cues. These neuronal activities are thought to contribute to the integration of episodic memory. However, since the variables to which hippocampal activity is tuned and the degree of such tuning vary depending on task demands, it is likely that the hippocampus is also used for the online perception of currently relevant variables and for ongoing action planning. In this study, we focused on time cells that are modulated by temporal variables, and investigated whether hippocampal activity contributes to the online perception of elapsed time. Long-Evans rats were trained to self-generate a treadmill running period of 5 to 8 seconds in order to obtain a reward. Running was initiated and terminated via nose pokes, and trained animals were able to reliably reproduce a 5-second interval. To investigate the neuronal correlates of this behavior, we recorded hippocampal activity using either tetrodes or silicon probes implanted in the dorsal hippocampus after task learning (n = 8). CA1 neurons exhibited transient increases in firing at specific moments, collectively representing elapsed time from the start to the end of the self-timed period. Importantly, neurons fired at consistent relative positions within the self-generated timing interval, rather than at fixed absolute times. Notably, a subset of "time cells" showed peak activity just before the terminating nose poke. These findings suggest that the activity of these neurons is associated with the online perception of elapsed time and the generation of self-timed actions. To further examine the contribution of CA1 time cell sequences, we induced selective lesions in dorsal CA1 using ibotenic acid in a separate cohort of trained rats. Lesioned animals displayed significantly reduced accuracy in temporal reproduction compared to controls (40.6% ± 18.2% vs. 68.3% ± 8.1%, n = 9 per group; $P < 0.0016$, Wilcoxon rank-sum test). These findings indicate that CA1 generates time cell sequences during behavior requiring online timing, and that lesions in this region impair temporal accuracy. Our results suggest that the hippocampus supports not only the integration of temporal features in memory but also ongoing task execution. We will further discuss the role of theta-frequency coordination and the differences in temporal coding between simultaneously recorded CA1 and CA3 regions.

Disclosures: F. Sawatani: None. **K. Ide:** None. **H. Azechi:** None. **S. Takahashi:** None.

Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.04/KK11

Topic: I.08. Learning and Memory

Support: Whitehall Foundation
Research Corporation for Science Advancement
Chan Zuckerberg Initiative

Title: Neural responses to unexpected sensory omissions: temporal coding or predictive coding?

Authors: *Y. HUANG[1], A. SHAMSNIA[2], S. AMINNAJI[3], S. MEDICO[3], S. WU[3], M. CHEN[3], Y. YU[2], E. CHOUDHARY[3], F. NAJAFI[3];
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Abstract: Predicting the timing of temporal events based on prior experience is essential for survival and adaptation in dynamic environments. Temporal singling refers to encoding the timing of sensory events, while predictive processing refers to the brain's ability to anticipate incoming sensory stimuli and adjust predictions based on discrepancies. The relationship between these two distinct processes remains complex. While previous studies have identified distributed temporal signals across brain regions, including primary and higher order cortical areas, as well as the cerebellum, the underlying cell-type specific circuits and interactions among these brain regions during temporal and/or predictive processing are yet to be determined.
We addressed this question by designing novel stimulus interval paradigms for mice to disentangle the contributions between temporal signaling and predictive processing in the primary visual cortex (V1), posterior parietal cortex (PPC), and the cerebellum. To study the cell-type specific mechanisms, we performed two-photon calcium imaging from excitatory and inhibitory neuronal subtypes in V1 and PPC, as well as Purkinje cell dendrites, in awake mice passively receiving repeating audio-visual stimuli.
Our results reveal diverse functional subtypes, which encode sensory inputs, as well as temporal intervals and unexpected event timings. Our ongoing experiments assess how distinct cortical and cerebellar cell types may interact to process, generate, and update temporal predictions.

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Poster

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Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (25H01096)
JSPS KAKENHI (22K18263)

Title: Asymmetric sequential effects between generalization and motor effector-specificity in the learning of two prior distributions in human coincidence timing

Authors: *T. INAGAKI[1], Y. OKUMURA[2], N. ROACH[3], M. MIYAZAKI[1,2];
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Abstract: During timing tasks, the brain acquires a prior distribution of target timing to improve the precision of behavioral responses. Targets in daily tasks can have different temporal statistics (e.g., fastball/slowball in baseball). To generate optimal estimates in the real world, the brain must acquire multiple prior distributions. Recent psychophysical studies have revealed how participants acquire short and long prior distributions in timing tasks. For example, Roach et al. (2017) showed that when participants responded only using a single motor effector (hand) irrespective of the priors, they acquired a single prior by generalizing over the two distributions ("generalization"). Matsumura et al. (2024) showed that participants acquired two independent priors by using two distinct motor effectors (e.g., hand and foot) according to the priors ("body-part specificity"). In this study, we investigated how learning one or two priors affects subsequent prior acquisitions under the two- and single-effector contexts. Each participant performed 640 trials of a coincidence timing task. Target timing for each trial was randomly sampled from either short (450-1050 ms) or long (1200-1800 ms) prior distributions. In Experiment 1, participants initially performed the timing task by pressing a handheld switch using only their dominant thumb, regardless of the prior. Then, they performed the task by pressing a handheld switch or foot switch using their dominant thumb or contralateral forefoot according to the priors. Participants acquired a single prior by generalizing across short and long distributions in the first half of trials (trials 1-320). After using the hand and foot, the divergence between the acquired priors remained small in trials 321-480 but then increased in trials 481-640. In Experiment 2, participants used their dominant thumb or contralateral forefoot, according to the priors, in trials 1-320. Then, they performed only used their dominant thumb, irrespective of the priors, in trials 321-640. Participants acquired two independent priors in the first half of trials, but the divergence between the acquired priors rapidly reduced immediately after only using the hand in the latter half of trials. Our results demonstrate asymmetric sequential effects between generalization and motor effector-specificity: a single generalized prior was strongly retained in the subsequent trials where two motor effectors are used, whereas two independent priors acquired by body-part specificity were less retained in the subsequent trials where only one motor effector was used.

Disclosures: T. Inagaki: None. **Y. Okumura:** None. **N. Roach:** None. **M. Miyazaki:** None.

Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.06/Web Only

Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (25H01096)
JSPS KAKENHI (22K18263)

Title: Can two independent timing priors acquired using vocalizations be retained in subsequent trials without vocalizations?

Authors: *Y. OKUMURA[1], N. W. ROACH[3], M. MIYAZAKI[1,2];
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Abstract: Multiple events with distinct statistics appear in the real world. Therefore, the brain needs to acquire multiple prior distributions to effectively utilize Bayesian estimation in daily tasks. Roach et al. (2017) demonstrated that in a timing task, participants could concurrently acquire short and long prior distributions when two distinct motor responses such as keypress and vocalization were assigned to the priors ("motor specificity"). Recently, Natsume et al. (2025) found that participants could concurrently acquire the two priors by selectively adding a concomitant vocal response to the dominant-hand timing response for one of the priors. While these studies demonstrated that vocalizations can assist the acquisition of multiple timing priors, it is unclear whether these acquired priors remain tied to this behavioral context or can be used later even in the absence of vocalization. In this study, we tested the retention of two independent prior distributions acquired using motor specificity and concomitant vocalization in subsequent trials without vocalization. Each participant performed 640 trials of a coincidence timing task, in which stimulus intervals were sampled from a short (450-1050 ms) or long (1200-1800 ms) prior distribution. In Experiment 1, participants responded using either their dominant hand or their voice, according to the priors, in trials 1-320. They then responded using only their dominant hand, regardless of the priors, in trials 321-640. The participants acquired two independent priors in trials 1-320, but the divergence between the acquired priors disappeared immediately after using only the dominant hand. In Experiment 2, participants selectively added a voice response concomitantly to the dominant hand response for one of the priors in trials 1-320. They then responded using only their dominant hand, regardless of the priors, in trials 321-640. The participants acquired two independent priors in trials 1-320. The divergence between the acquired priors decreased, but was retained in trials 321-480. Then, it disappeared in trials 480-640. Thus, the multiple priors acquired using motor specificity were tied to the behavioral context with vocalization, whereas those acquired using concomitant vocalization could be used later even in the absence of vocalization for a hundred trials or so.

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Poster

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Program #/Poster #: PSTR141.07/Web Only

Topic: I.08. Learning and Memory

Title: The Impact of Stochastic Noise on Interval Reproduction Accuracy in Human Temporal Perception

Authors: *H. GALVAN[1,2], O. BECERRA CASILLAS[2], K. DIAZ LOZANO[2], V. RAMOS SCALABRIN[2], A. AVALOS SALGADO[2], L. P. OSUNA CARRASCO[2], M. TREVINO VILLEGAS[3], B. DE LA TORRE[2];
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Abstract: Human ability to perceive and reproduce time intervals is fundamental to a wide range of cognitive and motor functions, including speech, music, coordination, and timely decision-making. Temporal perception plays a central role in how we predict, adapt, and interact with dynamic environments. Deficits in timing accuracy have been linked to various neurological and developmental disorders and improving temporal precision could enhance both everyday functioning and specialized skills. This study explores whether stochastic resonance a phenomenon in which the presence of an optimal level of noise enhances the detection of weak signals can be used to improve interval reproduction accuracy in humans. In a within-subjects experiment, healthy adult volunteers (age 18-30 years) were asked to synchronize taps with a 300-ms and a 4.3s reference rhythm delivered either auditorily (metronome tones) or tactilely (vibrotactile pulses). After a perception phase consisting of 30 taps, the pacing cue was removed beginning with the reproduction phase and participants continued tapping at the learned interval for 30 taps. Before each block, controlled white noise at seven amplitudes was superimposed on the pacing stimulus; a “no-noise” condition served as baseline. Temporal reproduction performance was quantified by mean asynchrony and coefficient of variation of inter tap-intervals. Optimal noise amplitude was defined as the level yielding the smallest replication error across modalities. Preliminary findings indicate an inverted-U relationship between noise level and tapping accuracy: optimal noise levels tend to enhance both the precision and consistency of interval reproduction compared to baseline, whereas no or high noise levels show no clear benefit. These optimistic early results suggest that stochastic resonance may play a constructive role in human timing behavior. Understanding how environmental noise interacts with internal timing mechanisms could inform the development of novel interventions for motor rehabilitation, neural prosthetics, and performance training in music and athletics.

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Poster

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Topic: I.08. Learning and Memory

Support: NINDS Grant NS116323
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NINDS Grant NS136534

Title: A new behavioral phenotype in an Fmr1 KO rat model: Learning and perceptual deficits in an interval timing task

Authors: M. CASEY, *B. AVLAR, E. IUDICA, K. GUDE, A. CAVALIERI, D. IYER, D. BESPROZVANY, E. J. LANG;
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Abstract: Fragile X syndrome (FXS) is caused by mutations that silence the fragile X messenger ribonucleoprotein1 (*FMR1*) gene and is among the most common forms of inherited intellectual disability. Individuals with FXS present with learning deficits, and impairment of executive functions and attention. Although less studied than other aspects of FXS, some evidence exists that temporal information processing is also distinct and potentially abnormal in FXS. However, temporal learning and perception deficits have not been characterized in detail in FXS or in animal models of FXS. Here, we investigated the learning and timing abilities of a *Fmr1* KO rat model of fragile X using a temporal bisection task, which is a perceptual interval discrimination task that provides a quantitatively rich description of the timing behavior that can be assessed across species and is relatively independent of general activity levels, arousal factors, or motor ability, including the speed or persistence of responding. Adult Long-Evans rats, wild type (WT) and *Fmr1* KO, were trained to discriminate the duration of 1 kHz tones in the interval range of 300 ms to 1200 ms. Although most animals in both groups could learn the discrimination, a significant delay was found in learning the temporal contingency in *Fmr1* KO rats as compared to WT controls. During learning, *Fmr1* KO rats showed significantly more perseveration, as measured by the presence of a response bias for the previous choice. Furthermore, the amount of perseveration was correlated with the number of days required to reach the learning criterion. *Fmr1* KO rats also showed altered timing, perceiving tones as shorter than did WTs. There were no differences between the *Fmr1* KO and WT groups in motor performance, spatial bias, or motivational state that could explain the differences in timing or learning between groups. Therefore, the results of the present study provide evidence for altered temporal information processing in *Fmr1* KO rats. These findings may have implications for understanding FXS more broadly, as impaired temporal function could contribute to the intellectual disability observed in FXS.

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Poster

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Program #/Poster #: PSTR141.09/KK13

Topic: I.08. Learning and Memory

Title: Hippocampal CA1 pyramidal neurons display persistent activity during timing behavior in mice

Authors: *K.-A. CITRIN, Y. WANG;
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Abstract: Hippocampal 'time cells' are a specialized subset of pyramidal neurons that fire at particular moments during structured experiences. These neurons have been thought to provide a temporal scaffold for memory encoding. However, recent evidence casts doubts on the necessity of time cells in performing hippocampal-dependent memory tasks [1, 2]. This raises questions about alternative hippocampal mechanisms underlying timing behaviors. To address this, we performed longitudinal in vivo two-photon calcium imaging of CA1 pyramidal neurons as head-fixed mice were trained on an immobile goal-directed timing task. Our experiments revealed a distinct subpopulation of CA1 neurons exhibiting persistent activity throughout the entire timing interval until the animal's behavioral response to an upcoming reward. Furthermore, the proportion of these neurons increased as animals learned the task. Collectively, our findings uncover hippocampal persistent neuronal activity as a mechanism capable of supporting accurate temporal encoding and guiding goal-directed behaviors.
References:

Sabariego, M. et al. 2019. Time Cells in the Hippocampus Are Neither Dependent on Medial Entorhinal Cortex Inputs nor Necessary for Spatial Working Memory. Neuron.102(6):1235-1248.e5.

Yong, H. et al. 2022. Optogenetic reduction of theta oscillations reveals that a single reliable time cell sequence is not required for working memory. bioRxiv doi: 10.1101/2022.06.25.497592

Disclosures: K. Citrin: None. **Y. Wang:** None.

Poster

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Topic: I.08. Learning and Memory

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Title: Investigating the proportion of task-related cell ensembles in the rat hippocampus using unsupervised ensemble detection

Authors: *D. ARTHUR[1], L. SCHIMANSKI[3], S. L. COWEN[4], C. A. BARNES[5], M. TATSUNO[2];
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Abstract: The hippocampus is involved in the storage and recall of episodic memories. During sleep, cell ensembles (CEs) in the hippocampus related to remote and recent experience are reactivated, and this 'replay' is believed to contribute to memory consolidation. When studying memory, earlier research often focused on CEs associated with recent experiences, such as learned tasks. However, CEs linked to remote experiences may also be active during an experiment. This raises the question: What proportion of hippocampal CEs are dedicated to recent experience? To this end, we first aimed to characterize the variety of CEs by detecting them using an unsupervised method (Russo & Durstewitz, 2017, eLife). We analyzed 250 datasets of single-unit recordings from CA1 pyramidal cells in five young (132 datasets) and four old rats (118 datasets) (Schimanski et al., 2013, J Neurosci). Rats participated in a session composed of 15-45 minutes of a place-dependent eyeblink conditioning task and 30 minutes of pre- and post-task rest. The session was repeated twice daily, and the experiment lasted for 31 days. Periods of NREM and REM sleep during rest epochs were determined by the delta-theta ratio. The activations of each CE were counted during NREM, REM, running on the track, and immobility on the track. For each dataset, the overall CE activation counts were assessed using classical multidimensional scaling with a correlation distance matrix, followed by k-means clustering. We found the CEs were primarily grouped into one or two clusters of mostly task-active and another of mostly rest-active. To investigate the dynamics further, the CE activation counts were manually sorted into seven categories: task-only, sleep-only, reactivation in sessions 1 and 2, decrease in activations from pre- to post-rest (anti-reactivation) in sessions 1 and 2, and unclassified. Consistent with the clustering results, task-only CEs represented the largest group (63.2%). Reactivating CEs accounted for about 4.1%, while anti-reactivating CEs made up about 0.9%. Together, approximately 68% of CEs were associated with task epochs. The sleep-only CEs constituted the second-largest group (14.0%). There was no significant difference between young and old rats in these analyses. There is a possibility that the sleep-only CEs represent a time-compressed version of the task. Thus, these CEs must be considered further to examine this question, and we will have an answer for this by the time of the conference. In summary, our

results show that CEs are activated within several epochs surrounding the place eyeblink conditioning task, and approximately two-thirds of these are related to recent task experience.

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Poster

PSTR141: Timing and Temporal Processing

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Topic: I.08. Learning and Memory

Support: NIEHS Grant T32 ES033955

Title: The role of the ventral midline thalamus in the retrieval of interval timing memories

Authors: *A. P. LORENZO GONZALEZ;
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Abstract: The accurate retrieval of interval timing memories, in the range of seconds to minutes, has been shown to be impaired by inactivation or damage to memory associated structures like the hippocampus and the medial pre-frontal cortex (De Corte et al., 2022; Dietrich & Allen, 1998; Kim et al., 2009; Yin & Meck, 2014). These two areas are bidirectionally connected to the rhomboid (Rh) and reuniens (Re) nuclei of the ventral midline thalamus (VMT) (Cassel et al., 2013; Dolleman-van der Weel et al., 2019); which in turn, have been shown to participate in several memory functions including memory consolidation, extinction and reversal learning, context-dependent memory retrieval/expression, and behavioral flexibility (e.g. Xu & Sudhof, 2013; Cholvin et al., 2013; Dolleman-van der Weel et al., 2009). Rh and Re are thought to coordinate the hippocampal-prefrontal communication that underlies the retrieval of sequential context memory, contextual fear memory, spatial working memory as well as remote spatial memory (Loureiro et al., 2012; Ratigan et al., 2023; Ramanathan et al., 2018; Viena et al., 2018). Here we explored the role of the VMT in the retrieval of fixed-interval time memories. First, water restricted rats were trained to nose-poke within a short time-interval (5s) signaled by an auditory cue (white noise) to obtain a small water reward delivered for the first poke after the time interval had elapsed (daily 60-trial sessions for weeks). Rats demonstrated interval timing memory by poking predominantly at the time of the expected reward. We also found that, across trials, rats displayed diverse types of responses that we classified and clustered into early, on-time, and random. The number of these response trials per session changes over time, with the number of random response trials decreasing and remaining low with training. Next, the rats were switched to longer intervals (20s or 80s) (daily sessions for weeks), and nose poke activity quickly accumulated at the new learned times. To probe the role of Re and Rh in memory retrieval we infused the $GABA_A$-agonist muscimol, or saline, for both the 20s and 80s intervals trained (pre-session infusion). Results show that muscimol infusions decreased timing accuracy

and precision at both time intervals, suggesting a role for the VMT in interval time memory generally. More specifically, muscimol infusions significantly decreased the number of on-time response trials at both 20s and 80s; the number of random response trials significantly increased only at 20s, and no significant change was observed for the early response trials.

Disclosures: A.P. Lorenzo Gonzalez: None.

Poster

PSTR141: Timing and Temporal Processing

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Topic: I.08. Learning and Memory

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Title: Quantifying hippocampal sequence replay of non-spatial states using transformer

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[4]Dept. of Computer Sci., UC Irvine, Irvine, CA

Abstract: The ability of the hippocampus to sequentially replay information during offline periods is important for encoding and integrating memories and for planning future behavior. While replay of spatial trajectories is well established, prominent computational models proposing unifying principles of hippocampal function across modalities and species predict the phenomenon should extend to abstract nonspatial relationships across discontiguous experiences. Here we recorded hippocampal activity as rats remembered an extended sequence of nonspatial events and analyzed ensemble activity during offline intervals separating each event of the sequence. Specifically, we decoded ensemble activity during offline intervals into probability time series and quantified the strength of sequential replay using transformer. This framework enables us to model flexible replay duration and fluctuated replay strength while capturing long-term relationship robustly without losing interpretability. We found that forward replays clustered between events and reactivated upcoming segments of the sequence, whereas reverse replays tend to be distributed after the completion of the sequence. These findings provide evidence for the potential of transformers in quantifying noisy and complex sequential coding dynamics, thereby offering a more rigorous and interpretable framework to investigate the fundamental mechanisms by which the hippocampus extracts and replays abstract multi-step associations.

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Poster

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Program #/Poster #: PSTR141.13/KK16

Topic: I.08. Learning and Memory

Support: R01

Title: Electrophysiological dynamics of the external globus pallidus during a cognitive task

Authors: *M. M. CONLON[1], M. A. WEBER[2], A. BOVA[2], V. KHANDELWAL[4], X. DING[2], N. S. NARAYANAN[3];
[1]Dept. of Neurol., [3]Neurol., [2]Univ. of Iowa, Iowa City, IA; [4]Programs in Systems Neurosci., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The external globus pallidus (GPe), a key component of the basal ganglia, is increasingly recognized for its role beyond motor control, with recent evidence suggesting its involvement in cognitive functions. Interval timing, or the estimation of several second intervals, is a cognitive task that has high translational value. Accurate interval timing requires executive functions such as attention to the passage of time and working memory for the rules of the task, is dependent on striatal dopamine (DA), and is reliably impaired in Parkinson's disease (PD) patients. Striatal dopamine has differential effects on direct (dMSN) and indirect (iMSN) pathway spiny projection neurons. We sought to characterize the role of these projections and their target structures in interval timing using striatal dopamine manipulations and electrophysiology recordings. Wild type C57BL/6 mice were trained on an interval timing task that requires mice to estimate the duration of a cue and make a time-based decision to respond at either a long or short port. We optogenetically stimulated or inhibited dMSN terminals in the substantia nigra pars reticulata or iMSN terminals in the external globus pallidus. Inhibition of both pathways led to an increase in the estimation of time. Activation of the direct pathway also led to overestimations, but activation of the indirect pathway led to an underestimation of temporal intervals. To further interrogate the role of the iMSNs, we recorded electrophysiology in the GPe using high-density silicon probes. Preliminary results reveal distinct changes in GPe firing rates and oscillatory activity associated with different phases of the timing task. Our results suggest a complex role for striatal dopamine in interval timing, with differential involvement of dMSN and iMSN responses. These findings provide novel insights into GPe dynamics during interval timing and contribute to a broader understanding of the basal ganglia's involvement in cognitive functions. Further analysis will focus on characterizing the specific neuronal subpopulations within the GPe that are engaged during this task and determining the relationship between GPe activity and behavioral performance. Our work may lead to targeted, cell-type specific, and novel pharmacological interventions for disorders such as Parkinson's Disease.

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Poster

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Topic: I.08. Learning and Memory

Support: NIH Grant R01MH078064
NIH Grant R01MH108837

Title: Dorsal CA2's role in linking temporally discontinuous events

Authors: *T. E. BASSETT[1], A. CICVARIC[1], H. ZHANG[1], Z. PETROVIC[1], J. M. RADULOVIC[1,2,3];
[1]Neurosci., [2]Psychiatry, Albert Einstein Col. of Med., Bronx, NY; [3]Biomedicine, Aarhus Univ., Aarhus, Denmark

Abstract: Associative memory enables organisms to link events separated in time, supporting behaviors like spatial navigation, sequence learning, and decision making. Temporal learning—in which a conditioned stimulus and unconditioned stimulus are separated by a brief interval—relies on the hippocampus to bridge this gap. Although CA1 plays a known role in temporal learning, CA2's role in non-social temporal associations remains poorly defined. Given CA2's direct input from entorhinal cortex layers II and III—regions implicated in temporal association formation—CA2 is well positioned to influence hippocampal processing during trace intervals. However, past CA2 research largely centers on social recognition, leaving open whether CA2 contributes to temporal learning.

Using the Amigo2-Cre mouse line, we expressed tetanus toxin light chain (TeNT) selectively in dorsal CA2 pyramidal neurons to block synaptic output. Mice with dorsal CA2 TeNT exhibited a significant reduction in freezing behavior during trace fear conditioning (TFC), a paradigm in which a temporal gap separates the conditioned and unconditioned stimuli, compared to control littermates. This finding demonstrates that dorsal CA2 is required for associating temporally discontinuous stimuli. Notably, dorsal CA2 TeNT had no effect on delay fear conditioning (DFC), a paradigm in which the conditioned and unconditioned stimuli co-terminate, highlighting that CA2's contribution depends on the presence of a temporal gap. In contrast, similar TeNT inhibition of intermediate or ventral CA2 subregions did not alter TFC freezing, indicating a functional specialization along the septotemporal axis. Fiber photometry recordings of CA2 pyramidal neurons during TFC revealed a pronounced elevation in activity immediately following the foot-shock, mirroring patterns observed in CA1 with slightly different dynamics. To confirm and extend these results, we applied chemogenetic inhibition (hM4Di) to dorsal CA2 during TFC training. Inhibited mice also showed markedly decreased freezing, underscoring CA2's specific involvement in the encoding of trace memories. These convergent approaches establish that dorsal CA2 exerts a critical excitatory drive necessary to maintain a memory trace during the delay interval, a function not shared by intermediate or ventral CA2.

By revealing a novel, region-specific role for dorsal CA2 in non-social temporal association

learning, our data advances the understanding of hippocampal circuit mechanisms underlying trace fear memory. These insights into how CA2 bridges temporally separated cues will inform future studies of complex learning and memory processes.

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Poster

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Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (22K18263)

Title: High-frequency tactile flicker enhances the postdictive component of the cutaneous rabbit effect

Authors: *K. TAKAMA[1], M. HAKAMATA[1], N. KAWAGUCHI[2], M. MIYAZAKI[1,3]; [1]Grad. Sch. of Integrated Sci. & Tech., Shizuoka Univ., Hamamatsu city, Japan; [2]Epileptology, Natl. Epilepsy Center, NHO Shizuoka Inst. of Epilepsy and Neurolog. Disorders, Shizuoka-city, Japan; [3]Fac. of Informatics, Shizuoka Univ., Hamamatsu city, Japan

Abstract: The cutaneous rabbit effect (CRE) is a tactile illusion in which successive pair of taps on the skin are perceived as shifting toward each other. The first tap is perceived as shifting toward the location of the second tap, whereas the second tap is perceived as shifting toward the first one. The former effect reflects postdiction, whereas the latter reflects prediction. This illusion occurs with the short interstimulus intervals (ISI, e.g., < 100 ms) and intensifies as the ISI decreases. Notably, high-frequency visual flickers (repetitive stimulus sequences) shorten the perceived duration of subsequent visual stimuli compared to low-frequency flickers (e.g., Johnston et al., 2006). Based on the Bayesian estimation model (Goldreich, 2007), the CRE should be enhanced if the perceived ISI is shortened. In this study, we investigated the effects of high- and low-frequency tactile flickers on CRE. First, we examined how tactile flickers modulate tactile time perception using a simultaneity judgment (SJ) task. After either high-frequency (25 Hz) or low-frequency (5 Hz) tactile flicker (5-s duration), two tactile stimuli were presented as test stimuli. The results indicated that the perceived ISIs of the test stimuli were shorter after high-frequency flickering than after low-frequency flickering when the flickers were presented at the skin location of the first test stimulus. However, after flickering at the location of the second test stimulus, no difference appeared in the effect between the high- and low-frequency flickers. Next, we examined how tactile flickers modulated the CRE. As a result, the first tap was perceived as closer to the second tap after the high-frequency flicker than after the low-frequency flicker when flickering on the first-tap skin location. Conversely, no difference in the perceived location of the second tap was observed between high- and low-frequency flickers

at the first-tap location. When the flickers were presented at the second-tap location, no difference was observed in the perceived locations of both the first and second taps, comparable to the SJ task results. Thus, high-frequency flicker shortened the perceived ISI of tactile stimuli and enhanced the CRE, supporting the Bayesian model of CRE. Meanwhile, high-frequency flicker enhanced the postdictive component of the CRE, however, did not affect the predictive component. The Bayesian model suggested that a common mechanism governs both the postdictive and predictive components of CRE; however, our results suggested that distinct mechanisms are involved in these two processes.

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Poster

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Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (25H01096)
JSPS KAKENHI (22K18263)

Title: Concomitant motor responses can facilitate the acquisition of multiple timing priors beyond upper limb contexts

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Abstract: During timing tasks, the brain acquires the prior distribution of target timing and integrates it with sensory inputs to optimize timing behavior. In natural environments, we encounter events with different temporal statistics (e.g., fastball/slowball in ball sports). Effective use of Bayesian estimation for everyday tasks therefore requires the ability to learn and retain multiple prior distributions. Our recent study demonstrated that selective addition of a concomitant motor response (CMR) facilitates simultaneous acquisition of short and long prior distributions on a manual timing task (Natsume et al. 2025). The facilitation occurred both when a non-dominant hand movement or a vocal response was executed along with the primary dominant hand response for one of the two priors. This suggests that the CMR effect generalizes to various motor responses. However, a finding on force-field learning in reaching (Nozaki et al., 2006) suggests the CMR effects may not appear if using foot responses as CMR. In the present study, we tested whether a concomitant foot response can facilitate multiple-prior acquisition in timing. Three sequential visual stimuli (S1, S2, and S3) were presented at the center of the display. The time interval between S1 and S2 was the same with that between S2 and S3 in each

trial. Using the dominant index finger, participants attempted to press a key to coincide with the onset of S3. The stimulus time intervals were selected from one of two prior distributions: the short prior (450-1050 ms) and the long prior (1200-1800 ms). For each trial, the stimulus sequence was colored by either green or orange, each of which were assigned to one of the prior distributions. The orange and green stimulus sequences (i.e., priors) alternately appeared. Each participant completed 640 trials of the timing task. Participants were divided into three groups. The non-CMR group pressed the key only using their dominant hand. The H-CMR group selectively added a non-dominant hand response concomitantly to the dominant-hand timing response. The F-CMR group selectively added a contralateral foot response. The H-CMR and F-CMR groups exhibited greater divergence between the two acquired priors than non-CMR group in the latter half of the trials. The results indicate that the facilitation of multiple-prior acquisition by CMRs is not limited to the upper-limb context but generalized to the contexts across the upper and lower limbs. Reaching is usually conducted using the upper limbs. In contrast, timing is involved in various motor behaviors and effectors, and takes a crucial role in whole-body motor coordination, which may be associated with the diverse CMR effects in timing.

Disclosures: R. Takaki: None. **Y. Tanaka:** None. **N. Roach:** None. **M. Miyazaki:** None.

Poster

PSTR141: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR141.17/KK20

Topic: I.08. Learning and Memory

Support: RO1-MH134000 (R.C.L)
Aligning Science Across Parkinson's ASAP-020-519

Title: Lateral frontal pole autocorrelation tracks temporal memory fidelity in emotional contexts

Authors: *J. WANG[1,2], J. STASIAK[3], S. T. GRAFTON[4], R. C. LAPATE[5];
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Abstract: Daily events unfold linearly over time, but the emotional states they produce can shape how those events are stored in episodic memory. Growing evidence suggests that emotion influences temporal aspects of memory-such as remembering when an event occurred (Palombo & Cocquyt, 2020; Wang & Lapate, 2022). Lateral frontal pole (FPl) function is sensitive to event sequences (Desrochers et al., 2015), and the multivariate similarity of FPl activity patterns across distinct events tracks the fidelity of temporal memory (Jenkins & Ranganath, 2010). Moreover, neuroanatomical data indicate that FPl has privileged access to amygdala-originated affective information relative to other lateral prefrontal regions (Folloni et al., 2019), positioning FPl as a potential hub for integrating temporal and emotional information in memory. Recent work shows

that changes in neural pattern similarity during the encoding of a single event (i.e., autocorrelation) are sensitive to contextual shifts (Sinclair et al., 2021). However, whether emotional state changes modulate FPl autocorrelation—and thereby shape temporal memory accuracy for that event—remains untested. To address this, participants (n = 71) completed an Approach-Avoidance task in the MRI scanner, in which emotional valence and action goals (approach vs. avoid) were orthogonally manipulated using trial-unique emotional pictures. After the experiment, participants completed a surprise temporal memory task, using a timeline to indicate when they thought each emotional picture had been presented during the session. Stimuli rated as more negative were associated with greater temporal memory accuracy ($p = 0.005$), suggesting that negative emotion may sharpen temporal memory for when events occurred. Negative stimuli evoked higher amygdalar activation ($p = 0.024$), consistent with well-established emotional valence effects in the amygdala. Critically, more negative stimuli were also associated with lower FPl autocorrelation ($p = 0.014$), which was in turn correlated with greater temporal memory accuracy ($p = 0.031$) — a relationship not seen in other lateral prefrontal regions. Moreover, higher amygdalar activation was associated with lower FPl autocorrelation ($p = 0.007$), suggesting a close link between amygdalar coding of emotional valence and FPl function in emotional temporal memory processing. Collectively, our findings extend the role of FPl in temporal memory to a finer temporal scale—autocorrelation of neural activity patterns after the encoding of a single event—and suggest that FPl function may partially underlie emotion-modulated temporal memory, potentially via input from the amygdala.

Disclosures: J. Wang: None. **J. Stasiak:** None. **S.T. Grafton:** None. **R.C. Lapate:** None.

Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.18/KK21

Topic: I.08. Learning and Memory

Support: NIH R01

Title: Evidence of temporal tracking at multiple timescales along the hippocampal longitudinal axis

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Abstract: Prior work shows that activity patterns in hippocampal place cells become increasingly dissimilar as the same task is performed over progressively longer intervals, suggesting that time is intrinsically coded in the hippocampus at the population level (Mankin et al., 2015). Even without explicit task demands, hippocampal-whole brain resting-state functional

connectivity patterns drift and correlate with elapsed time over a 30-day period in humans (Wang et al., in revision). However, it remains unclear whether hippocampal connectivity patterns reliably track time across variable intervals. Previous research suggests that the posterior hippocampus (pHPC) supports fine-grained representations, whereas the anterior hippocampus (aHPC) has been associated with coarse-grained representations, including temporal coding at longer timescales (Bouffard et al., 2023; Nielson et al., 2015; Poppenk et al., 2013)-suggesting that the timescale of temporal coding in hippocampal connectivity patterns may vary along the longitudinal axis. Here, we examined hippocampal-whole brain temporal drifts across timescales using resting-state fMRI dense sampling data from 3 subjects collected over a 90-day period (2F, 1M; 24-26 sessions each; Miller et al., 2022; Tambini et al., 2023). First, we computed whole-brain resting state functional connectivity (rsFC) pattern similarity across session pairs for anterior and posterior hippocampal ROIs (aHPC, pHPC) and a control ROI (primary motor cortex/M1). Next, we used linear mixed-effects models to test whether the time interval elapsed between session pairs predicted reduced rsFC pattern similarity-thereby indexing temporal drift. At the shortest interval (15 days), pHPC-whole brain rsFC pattern similarity correlated negatively with elapsed time, indicating reliable temporal drift in the pHPC-an effect not found in the aHPC or M1. At the 30-day interval, both pHPC and aHPC showed significant temporal drift, replicating prior work. At longer intervals (60 and 90 days), the aHPC continued to show reliable temporal drift, whereas pHPC did not. Temporal drift in the aHPC (but not pHPC) was more reliable at the 30-day than the 90-day interval, and significantly stronger than that observed in the control ROI at the 30- and 60-day intervals. Collectively, these findings suggest that hippocampal rsFC patterns reflect the passage of time with varying temporal sensitivity along the hippocampal longitudinal axis: while the pHPC preferentially reflects shorter timescales, the aHPC supports more extended representations of elapsed time.

Disclosures: S. Fortner: None. **J. Wang:** None. **R.C. Lapate:** None.

Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.19/KK22

Topic: I.08. Learning and Memory

Support: NIH/NIMH 1 395 DP2 MH129958-01
NSF CAREER Award: IOS-2145814
University of Utah

Title: Medial entorhinal cortex flexibly encodes elapsed time during adaptive foraging

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Abstract: The brain has evolved systems for rapid learning, enabling animals to extract spatial and temporal information across contexts. 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. Recent work has used reductionist timing tasks to demonstrate the existence of time cells in MEC and their role in abstract decision-making. However, the field lacks a mechanistic understanding of how these populations of cells interact with spatial codes to facilitate optimal behavior in a naturalistic environment. Thus, we developed a novel foraging paradigm in which mice must learn to alternate between two spatially separated "patch" zones connected by a hallway. This reactive environment allows for dynamic manipulations of reward functions and cues based on animal behavior through the integration of computer vision and a real-time control platform. By providing rewards in each patch according to distinct stochastic decay functions, we create predictable, patch-specific opportunity cost profiles that animals must learn to optimize patch residence time (PRT). Mice reliably adjust their PRTs in response to the differing reward decay rates (τ) over the course of learning. Using chronically implanted Neuropixels 2.0 probes, we found that time cells emerge in MEC at regular epochs during immobility at reward ports. Interestingly, tuning curves of individual time cells as well as LDA decoder analysis of population activity suggest that temporal dynamics are highly context dependent. We also found that when patch-specific τ values change covertly between blocks, mice quickly adjust PRTs, indicating that they update internal models of patch value in response to new temporal contingencies. Preliminary decoding analyses reveal that temporal codes in MEC are preserved across distinct spatial environments when the temporal context is held constant. To further investigate the flexibility of MEC representations, future work will use a dual subtask foraging paradigm in which spatial and temporal demands vary independently. By comparing MEC activity during spatial working memory and stochastic timing tasks, we will test whether the MEC adaptively prioritizes time or space based on task demands. These experiments will elucidate how the MEC integrates spatial and temporal information to guide adaptive behavior, providing insight into the neural basis of flexible decision-making across changing environmental contexts.

Disclosures: J.R. Morris: None. **J. Bowler:** None. **J.G. Heys:** None.

Poster

PSTR141: Timing and Temporal Processing

Location: SDCC Halls B-H

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Program #/Poster #: PSTR141.20/LL1

Topic: I.08. Learning and Memory

Support: NIH/NUMH 1 395 DP2 MH129958-01
NSF Career Award: IOS-2145814
Univserity of Utah
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Title: Structured experience shapes strategy learning and neural dynamics in the medial entorhinal cortex

Authors: *J. C. BOWLER[1], D. AZHAR[1], C. JENSEN[2], H.-W. LEE[3], J. G. HEYS[4];
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Abstract: Prior experience instructs how animals learn to adapt and develop solutions to the novel problems they encounter in the future. We investigate how the structure of prior experience alters the strategies animals adopt. Specifically, we leverage a context-dependent timing task, originally developed for mice, wherein animals are trained to time odor cues and report when the cues are of different durations-a temporal variant of Delay Non-Match to Sample (tDNMS). In order to investigate how strategies for solving the task develop with learning, we trained recurrent neural networks (RNNs) to perform a version of the same task. We dissect the dynamical states exhibited by RNNs trained with and without structured prior experience in order to see how the networks solve the tDNMS task. We find that properly structured prior experience permits RNNs to learn a robust strategy and achieve high performance on the task; without that prior experience, the RNNs make stereotypical errors, often responding at the incorrect times. In addition, based on experience, RNNs consistently use very different mechanisms to identify the proper response window in the task: RNNs without well-structured training develop a simple fixed-point based strategy, meaning that cue duration is integrated along a single dimension as dynamics evolve towards the cue-on or cue-off attractor states. RNNs exposed to a shaping procedure that mimics the one used to train animals build an abstract representation of the task structure that scaffolds future learning based on trial timing. This is represented through the appearance of a limit cycle in addition to the cue-on fixed point in the population dynamics. Further, we find that not all experience is equal and that poorly designed training paradigms result in dynamics similar to those that are observed after no pre-training. We leverage these findings to make predictions about the neural dynamics in the medial entorhinal cortex, a region high in recurrent connectivity that has been shown to be necessary for learning the tDNMS task. Patterns of activity in the medial entorhinal cortex reveal that high-performing animals use similar dynamical mechanisms as the RNN models and that properly structured prior experience is necessary to form these representations.

Disclosures: J.C. Bowler: None. **D. Azhar:** None. **C. Jensen:** None. **H. Lee:** None. **J.G. Heys:** None.

Poster

PSTR141: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR141.21/LL2

Topic: I.08. Learning and Memory

Support: NIH/NIMH Grant 1 395 DP2 MH129958-01
NSF CAREER Award IOS-2145814
University of Utah

Title: Format of prior experience informs future learning and performance in novel tasks containing varying degrees of feature space overlap

Authors: *C. JENSEN, J. BOWLER, D. AZHAR, J. G. HEYS;
Univ. of Utah, Salt Lake City, UT

Abstract: Animals often leverage prior experience to solve new problems - but how such experiences are abstracted to support generalization, and the underlying neurobiological mechanisms, remain poorly understood. Furthermore, the structure of a training curriculum can critically determine the efficiency and success of learning. For example, the average person would not be able to play a complex piece of music on a piano without progressive training, yet someone who has been trained in playing the violin might be able to more readily pick up the piano and learn to play the complex piece quicker, despite the violin being a completely different instrument. This illustrates how the structure and content of past learning experiences can influence new learning across domains.
To investigate how prior experience shapes the ability to learn novel tasks, we first trained Recurrent Neural Networks (RNNs) to model variants of two distinct delayed non-match to sample tasks, both previously utilized in mouse behavioral studies: (1) a temporal DNMS (tDNMS) task and (2) an odor identity DNMS (iDNMS) task. We then tested these RNNs on either novel trial types in overlapping feature space (i.e., tDNMS-trained RNNs tested on novel temporal trials using the same odor cues) or 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 RNN models were also validated in vivo by presenting mice trained on the tDNMS task 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 an abstract comparison rule. Additionally, results from RNNs tested on novel tasks with non-overlapping feature space revealed variable task performance on both novel and previously learned tasks depending on the organization of training. Ongoing work aims to further validate these findings in vivo. Together, our results suggest that the structure and content of prior training experiences strongly influence the ability to generalize and learn new tasks, highlighting the importance of curriculum design in shaping flexible learning.

Disclosures: C. Jensen: None. **J. Bowler:** None. **D. Azhar:** None. **J.G. Heys:** None.

Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.22/LL3

Topic: I.08. Learning and Memory

Support: NIH/NIMH DP2 MH129958
NSF CAREER Award: IOS-2145814

Title: The dorsolateral striatum and medial entorhinal cortex support learning of a complex timing task

Authors: *H.-W. LEE, J. CUERO, J. G. HEYS;
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Abstract: There are multiple memory systems in the brain that support distinct forms of learning. However, how these systems interact to enable learning in complex timing tasks remains unclear. Recently, we demonstrated that the medial entorhinal cortex (MEC) mediates learning of the temporal delayed nonmatch-to-sample (tDNMS) task, in which head-fixed mice make go/no-go decisions based on a pair of odors presented on each trial (Bigus*, Lee* et al., 2024). Mice are trained to withhold licking on match-duration trials (Short-Short) and to lick after the second odor on nonmatch-duration trials (Short-Long or Long-Short). Inactivation of the MEC impairs task acquisition, and MEC activity correlates with behavioral performance, particularly model-based strategies (i.e., decisions based on an internal model of the task). Here, we investigated how the MEC and the dorsolateral striatum (DLS)—a region known to be involved in habit formation (Yin et al., 2004) and model-free learning through stimulus-response (S-R) associations (Featherstone and McDonald, 2004; Goodroe et al., 2018)—interact to support learning in the tDNMS task. We chemogenetically inactivated the DLS using DREADDs during training. Both the DLS inactivation group (n=4) and control group (n=4) received DCZ injections prior to each session. In early sessions, control mice rapidly learned to associate odor offset with reward delivery and developed odor-aligned licking behavior. Over subsequent sessions, they learned the temporal structure of the task (first odor - second odor - response), suppressing licking after the first odor and responding only at the offset of the second. In contrast, DLS-inactivated mice showed slower development of odor-lick associations and failed to inhibit licking at the offset of the first odor, resulting in impaired task performance (two-way ANOVA; significant main effect of group, $F(1, 30) = 12.41$, $p = 0.0014$). These findings suggest that, like the MEC, the DLS is also necessary for learning in this complex timing task, indicating that interactions between the MEC and DLS may be critical for acquisition of the tDNMS task. We are currently collecting simultaneous neural recordings from both regions using Neuropixels probes to investigate the underlying neural dynamics.

Disclosures: H. Lee: None. **J. Cuero:** None. **J.G. Heys:** None.

Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.23/LL4

Topic: I.08. Learning and Memory

Support: NIH/NIMH 1 395 DP2 MH129958-01
NSF CAREER Award: IOS-2145814
University of Utah

Title: Hippocampal time cell dynamics evolve through learning to support cognitive demands

Authors: *D. B. AZHAR, E. R. BIGUS, J. BOWLER, J. G. HEYS;
Neurobio., Univ. of Utah, Salt Lake City, UT

Abstract: The hippocampus is known to form cognitive maps—internal representations that reflect learned relationships in the world. While place cells encode spatial structure, hippocampal time cells are thought to represent temporal relationships across events. However, it remains unclear whether time cells display learning-related dynamics that reflect increasing knowledge of temporal context and its behavioral relevance. To address this, we trained head-fixed mice on a temporal Delayed Non-Match to Sample (tDNMS) task, in which animals discriminated between sequences of odor stimuli with different durations (2s vs. 5s) separated by a fixed interstimulus interval. Using two-photon calcium imaging in dorsal CA1, we recorded activity across four distinct training phases: early and late shaping (when stimulus duration is irrelevant) and early and late task (when animals must use duration to guide licking behavior). This structured curriculum enabled us to track how time cell properties and population dynamics evolved as mice acquired temporal knowledge.Time cells were active from the first session but changed systematically with learning. With experience, time fields emerged earlier, became more stable, and showed narrower widths—consistent with increased temporal precision. These changes were not explained by running speed or other motor variables. Population-level activity patterns also reorganized with training: during shaping, time cell activity generalized across trial types, whereas during task phases, distinct temporal contexts evoked diverging activity patterns. Cross-context correlations and PCA revealed that neural trajectories reflected the behavioral demands of each phase—contexts were encoded similarly when generalization was sufficient and distinctly when discrimination was required. Together, these results show that hippocampal time cells not only encode temporal structure but dynamically reflect how such structure is used to guide behavior, forming experience-dependent cognitive maps of time.

Disclosures: D.B. Azhar: None. **E.R. Bigus:** None. **J. Bowler:** None. **J.G. Heys:** None.

Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.24/LL5

Topic: I.08. Learning and Memory

Support: NIMH R01MH134515

Title: Evaluating the effect of chronic social isolation in aged CA1 spatial coding

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Abstract: The rising prevalence of neurodegenerative disorders such as Alzheimer's disease among the aging population in the United States presents a significant public health challenge. A key consideration in the care of cognitively impaired older adults, particularly those in assisted living environments, is the role of social connectedness. Emerging evidence indicates that the quality and quantity of social interactions significantly affect cognitive performance and mental health in aging populations. Conversely, chronic social isolation has been linked to declines in learning, memory, and emotional regulation, as well as neurobiological changes in key brain areas. This includes the hippocampus, which is critical for spatial learning and memory consolidation, and is especially susceptible to the effects of both aging and social deprivation. Given its dual role in memory and social behavior, we sought to investigate how social isolation and aging interact to influence cognitive aging in mice. We implemented two-photon calcium imaging in young and aged mice that had either undergone chronic social isolation for two weeks or remained in group-housing. We recorded dorsal CA1 place cell activity in a spatial memory task in VR where mice navigate to distinct reward location across different linear track environments. Our preliminary results show that young control mice can discriminate between VR environments and learn distinct reward locations. Mice displayed reduced place field correlations across different environments in addition to stable place cell reactivation within a familiar environment. Ongoing analyses will compare performance across age groups and socially isolated mice, focusing on metrics of spatial map correlations, stability across days, and emergence of place fields in novel environments. Through this work, we aim to advance understanding of how social environment and age-related changes jointly influence memory-related circuits, ultimately informing interventions to treat cognitive decline in socially vulnerable aging populations.

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Poster

PSTR141: Timing and Temporal Processing

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Program #/Poster #: PSTR141.25/LL6

Topic: I.08. Learning and Memory

Support: OPUS 2019/35/B/HS6/04389

Title: Role of orbitofrontal and anterior cingulate cortices in generation and evaluation of time intervals in rats

Authors: *L. LE BARILLIER[1], V. DOYERE[2], T. W. KONONOWICZ[2,1];
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Abstract: Animals self-generate time intervals in a precise and near optimal manner, raising a possibility that they may have a knowledge of their errors in their temporal behaviour. We recently developed a paradigm, temporal error monitoring (TEM) task (1), in which rats were able to report their temporal error in their own produced duration without any external feedback. We then sought to understand which frontal cortical areas carry computations relevant to performance monitoring of such an internally generated timing behavior, focusing on the orbitofrontal cortex (OFC), which carries confidence signals, and the anterior cingulate cortex (ACC), which carries error-dependent signals. In a first experiment, we tested the impact of muscimol-induced local inhibition of either region on the rats' performance in the TEM task. We found a hierarchical organization between these two structures with OFC contributing to the production of accurate time intervals, whereas disrupting ACC altered inference of temporal errors and evaluation of self-produced durations without impairing temporal performance. These results suggest distinct neural mechanisms for time production and error judgment supported by different neural populations in OFC and ACC, respectively. We further pursued the investigation of the computations by these two regions by recording local field potentials (LFP) activity simultaneously in OFC and ACC in 16 rats performing the TEM task. Preliminary analysis suggest a modulation in both structures at the time of the action and of the choice. After characterization of the neural responses during time production and error judgment, undergoing analyses investigate functional connectivity via time-frequency coherence analyses between these two structures to evaluate a possible modulation of communication at different epochs during the task that could reflect the readout of temporal information. (1) Kononowicz, T. W., van Wassenhove, V., & Doyère, V. (2022). Rodents monitor their error in self-generated duration on a single trial basis. *Proceedings of the National Academy of Sciences*, *119*(9), e2108850119.

Disclosures: L. Le Barillier: None. **V. Doyere:** None. **T.W. Kononowicz:** None.

Poster

PSTR142: Language: Neural Circuits and Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.01/LL7

Topic: I.11. Language

Support: Institutional funds, Penn State College of Medicine

Title: Neural basis of sound-shape associations for real words and pseudowords: insights from intracranial electrophysiology

Authors: *V. KUMAR[1], S. LACEY[1], L. NYGAARD[3], K. SATHIAN[2];
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Abstract: Sound symbolism refers to the non-arbitrary mapping between the sound of a word and its meaning, e.g. the pseudowords “lomo” and “teke” sound rounded and pointed, respectively. The neural basis of this phenomenon has mostly been studied using pseudowords. It remains unclear to what extent the mechanisms that mediate sound-symbolic associations for pseudowords apply to natural language (e.g. for real words such as “ball” and “spike”). Here, we studied neural responses in patients undergoing stereo-electroencephalography (sEEG) monitoring for seizure localization, while they classified auditory real words and pseudowords as rounded or pointed. 12 rounded (e.g. “bongo”) and 12 pointed (e.g., “scissors”) real words were selected based on their roundedness/pointedness sound symbolism score (from Sidhu et al., Psychonomic Bulletin & Review, 2021). To minimize differences in neural processing stemming from differences in the acoustic content of real words and pseudowords, the phonemes constituting the real words were used to generate 12 rounded and 12 pointed pseudowords, with the consonant-vowel order and syllable structure of pseudowords constrained to match real words. These stimuli were recorded by a native speaker of American English. Participants classified the stimuli as sounding rounded or pointed with over 80% accuracy. We used machine-learning classifiers to decode items as rounded or pointed, based on the temporal and spectral characteristics of neural activity at different electrode contacts. Real word auditory speech stimuli could be decoded from temporal features in parts of the inferior frontal gyrus, and from spectral features in inferior parietal and posterior cingulate cortex. Pseudoword speech sounds could be decoded from temporal features in mid-insular cortex, and from spectral features in inferior parietal and superior temporal cortex. Many of these regions receive multisensory input, and some are involved in language, suggesting that perception of sound-symbolic features recruits multiple neural processes. Moreover, the relevant processes differ between real words and pseudowords.

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Poster

PSTR142: Language: Neural Circuits and Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.02/LL8

Topic: I.11. Language

Support: Institutional funds from Penn State College of Medicine

Title: Neural encoding of acoustic information associated with sound symbolism in pseudowords

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Abstract: Sound symbolism is a correspondence between speech sounds and meaning. For example, the pseudoword /kɛke/ is typically judged as *sounding* pointed, while the pseudoword /molo/ is judged as *sounding* rounded. The neural processes associated with sound symbolism are not well understood. Here, we asked participants to rate how rounded/pointed each of 12 consonant-vowel-consonant-vowel pseudowords sounded during and immediately following a functional magnetic resonance imaging (fMRI) session. These pseudowords were selected from a larger set for which rounded/pointed ratings were available; we selected items to range from very pointed to very rounded. We constructed a representational dissimilarity matrix (RDM) from the post-scan ratings. We next calculated the duration, intensity, fundamental frequency (F0), and the central frequencies for the first (F1), second (F2), and third (F3) formants for each consonant and each vowel for each pseudoword. We constructed separate RDMs for each acoustic parameter and another RDM that combined all the acoustic information. Each acoustic RDM, except the F0 RDM, was significantly correlated with the ratings RDM. Next, we used a searchlight process to construct RDMs from the blood oxygenation level-dependent (BOLD) signal in spherical regions centered iteratively around every cerebral cortical voxel. We then computed the correlation of each BOLD RDM to the ratings RDM and each of the acoustic RDMs to test where the brain encodes sound-symbolic information (representational similarity analysis). Significant correlations were found between the ratings RDM and the BOLD RDMs in the left auditory cortex. The RDMs for the combined acoustics, F2, and intensity were each correlated with BOLD RDMs in bilateral auditory cortex, while the F1 RDM was correlated with BOLD RDMs in the left but not the right auditory cortex. These correlations with the acoustic parameter RDMs overlapped with those with the ratings RDM. Interestingly, the F1 RDM was also significantly correlated with BOLD RDMs in the left inferior frontal gyrus, an area associated with language processing, and BOLD RDMs in the right precuneus, an area associated with visual imagery. The ratings RDM and several acoustic RDMs were also correlated with BOLD RDMs in the sensorimotor cortex, which is likely related to the motor responses associated with the in-scan ratings task. These results indicate that sound symbolism is associated with auditory, visual imagery, and linguistic processes.

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Poster

PSTR142: Language: Neural Circuits and Mechanisms

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Program #/Poster #: PSTR142.03/LL9

Topic: I.11. Language

Support: NIH Grant R01-DC04290
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Title: Transcranial ultrasound stimulation impact on electrically induced field-potentials in the human brain: testing the neural excitability hypothesis

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Abstract: Transcranial Ultrasound Stimulation (TUS) is a promising non-invasive brain stimulation technique that delivers sonic energy through the skull to modulate brain activity with spatial specificity. Recent findings in both human and animal models suggest that certain TUS stimulation protocols can increase neuronal excitability of the targeted brain area for tens of minutes following relatively brief sonication periods (e.g., Caffaratti et al., 2024). There is substantial scientific and clinical interest in understanding how TUS influences neural signals directly recorded from the human brain (Darmani et al., 2024). In this study, we delivered 80-second theta-burst TUS (tbTUS) bilaterally to the anterior cingulate cortex (ACC) in epilepsy patients during their epilepsy monitoring period. The patients had intracranial electrodes providing recording contacts throughout several fronto-temporal brain regions, including the ACC, the target of our TUS stimulation. Before and after applying TUS or a sham (no TUS) condition, we continuously evaluated the excitability of electrically induced local-field potential (LFP) responses throughout the recording contacts available in the patient. This was done by periodically 'pinging' the excitability response of the brain, using an electrical stimulation tractography (esTT) approach, consisting of single biphasic electrical pulses of 0.2 msec, applied every 2 seconds to the ACC in one hemisphere. By comparing the esTT-evoked LFP responses before and after TUS, we tested the hypothesis that tbTUS would selectively magnify certain electrically induced LFP response components, relative to the pre-TUS baseline period, for at least 10 minutes in the area stimulated with TUS. We observed that tbTUS enhances certain LFP potentials in the ACC and adjacent middle frontal cortex, as reflected by an increased post-TUS amplitude of specific LFP potentials, which lasted for at least 10 minutes post-TUS. Some LFP potentials were affected for a longer period of time, and the LFP responses in other parts of the brain, more distant to the stimulation site (e.g., insula), showed the opposite pattern, a reduced LFP potential, highlighting the differential impact of TUS on the neural system. Analyses are underway on TUS effects on single units. The results provide initial insights into how TUS could have excitatory effects on at least the sonicated area that lasts longer than the sonication duration.
References: Caffaratti, H. et al. (2025). eLife, 100827. Darmani, G. et al. (2025). Nat Comm, 16(1),2693

Disclosures: H. Caffaratti: None. **R.M. Calmus:** None. **G. Sharma:** None. **S. Kumar:** None. **H. Oya:** None. **M. Bowren:** None. **Y.A. Ayala:** None. **J.I. Berger:** None. **N. Trapp:** None. **A.D. Boes:** None. **A.E. Rhone:** None. **H. Kawasaki:** None. **M.A. Howard:** None. **C.I. Petkov:** None.

Poster

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Program #/Poster #: PSTR142.04/LL10

Topic: I.11. Language

Support: NIH Grant K01 DC019265
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Title: Investigating speech audio contamination in intracranial sEEG recordings in the absence of participant perception

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Abstract: Intracranial recordings in an epilepsy monitoring unit (EMU) setting can reportedly be contaminated by the soundwaves of speech in the room where the recordings are made, both from the patient's own speech as well as the speech of others. This poses a challenge for intracranial language experiments involving speech. A key difficulty in interpreting such potential contamination is distinguishing between real neural responses to the perceived speech stimuli and artifactual speech contamination in the recordings. To circumvent this, we performed sEEG recordings in an EMU setting involving audio speech stimuli present in the room that the participant could not hear. 5 epilepsy patient participants performed an experimental task while wearing headphones on top of noise-canceling earbuds playing white noise that prevented the participant from hearing the audio speech stimuli of the experiment. The experiment was a word-to-picture matching task with 3 randomly interleaved trial conditions: Aud, Blank, and Vis. Aud trials start with an audio word stimulus played at a normal volume while the patient viewed a blank laptop screen, followed by an array of 8 pictures shown on the screen, one of which was a picture of the stimulus word. The participant was tasked with making their best guess at touching the picture that matched the audio word stimulus. Blank trials proceeded in exactly the same way, except that no audio stimulus was played when the initial blank screen was shown. On Vis trials, the word appeared as text displayed visually on the screen, followed by the search array. With this design, any effect of speech contamination will be apparent in the contrast of the neural recordings in the Aud and Blank conditions. The Vis trials served to maintain the participant's attention or the task, and also serve as a neural analysis control intended to indicate that the experiment included enough statistical power to detect a real difference in neural activity resulting from the perception of the visual word. Behavioral results showed that participants were at a chance level of performance for the Aud trials, indicating that they indeed could not hear the auditory words that were played. They performed the Vis trials at near ceiling performance, indicating that participants were attending to the task. Preliminary neural analyses did not show noticeable spectral differences in the sEEG recordings between the Aud and Blank conditions, with more formal analyses to follow. If these preliminary results are later confirmed, this would indicate that there is not a significant concern about speech contamination in sEEG recordings in this typical EMU setup.

Disclosures: C. Smith: None. **M.J. Nelson:** None.

Poster

PSTR142: Language: Neural Circuits and Mechanisms

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Program #/Poster #: PSTR142.05/LL11

Topic: I.11. Language

Title: Verbal working memory is subserved by distributed network activity between temporal and frontal lobes

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Abstract: Verbal working memory (vWM)—the short-term memory associated with language information—is integral to human cognition. The neural mechanisms of vWM remain poorly understood, although like other forms of working memory, are thought to consist of both distributed and persistent population activity. We hypothesized that vWM is subserved by activity between language and control networks and sought to test this hypothesis using intracranial electroencephalography (iEEG). We recorded iEEG activity from 48 epilepsy patients (mean age = 32 years old, 20 female) with stereotactically implanted depth electrodes while they performed a verbal working memory task. The patients performed a modified Sternberg task, with stimuli consisting of lists (length 3, 5, 7, or 9) of words or non-words. Activity in the high-gamma band (HG—70-150 Hz) band was extracted and used as a local index of neural computation. Non-parametric permutation tests were used to establish electrodes with significant activity during maintenance, which were used to decode list length and word/non-word stimuli using linear discriminant analysis. Pearson correlation was calculated as a measure of functional connectivity from averaged HG activity in seven regions of interest in a subset of 12 patients and used to classify length and word/non-word stimuli using logistic regression. After excluding electrodes localized to white matter, 1116 out of 9644 electrodes had significant activity during maintenance. The majority (524 electrodes) localized to 20 specific locations predominantly in hippocampus, temporal lobe, and prefrontal cortex. Initial results of decoding successfully differentiated between trials with high load (7 or greater items) and low load (mean accuracy=0.73, chance=0.50) and between trials comprised of words or non-words (mean accuracy=0.80, chance=0.50). Decoding performance using functional connectivity was similar with mean accuracy of 0.757 for memory load and 0.805 for word/non-word. Longer list length was correlated with greater connectivity between hippocampus and prefrontal cortex, while, surprisingly, word stimuli were associated with greater connectivity within the lateral temporal lobe and between temporal and prefrontal cortex. We found that vWM function can be accurately decoded from high-gamma activity in the hippocampus, temporal lobe, and prefrontal cortex. Importantly, effective maintenance of verbal working memory is associated with distributed activity across the temporal and frontal lobes. This distributed activity appears to couple language-supporting regions of the lateral temporal lobe to frontal cortex to maintain vWM items.

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Poster

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Program #/Poster #: PSTR142.06/LL12

Topic: I.11. Language

Title: Hierarchical Speech Encoding in Non-Primary Auditory Regions

Authors: *N. SHI[1], S. DURAIVEL[2], A. EARLE-RICHARDSON[3], D. G. SOUTHWELL[4], G. B. COGAN[5];
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Abstract: Beyond primary auditory regions, non-primary brain areas like the hippocampus and insula are increasingly recognized as contributors to speech perception. However, their specific roles in the hierarchical processing of speech remain poorly characterized. To address this gap, we recorded intracranial neural signals from 24 epilepsy patients implanted with stereoelectroencephalography (sEEG) electrodes (n = 4594). During the experiment, patients passively listened to naturalistic sentences from the TIMIT dataset. We extracted high-gamma power (70-150 Hz) from the recordings and applied linear models to examine how they encode the acoustic features.Using spectrotemporal receptive fields (STRFs), we identified 1,252 electrodes with significant responses to the acoustic spectrogram ($p < 0.001$, compared to permuted conditions). While most were located in classical auditory areas such as the superior temporal gyrus (STG; N = 232, 18.5%) and middle temporal gyrus (MTG; N = 193, 15.4%), a substantial number were also found in non-primary regions, including the fusiform gyrus (FuG; N = 85, 6.8%), insula (INS; N = 79, 6.3%), inferior parietal lobule (IPL; N = 66, 5.3%), precentral gyrus (PrG; N = 50, 4.0%), hippocampus (Hipp; N = 48, 3.8%), and inferior temporal gyrus (ITG; N = 40, 3.2%). Notably, electrodes in IPL and Hipp exhibited significant temporal delays in encoding compared to STG, suggesting a distinct role in auditory processing hierarchy.To explore the encoding of higher-order linguistic features, we further mapped HG features to embeddings from all 12 layers of a large language model (GPT-2 Small). The final layer (layer 11) showed the strongest encoding performance, with 238 electrodes reaching significance ($p < 0.001$). In addition to STG (N = 82, 34.5%) and MTG (N = 35, 14.7%), these representations extended to IPL (N = 27, 11.3%), FuG (N = 18, 7.6%), and INS (N = 15, 6.3%). Together, these findings demonstrate that non-primary regions systematically encode both low- and high-level speech features, with distinct spectrotemporal dynamics from those in classical auditory cortex. This motivates further investigation into their roles in processing syntactic and lexical information, expanding our understanding of the distributed neural architecture supporting natural speech perception.

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Poster

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Topic: I.11. Language

Support: NIH Grant R01DC04290

Title: Voice Pitch Representation on Cingulate and Insula Neural Activity

Authors: *F. TABASI[1], J. I. BERGER[2], H. CHO[3], A. ROHL[4], S. KUMAR[4], J. D. GREENLEE[5];
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Abstract: Vocal motor control depends on intricate interactions between primary and associative cortical regions to generate intended vocal patterns. To achieve this goal, these networks need to dynamically interact with areas that monitor ongoing behavior by processing sensory information against internal and external models. The cingulate cortex and insula are evolutionarily conserved regions that process sensory inputs in order to modulate ongoing behavior. However, their cytoarchitectural and functional heterogeneity suggests they operate at various hierarchical levels of vocal motor control, making large-scale electrophysiological investigation challenging. To address this, we recorded single-unit activity from the insula and cingulate cortex, as well as opportunistically the hippocampus and amygdala, in human subjects implanted with intracranial electrodes during a pitch-modulation vocalization task. Participants (n = 7) were epilepsy patients undergoing intracranial monitoring to localize seizure activity. They were asked to change their voice pitch during sustained vowel vocalization according to the target shown on screen, while their voice pitch was extracted and superimposed on the screen in real-time. Data were cleaned and spike sorted offline to isolate single neurons. Peristimulus raster plots & spike density functions were generated to examine modulation locked to voice onset and target movement onset. We isolated more than 600 neurons across all brain regions. Within and between regions, we found a diverse array of response types, with increases in activity most dominant but suppression also present in some neurons following voice onset, and some neurons showing the greatest modulation at the onset of target movement (i.e., during updating of the internal behavior based on the external stimulus), while others are time-locked to onset and offset of the vocalization. Analyses are ongoing to examine correlations between spike density and produced pitch, pitch change, and accuracy in responsive subdivisions of both regions. Overall, these data highlight that the insula and cingulate cortex are involved in vocal motor control and pitch production. These results have implications for better understanding how associative cortices are engaged in self-monitoring during vocalization and real-time feedback to update the underlying network.

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Poster

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Topic: I.11. Language

Title: Metacognition in Large Language Models and Humans in Post-Decision Wager

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Abstract: Large Language Models (LLMs) have made significant progress, e,g, OpenAI 2025, Petrov et al. 2025. The state-of-the-art LLMs still have vulnerabilities falling into misalignment, including specification gaming and reward hacking (Christian 2020), as observed in, e.g., OpenAI o3 (Bondarenko 2025). Some cognitive scientists argue that LLM as a cognitive model is useful for investigating human cognition (Frank & Goodmann 2025, Saftori & Orrù 2023). Ying et al. (2025) criticized that many AI benchmark depends on majority voting to determine the single "ground-truth" label, discarding rich information about the distribution of annotators. Frank (2023) pointed out that it is necessary to evaluate the cognitive capabilities of LLMs using different measures from many aspects. Metacognitive capabilities in LLMs and humans have also been investigated and evaluated using benchmarks based on the confidence judgment paradigm explicitly (Griot et al. 2025, Yoshizawa & Mogi 2023), with LLMs lacking aspects of metacognition and exhibiting overconfidence. Here we examine metacognitive capabilities in humans and LLM implicitly based on the "Post-Decision Wager (PDW)" paradigm (Persaud 2007). The implicit measure PDW is a more robust paradigm than the confidence judgment paradigm, because it avoids misinterpreting the ambiguous meaning of "confidence" by subjects (Persaud 2009), and the subject's financial incentive can be aligned to report confidence accurately (Weise 2024). In PDW, a subject can wager when a subject considers correct, with high wagers indicative of high confidence. PDW is often influenced by factors like loss aversion (Schurger & Sher 2008) and risk aversion (Dienes & Seth 2009). We designed tasks based on PDW, in particular the Artificial Grammer task and the Iowa Gambling Task. We also evaluated the strategy awareness using the Iowa Gambling Task, as well as loss aversion , risk aversion, and trust in LLMs/humans by designing different payoff matrices. We analyze the results in comparison with human implicit metacognitive abilities subserved by the medial prefrontal cortex (Vaccaro & Fleming 2018). Finally, we discuss our results from a Neuroeconomics perspective (Glimcher & Rustichini 2004).

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Poster

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Title: Neural Encoding of Korean /n/ Allophones: Distinguishing Articulatory vs. Abstract Phonemic Representations

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Abstract: Speech decoding from intracranial electroencephalography (iEEG) has advanced rapidly, with most systems targeting phoneme-level outputs. Because these systems typically treat phonemes as merely descriptive notations, they seldom distinguish between articulatory representations—which capture concrete gestural realizations—and abstract representations that generalize across allophones. Consequently, the same phoneme can surface in divergent acoustic patterns. In Korean, for example, word-initial nasals are frequently denasalized, exhibiting spectral patterns similar to those of plosives. To determine whether neural activity during speech production tracks abstract phonological categories or fine- grained articulatory detail, we recorded iEEG from a native Korean speaker. We asked specifically whether denasalized word-initial /n/ is encoded more like a nasal or a plosive. For every word-initial alveolar /n/, /t/, /t^h/, and /t*/ appearing in 33 sentence contexts, band- limited power (theta-high gamma) was extracted and used to train decoders that discriminated /t, t^h, t*/ from /n/. The six top-performing decoders (85-72 % in balanced accuracy) were then probed with five held-out denasalized /n/ tokens. All six decoders labeled these tokens as plosives; five of them classified every token as /t, t^h, t*/, while one decoder labeled two tokens as nasals. Although the data come from a single participant, the consistency of the results points unequivocally to an articulatory-based, rather than abstract- based, neural encoding of Korean /n/ allophones. We therefore contend that future speech- decoding research should explicitly separate articulatory from abstract phonemic representations.

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Poster

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.10/LL16

Topic: I.11. Language

Title: Shared articulatory representations across languages in speech motor cortex

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Abstract: Human speech production relies on the precise coordination of vocal articulators, and classical neuroimaging and stimulation studies revealing a somatotopic organization of articulators along the ventral sensorimotor cortex (vSMC). However, the extent to which articulatory representations are preserved across languages remains largely unexplored. To investigate the neural encoding of speech across languages, we analyzed broadband high-gamma activity (70-150 Hz) from intracranial stereoelectroencephalography (sEEG) recordings in two bilingual (English-Spanish) subjects performing sentence reading tasks.
We trained multivariate temporal response function (mTRF) encoding models using a shared phoneme set and articulatory kinematic trajectories (AKTs) to predict vSMC neural responses. Phoneme encoding models fit on one language still explained majorities of neural variance when evaluated on trials of the other language. AKT models demonstrated superior cross-language generalization compared to phoneme-based models. Reconstruction of AKTs with seq-to-seq models retained decoding accuracy even when trained on the non-target language, suggesting a shared articulatory latent space underlying speech production.
At the single-electrode level, mTRF filter weights revealed consistent tuning to phonemic classes and articulatory gestures across languages.Low-dimensional projections of filter weights preserved geometric separability between articulatory groups (labials and lingual) in both languages.
These findings demonstrate that phonological and articulatory representations in vSMC are robust across languages, suggesting a shared neural code for articulatory control. This cross-linguistic generalizability could inform the design of future speech BCIs, enabling multilingual decoding via a core set of latent articulatory primitives.

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Poster

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Program #/Poster #: PSTR142.11/LL17

Topic: I.11. Language

Title: Computational hierarchies of intrinsic neural timescales for speech perception and production

Authors: *N. C. LIDDLE[1], A. EARLE-RICHARDSON[2], D. G. SOUTHWELL[3], G. B. COGAN[4];
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Abstract: Intrinsic neural timescales (INTs) reflect distinct processing windows in neural activity and are proposed to underlie computational gradients across cortical regions. Short INTs are thought to optimize encoding, while longer windows sustain higher-order integration of hierarchical inputs. In speech processing, the dual-stream model delineates functionally distinct auditory and motor pathways, with an ascending ventral auditory stream for perception and a descending dorsal motor stream for production. However, whether INTs in the speech network are anatomically discrete and reflect functional hierarchies within these streams remains unexplored. We sought to investigate how INTs shape computational gradients in the auditory and motor speech pathways by analyzing resting-state and task-evoked activity during speech processing. We used intracranial neural recordings (iEEG) across 12 regions of interest (ROIs) to compare INTs at rest and during a speech repetition task. Data were collected from 36 subjects (mean age = 31, 18 female) during inpatient monitoring for surgical treatment of epilepsy. We hypothesized that both resting- and task-state INTs would exhibit a discrete anatomical hierarchy of duration and variance that increases across the ascending auditory pathway and decreases across the descending motor pathway. We further hypothesized that rest-task INT modulation during speech perception and production would reveal task-selective regional differences. Our results demonstrated a robust INT hierarchy across states aligned with each pathway, increasing from Heschl's gyrus (A1) to higher-order superior, middle, and inferior temporal auditory ROIs, and decreasing from inferior parietal to frontal and sensorimotor (M1, S1) motor ROIs. Rest-task INT modulation reflected task-selective patterns, with auditory ROIs increasing by a mean of 8.25 ms during speech perception and only 3.81 ms during production. We then compared INTs to the duration of high gamma activity (70-150 Hz) during speech tasks, which revealed an unexpected inverse hierarchy across regions that is under ongoing investigation. Our findings show that the speech network exhibits anatomical INT hierarchies at rest and during processing that follow ventral and dorsal functional pathways rather than generalized topographic gradients. Regional differences in rest-task INT modulation between speech tasks suggest that INTs reflect computationally relevant activation patterns. Taken together, this work provides evidence that INTs demonstrate a dynamic temporal substrate for hierarchical neural computations in speech perception and production.

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Poster

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Title: Sensorimotor dynamics of singing and speaking

Authors: *A. L. PRACAR[1], M. PAGNOTTA[2], D. R. QUIROGA-MARTINEZ[4], R. GHUMAN[1], M. DASTJERDI[5], M. RUVALCABA[1], N. BIONDO[6], M. IVANOVA[1], J. J. LIN[7], J. T. WILLIE[8], P. BRUNNER[9], N. F. DRONKERS[1], R. T. KNIGHT[3];
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Abstract: Introduction: For over a century, some post-stroke individuals with aphasia have been observed to sing more fluently than they can speak. Despite extensive research, the neural mechanisms distinguishing speech from song remain unknown. Here, we leveraged the high spatial and temporal resolution of intracranial electroencephalography (iEEG) to characterize hemispheric contributions and network dynamics underlying singing and speaking. Speech is thought to depend more on feedforward control, supported by primary motor cortex (M1) and somatosensory cortex (S1) (Guenther, 2006). These regions enable planning, prediction, and monitoring of somatosensory, motor, and auditory information. Behavioral studies suggest singing may rely more on feedback control (Kleber et al., 2013; Zarate, 2013). Prosodic speech and pitch engage bilateral dorsal laryngeal motor cortex (in M1) in electrophysiological work (Dichter et al., 2018). This study provides the first direct electrophysiological evidence comparing feedforward and feedback dynamics in M1 and S1 during singing versus speaking of matched sentences.
Methods: iEEG data were collected from 15 participants undergoing monitoring for pre-surgical epilepsy evaluation. Participants repeated matched sentences in singing or speaking conditions. High-frequency activity (HFA; 70-150 Hz) and oscillatory power were extracted using Morlet wavelet convolution and tested via 1000 permutation tests. Intersite phase clustering (ISPC) was computed to assess phase-based functional connectivity.
Results: Cluster-based permutation tests ($P_{perm} < .05$) revealed hemispheric differences. In S1, HFA increased post-articulation in both conditions but showed opposite lateralization: speaking activated left S1 more, singing activated right S1 more. In M1, speaking was linked to greater alpha/beta power in the left hemisphere, while singing elicited stronger HFA in right M1.

Connectivity mirrored these results: speaking maintained elevated alpha/beta synchrony bilaterally, while singing induced a transient drop then rebound in left S1 and a brief rise then decline in right S1. The timing of power and synchrony modulations suggests the initiation of motor commands and monitoring of sensory feedback is distinct for speech versus song, providing a novel electrophysiological characterization of this feedforward and feedback circuitry. The right-lateralized HFA and unique left-hemisphere oscillatory profile for singing may help explain preserved fluency in individuals with left hemisphere damage.

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Poster

PSTR142: Language: Neural Circuits and Mechanisms

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Program #/Poster #: PSTR142.13/LL19

Topic: I.11. Language

Support: R01 DC019354
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Simons Collaboration on the Global Brain
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Title: Cortical planning dynamics during unstructured conversation

Authors: L. FLIPTS[1], Z. CHEN[1], M. MACKAY[2], J. D. GREENLEE[2], M. A. LONG[1], ***G. A. CASTELLUCCI**[1];
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Abstract: Humans interact using speech in a seemingly effortless fashion; however, these everyday conversations require highly flexible and efficient planning. Speakers plan not only immediately before they talk in such contexts - they must also plan while listening to their social partners and while articulating their own multiword responses. This complexity has rendered real-world language planning challenging to investigate, thus leaving its neurobiological underpinnings poorly understood. To address this gap, we performed intracranial recordings to assay cortical activity in patient-volunteers as they completed a question-answer task and engaged in free conversation. We observed robust modulation in the high gamma (70-150 Hz) and beta (12.5-30 Hz) bands during and prior to participant speech, and we conducted an unsupervised clustering analysis to further assess the organization of these dynamics. This revealed that the brain was partitioned into planning and motor networks that were nearly identical in both settings, indicating that the same localized systems underlie task-based and unstructured spoken interaction. Using a Hidden Markov Model-based approach, we then

determined that each of these networks entered distinct ‘active’, ‘suppressed’, and ‘neutral’ states at behaviorally relevant times. For example, some planning networks were active when participants listened to information-rich portions of their partner’s speech, while others were primarily active during pauses and prosodic breaks as participants spoke. These results therefore demonstrate that different networks support planning while listening versus planning while speaking, consistent with the idea that individual language-related preparatory processes (e.g., syntactic planning, phonological encoding) possess separate cortical substrates. Importantly, we also found that planning networks were often active concurrently with sensorimotor regions throughout periods of perception and articulation, suggesting that this planning-related multitasking is enabled by dividing function across independent cortical modules. Our study therefore offers foundational insight into the neural basis of natural language use and provides a detailed description of how planning unfolds on a moment-to-moment timescale during interactive speech production.

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Poster

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Topic: I.11. Language

Support: University Research Award (University of Rochester)

Title: Neural markers of speech processing during interactive vs. passive listening

Authors: *C. SMITH[1], A. R. NIDIFFER[2,3], E. C. LALOR[3,4,2], E. A. PIAZZA[1,2];
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Abstract: How does interaction impact language processing? Prior research has investigated neural markers of language processing either during interaction or passive listening. However, no study has directly tested how neural processing might differ between the two situations in order to identify distinct neurophysiological mechanisms of interpersonal spoken interaction. To do so, we asked pairs of “interactors” to engage in a series of prompted (but unconstrained) conversations while we recorded EEG and audio. In separate sessions, we then recorded EEG from “observers” who listened to conversations from a previous pair of interactors. Cortical tracking of acoustic (spectrogram) and linguistic (lexical surprisal) features of the conversations was estimated using forward encoding models that predicted the EEG responses of each participant from the speech features. In preliminary data, interactors tracked linguistic features more closely than observers, while observers tracked acoustic features more closely than interactors. Across groups, acoustic features contributed more to models than linguistic features.

Participants rated their own overall attentiveness similarly across the two groups, although interactors rated the conversations as higher quality (enjoyment, naturalness, connection, feeling "on the same page"). Early trends also suggest a complex relationship between quality ratings and neural measures of conversation tracking. Better tracking of linguistic features was associated with higher quality ratings in both groups, but for observers, better tracking of acoustic features predicted lower quality ratings. Future analyses will compare additional aspects of language processing across participant roles.

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Poster

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Topic: I.11. Language

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Title: Stimulation of cingulate alters speech timing during vocal turn-taking

Authors: *M. MACKAY[1], G. A. CASTELLUCCI[2], F. TABASI[3], J. D. GREENLEE[4]; [1]Univ. of Iowa Human Brain Res. Lab., Iowa City, IA; [2]Neurosci., NYU Sch. of Med., New York, NY; [3]Dept. of Neurosurg., [4]Dept Neurosurg, Univ. of Iowa, Iowa City, IA

Abstract: Planning and executing speech during natural conversation relies on coordinated neural activity across frontal cortical networks. Prior work has implicated the caudal inferior frontal and middle frontal gyri (cIFG, cMFG) in speech response planning during turn-taking, but the role of non-primary sites remains less defined. Previous lesion studies in non-human primates have implicated associative cortices, including the cingulate cortex, in volitional vocalization and vocal motor control; however, the contribution of these regions to language processes during natural conversation in humans is not fully explored. Existing human lesion studies have been confounded by factors such as lesion severity and poor anatomical specificity, limiting their interpretability. To address this, we investigated the functional contributions of frontal and midline cortical areas—particularly the cingulate cortex—during a vocal turn-taking task. Patient-volunteers undergoing intracranial monitoring for seizure localization performed a structured question-answer task simulating natural conversation. An initial recording session allowed us to identify active sites using narrow-band high-frequency power changes and broadband time-frequency analyses. We then applied direct electrical stimulation (DES) during the same task to transiently perturb local neural activity. Stimulation across several frontal and cingulate sites led to diverse behavioral effects, including delayed responses, speech errors, and, in some cases, faster response initiation. Notably, stimulation of the middle cingulate cortex (MCC) reliably delayed turn-taking without affecting articulation, suggesting a role in the temporal coordination of speech. These findings build on prior work by extending the set of

regions implicated in vocal turn-taking and highlight the potential contributions of midline structures to interactive speech timing.

Disclosures: M. MacKay: None. **G.A. Castellucci:** None. **F. Tabasi:** None. **J.D. Greenlee:** None.

Poster

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Title: Cross-frequency Spatiotemporal Dynamics of Neural Coding Underlying Logographic Reading

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Abstract: Reading in logographic languages such as Chinese involves a unique transformation from complex visual forms to both phonological and lexical-semantic representations, bypassing the linear grapheme-to-phoneme mapping characteristic of alphabetic systems, such as English. However, the neural mechanisms that support this transformation remain incompletely understood. Previous studies have produced inconsistent findings regarding the spatiotemporal distribution of these processes in Chinese, especially with very limited investigation into the spatiotemporal neural activity patterns across different frequency bands. Here, we leverage high-density electrocorticography (ECoG) recordings from 11 participants performing reading tasks to characterize the spatiotemporal dynamics of reading Chinese characters.Utilizing neural decoding and representational similarity analysis, we have identified a spatiotemporally and cross-frequency differentiated cortical network map that underlies Chinese word reading. Specifically, the anterior and middle superior temporal gyrus (STG) and middle temporal gyrus (MTG) demonstrated significant responses to orthographic, phonological, and lexical processes in lower frequency bands (alpha, beta1, beta2), while frontal and posterior temporal regions exhibited more distributed, broadband patterns. Notably, high gamma activity in middle

precentral gyrus (midPrCG) was specific to orthographic processing. In contrast, alpha activity in the anterior MTG and beta1 activity in the middle STG were associated with semantic processing. Single-electrode amplitude clustering further revealed temporally and spatially distinct theta and high gamma networks. In theta, clusters followed a sequential topography along dorsal and ventral language pathways. In high gamma, orthographic and phonological processing predominated in the posterior STG and midPrCG at 250 ms after stimulus onsets, whereas by 400 ms, all three processes were evident in the precentral gyrus (PrCG) and inferior frontal gyrus (IFG). These findings provide novel insights into the fine-grained spatiotemporal and cross-frequency neural mechanisms underlying Chinese reading, addressing key gaps in understanding of logographic language processing.

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Poster

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Program #/Poster #: PSTR142.17/MM1

Topic: I.11. Language

Support: NIH NS098981

Title: Intracranial signatures of conceptual features are invariant of subjective semantic judgements

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[1]Vivian L. Smith Dept. of Neurosurg., Univ. of Texas Hlth. Sci. Ctr., Houston, TX; [2]Vivian L Smith Dept. of Neurosurg., UTHealth Houston, Houston, TX; [3]Neurolog. Surgery, McGovern Med. Sch. at UT Hlth., Houston, TX

Abstract: The distinction between abstract and concrete concepts is a major organizing principle of semantics. Neurobiological assessments have been limited in their spatiotemporal resolution, and uncertainty remains about the causal role of specific regions in concept representation. We utilized intracranial recordings in human epilepsy patients (n=19) during a concreteness judgement paradigm of single word reading. Patients were tasked with reading words (presented for 1000ms on screen) and pressing a button (2AFC) to determine whether the word was something they could directly perceive (e.g., ‘laptop’ vs. ‘justice’). Abstract words are thought to rely more on language-internal semantic features and lexical associations. Only accurate trials were included in our analyses. We implemented a surface-based linear mixed effects (sbLME) model for the window 300-700ms after stimulus onset, a period we have previously demonstrated as crucial for semantic processing of written words. This allowed us to combine responses across individuals in a standardized cortical space, isolating effects of concreteness and regressing out confounders such as word length and frequency. In broadband high gamma activity (BGA; 70-150Hz), concrete concepts showed greater activation across a frontal and

ventrotemporal network (ordered in terms of early-to-late responses): mid-fusiform cortex, parahippocampal gyrus, orbitofrontal cortex, inferior frontal gyrus, and temporoparietal junction. Greater activation for abstract words was found in lateral posterior middle temporal cortex, a region that has previously been implicated in computing language-specific structures. Intercortical communications, measured by high-frequency partial direct coherence, revealed bidirectional frontal and ventral plus lateral temporal interactions. What we term 'midscale' words - occupying the middle range of the concreteness scale (e.g., 'profit') for which there was technically no correct answer - activated similar regions, but support vector regression decoders revealed BGA was not modulated by the participants' semantic decisions about these words and were instead better captured by a model predicting that midscale trials should fall between concrete and abstract, regardless of behavioral response. Cortical stimulation of ventrotemporal cortex and inferior frontal cortex disrupted the ability to make concreteness judgements. This work reveals a distributed neural code for conceptual features that is independent of subjective judgement, suggesting that BGA serves as a reliable index of semantic properties that do not reduce to direct task demands.

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Poster

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Topic: I.11. Language

Support: Kakenhi 22K03197
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Title: Neural modulation of meta-cognition in sentence processing by self-mirroring: Interaction of mentalizing and executive control networks

Authors: N. TOKIMOTO[1], ***S. TOKIMOTO**[2];
[1]Shobi Univ., Kawagoe, Japan; [2]Mejiro Univ., Tokyo, Japan

Abstract: Traditional views of modularity have posited that the language faculty is informationally encapsulated and unaffected by other cognitive modules. However, recent neuroscientific findings suggest dynamic interactions between the language module and other cognitive systems. Referring to the recent evidence that self-related information can influence language processing, this study investigated whether visual self-mirroring modulates neural activity during sentence processing and identified the underlying neural networks using EEG. Twenty-seven native Japanese speakers listened to 180 Japanese sentences varying in semantic typicality: high-typicality (e.g., Buses are vehicles.), low-typicality (e.g., Roller coasters are vehicles.), and semantically anomalous (e.g., Potato chips are vehicles). Participants judged sentence acceptability via button press while scalp EEG was recorded from 62 channels. The

experiment consisted of two blocks (90 sentences each); during one block, a mirror was placed in front of participants to reflect their full-body image. Results revealed a typical N400 ERP for the anomalous sentences, with broader scalp distribution under the mirror condition. ERSP analysis during the N400 time-window showed significantly greater theta-band activity over central to left-frontal scalp regions in the mirror condition. For low-typicality sentences, ERSP in the 100-300 ms window showed significantly increased gamma-band (30-50 Hz) activity over widespread right hemisphere when the mirror was present. To examine neural mechanisms mediating these effects, we calculated neural activities at 28 cortical regions of interest and analyzed effective connectivity among the regions using partial directed coherence (PDC). In the N400 time-window for anomalous sentences, the mirror condition was associated with a significant reduction in theta-band information flow among the right inferior parietal lobule, precuneus, and medial frontal gyrus. For low-typicality sentences in the 100-300 ms window, mirror presence led to increased information flow toward the premotor cortex and decreased flow toward bilateral inferior parietal lobules. Finally, multiple regression analyses revealed that changes in PDC related to the mirror condition were significantly predicted by subscale scores of the Autism Spectrum Quotient, specifically Communication, Imagination, and Local Details. These findings suggest that the modulation of language processing by self-mirroring is mediated by the mentalizing and executive control networks, highlighting the active involvement of theory of mind and attentional mechanisms in meta cognition.

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Poster

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Title: Temporal and Spectral Dynamics in Speech Lateralization: Testing AST and Spectro-Temporal Theories via Mandarin Obstruents

Authors: *Z. WANG[1], Z. CHEN[1,2], K. XU[2];
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Abstract: Hemispheric lateralization in speech perception reflects asymmetric neural processing, with models such as the Asymmetric Sampling in Time (AST) hypothesis and spectro-temporal division theories offering distinct explanations. This study investigates how temporal and spectral cues—specifically aspiration and Place of Articulation (PoA) contrasts in Mandarin obstruents—influence lateralization patterns. We examine how lateralization is modulated when

Voice Onset Time (VOT) falls within the right-hemisphere integration window posited by AST. By varying VOT, we test whether lateralization aligns more with phonemic category or acoustic duration, and how spectral complexity (PoA) further shapes this engagement. Mandarin serves a compelling case, as its phonological system relies on aspiration, not voicing, as the primary temporal cue, minimizing interference from spectral elements like vocal fold vibration. Affricates exhibit both longer VOT and higher spectral complexity than stops, enabling examination of how cue duration and complexity affect lateralization.

Employing dichotic listening paradigm and EEG, we investigated the neural responses to aspiration and PoA across consonant types. 38 participants (M = 21.9, SD = 3.7) completed the behavioral task. A separate group of 23 (M = 22.3, SD = 2.1) participated in the EEG study. Contrary to prior research, our behavioral data showed no significant difference in lateralization between aspiration and PoA contrasts, highlighting Mandarin aspiration's role in reducing spectral interference and revealing spectro-temporal integrated nature of voicing contrast in some Indo-European languages. Notably, affricates consistently evoked stronger Right Ear Advantage (REA) than stops, despite longer duration and greater complexity, supporting a category-based mechanism.

Neurophysiological findings corroborated the behavioral results. Aspiration contrasts elicited significant left-lateralized MMN and P3a components, while affricates in PoA contrast triggered enhanced bilateral activity, particularly in the right hemisphere—reflecting increased spectral processing demands. Despite these modulatory effects, left-hemisphere dominance persisted. Together, these results suggest that the brain prioritizes phoneme-level temporal cues for left-lateralized processing, even when acoustic duration exceed the optimal integration window. Spectral complexity modulates but does not override this asymmetry. The findings underscore dynamic spectro-temporal interactions and highlight the value of language-specific contrasts in reconciling competing speech processing models.

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Poster

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Title: Linguistic priors shape the neural representation of numbers

Authors: S. MANSI[1], V. BIANCO[1], P. PREVITALI[1], L. CIACCIO[1], M. MARELLI[2], L. GIRELLI[2], T. VECCHI[1], ***L. RINALDI**[1];
[1]Univ. of Pavia, Pavia, Italy; [2]Univ. of Milano-Bicocca, Milano, Italy

Abstract: There is an ongoing, vibrant debate about whether numerical information in symbolic notations would be supported by a preverbal approximate number system, located in the parietal lobes. Recent behavioral evidence using distributional semantic models have nevertheless started challenging this view, showing that linguistic priors accounts for symbolic number processing. This study examines whether linguistic priors also account for neurophysiological responses, using EEG in 36 healthy adults. EEG data from 64 channels were recorded while participants completed three tasks: (1) passive viewing of single digits, (2) sequential number comparison, and (3) simultaneous number comparison. Representational Similarity Analysis (RSA) was used to determine whether neural patterns align with predictions from distributional semantic models. Our results replicate the behavioral pattern observed in previous studies, with linguistic priors predicting performance better than real numerical distance. Importantly, EEG patterns also align better with the linguistic distribution of numbers. These findings challenge the approximate number system view, calling in turn for more comprehensive accounts integrating the role of experiential priors.

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Poster

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Topic: I.11. Language

Title: Bridging the Divide: A Developmental and Functional Continuum of Temporal Modulations in Speech and Music

Authors: *J. WANG, N. DING;
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Abstract: Speech and music are commonly distinguished by their characteristic temporal modulation spectra, typically peaking at ~5 Hz for speech and ~2 Hz for music. While this distinction has been robust across languages and musical genres, it remains unclear whether the observed rhythmic timescales merely reflect acoustic properties or also encode communicative functions and cognitive development. In this study, we examined how temporal modulations vary across vocal expressions and over development, revealing a functional continuum between speech and music shaped by both expressive context and maturational changes. To examine this, we analyzed a broad range of vocal productions, including canonical speech, sports command,

city cries, expressive utterances (e.g., crying, sobbing, laughter), character-by-character reading, single-character interjections reading, and song. Modulation spectrum analysis revealed that these vocal forms occupy intermediate positions between prototypical speech and music, forming a speech-music continuum. For instance, sports command, city cries, and crying exhibited strong energy below 4 Hz, overlapping with music-like patterns. In contrast, character-by-character reading consistently peaked near 5 Hz. This suggests that modulation spectra vary systematically with communicative function and vocal style, rather than binary category membership. Crucially, a cross-sectional analysis of speech and singing from children aged 2 to 12 revealed that slow modulations (~0.5-1 Hz)—a hallmark of adult music and expressive prosody—only emerge robustly after age 10. This pattern suggests that the ability to generate or process extended rhythmic structures is not innate but emerges gradually with neurocognitive and motor development. Together, these findings challenge the strict dichotomy between speech and music and highlight a shared temporal architecture that is graded across contexts and emerges with development. We propose that slow temporal modulations reflect not only acoustic features but also evolving capacities for affective, artistic, and rhythmic communication.

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Poster

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Title: Cortical temporal dynamics of speech perception: Dissociating linguistic and paralinguistic elements

Authors: *J. XING[1], L. M. OSTROWSKI[2], B. LANG[3], K. URRUTIA[1], M. HUANG[4], T. Q. GENTNER[5];
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Abstract: Emerging evidence suggests temporal neurodynamics track a broad spectrum of linguistic features, including acoustic-phonetic, syntactic, lexico-semantic, and prosodic elements across multiple hierarchically organized timescales. While the neurodynamics of

linguistic processing are becoming increasingly well-characterized, it remains unclear how the brain encodes and tracks paralinguistic elements such as speaker emotion. Paralinguistic information varies temporally with speech, relies on overlapping acoustic elements such as pitch and voice quality, and provides social and affective context that contributes to a speaker's intended meaning. We hypothesize that paralinguistic and linguistic information are jointly encoded within a unified hierarchical structure, with paralinguistic processing unfolding at similar timescales and in parallel with linguistic processing.

We investigate this hypothesis with a natural listening task using magnetoencephalography (MEG). Stimuli consist of 90 speech excerpts (30-90 seconds each) from an American English speech corpus, first selected based on computational estimates of emotional valence diversity, and subsequently evaluated by naïve human raters (N = 156), who rated speaker valence continuously over time from most positive to most negative. In a between-subjects design, participants also rated excerpts with degraded semantic content (via low-pass filtering) and abolished prosody (via reading time-locked transcript). Valence ratings demonstrate strong inter-rater reliability (mean standardized Cronbach's $\alpha = 0.86$). As expected, perception of speaker emotion was modulated by availability of acoustic and lexical content, where all stimulus excerpts show significant condition differences in average time-resolved valence ratings above condition-shuffled controls.

Emotional valence ratings and acoustic feature vectors inform our analysis of MEG responses to naturalistic speech. We predict that speaker emotion can be uniquely decoded from whole-head MEG sensor data independent of linguistic elements, with broader temporal generalization than that of linguistic decoding. We further hypothesize that valence decoding accuracy scales with the magnitude of valence ratings, rating divergence across conditions, and specific linguistic features present in the signal. Finally, we examine the spatiotemporal dynamics of linguistic and paralinguistic processing by using continuous rating regressors to constrain MEG source localization and projecting time-varying feature vectors onto source space to reveal how these representations interact across cortical regions over time.

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Poster

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Topic: I.11. Language

Title: Neural Responses to Voice Predict Second Language Word Reading Ability

Authors: *F. KANG, Y. JIA, Y. LI;
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Abstract: Voice processing ability can predict reading ability in native language, as revealed in increasing behavioural studies. However, it remains unclear whether second language voice processing ability can predict second language reading ability and what the neural mechanisms underlying this association are. Using functional near-infrared spectroscopy (fNIRS) techniques, this study aimed to investigate the neural activations of voice recognition in both native and second languages and how these neural representations predict second language word reading ability. To this end, we recruited 30 bilinguals who speak Chinese as their native language and English as their second language and asked them to complete two voice recognition tasks (one Chinese, the other English), during which their bilateral frontotemporal activities were measured by fNIRS. The neural results showed differences in the patterns of brain activity between native language and second language, with the latter having increased activations in the left inferior frontal gyrus, suggesting more neural resources are needed for second language voice processing. Furthermore, the neural differences in the left inferior frontal cortex between native and second language voice recognition tasks positively predicted second language word reading ability. The involvement of the left inferior frontal cortex was likely related to second language phonological ability reflected in the second language voice processing. In addition, our behaviour data indicates that participants performed better in the voice recognition task when using their first language compared with their second language, replicating the language familiarity effect. This study filled in the research gap by providing cortical evidence regarding the relationship between second language voice processing and reading ability.

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Poster

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Support: NIH Grant DC016297
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Title: Sub-lexical processing of audiovisual speech constrains lexical competition

Authors: *A. R. NIDIFFER, E. C. LALOR;
Univ. of Rochester, Rochester, NY

Abstract: As we listen to natural connected speech, we rapidly transform speech acoustics into linguistic representations. As that transformation begins and the brain makes inference on the articulations, so does a lexical inference process that updates as each phoneme is articulated. In challenging listening environments, this process can become disrupted by noisy inference at the phoneme level, leading to increased lexical competition and reduced word comprehension. Seeing a speaker's face and especially the shape of the articulators can restore comprehension, in

part by constraining the competition to words consistent with both auditory and visual speech. There is evidence that vision can constrain inference at the lexical level, but it is unknown whether those effects can be attributed to sub-lexical interactions or whether constraint happens only after auditory and visual lexical processes are complete. In this study we fit and evaluate EEG encoding models of lexical competition that vary depending on acoustic and visual uncertainty, and the constraint imposed by their set intersection. We use linear modeling to predict scalp electrophysiology from input features that represent the lexical competition during auditory, visual, and combined audiovisual (i.e., set intersection of A and V) speech and at different levels of clarity (background noise). We find evidence that audiovisual lexical processing is affected by visual constraint as a word unfolds, indicating that the phoneme read-out that determines lexical competition and selection is likely a combined audiovisual process rather than one built upon multiple unisensory representations.

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Poster

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Topic: I.11. Language

Support: FAPESP grant 2018/18900-1

Title: Lexicosemantic complexity in verb generation: behavioral and multivariate evidence from brazilian portuguese

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Abstract: Verb generation tasks are widely used to assess lexicosemantic processing, as they require more cognitive control and semantic analysis than simpler tasks like picture naming. While naming usually yields limited responses, verb generation demands choosing among many competing answers for a given noun. This complexity makes the task valuable for studying word selection and semantic associations. Electroencephalography (EEG) can reveal the timing of lexicosemantic retrieval. In particular, event-related potentials (ERPs) could offer insights into how the brain handles this complexity, though few studies have explored this. Our study aimed to understand what makes some nouns more or less complex for verb generation. A behavioral study created normative data for a verb generation battery in Brazilian Portuguese. A total of 133 participants (70 female; mean age = 32.7±14.36 years) generated three verbs for each of 52 prompt nouns, resulting in 3,615 valid responses. Reaction times (RTs) and the diversity of

answers were recorded. Principal component analysis identified two main components explaining 82% of the variance: PC1 (61.9%) represented “RT and diversity vs. quantity of responses”, while PC2 (20.4%) reflected “total number of responses.” K-means clustering, validated by the Silhouette method, revealed two clusters of prompt words. Cluster 1 included prompts with shorter RTs and more frequent, less diverse answers; Cluster 2 had longer RTs and more diverse, less frequent responses. Component scores significantly explained cluster differences (PC1:$p<0.000001$;PC2:$p<0.0191$). These results support the idea that more “broad” nouns - that can be associated with many different verbs - require more cognitive effort, slowing semantic retrieval processes. In a next step, we plan to explore if these behavioral results are reflected in brain activity patterns, using EEG/ERP analysis, which could help to better understand how the brain deals with semantic retrieval and language production during more complex tasks.

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Poster

PSTR142: Language: Neural Circuits and Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.26/MM10

Topic: I.11. Language

Support: TUM Innovation Network Neurotechnology in Mental Health

Title: Neuronal inventory of a right-hemispheric language network in an individual with aphasia

Authors: *L. SCHIFFL[1,2], L. M. HELD[1,2], J. HEDEMANN[3], A. WAGNER[2], B. MEYER[2], J. GEMPT[4], S. N. JACOB[1,2];
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Abstract: The role of the right hemisphere in residual language functions after brain damage is strongly debated. This is because very little is known about the role of individual neurons in healthy and impaired language (aphasia). Aphasia typically disrupts word retrieval - prior to the engagement of motor planning. Thus, decoding intended speech, the goal of state-of-the-art brain-computer-interfaces for individuals with speech motor deficits, poses a fundamentally different and more complex challenge in aphasia. To gain an in-depth understanding of right-hemispheric neuronal activity in language processing, we chronically implanted a patient with stroke-induced expressive (“Broca”) aphasia with planar microelectrode arrays in four frontoparietal association areas homotopic to the left language network (256 electrodes total). Over the span of ten months, we recorded over 10.000 single- and multi-units as the patient performed repetition, comprehension and naming tasks. The firing rates of the majority of

recorded units were modulated by the performed language tasks, and a substantial subset was dissociable from sensorimotor-driven responses: modulations occurred during word retrieval in picture naming, but not during identical stimulus presentation in a different context. Clustering unit activities revealed that while most response profiles were present in all regions, their distribution was region-specific: in the inferior frontal gyrus (IFG), for example, we observed an early and robust deactivation of large neuronal subsets across tasks; in the middle frontal gyrus (MFG) units showed a systematic increase in activity aligned to trial events irrespective of task type; and the supramarginal gyrus (SMG) exhibited the highest proportion of units with overlapping response modulations during speech production in both naming and repetition tasks. Firing rates varied with target words. Clusters of word-selective units were present in all four regions. The strongest selectivity for target word was observed in the naming task. During repetition, we found increased selectivity in similar trial epochs as in naming, however to a lesser degree. In contrast to firing rate modulations that were correlated across tasks, unit selectivity to target words was uncorrelated across tasks. Such task-specificity suggests that the extent and temporal dynamics of target word encoding vary according to the specific linguistic demands of each task. Our study provides fundamental new insights into the neuronal basis of language and marks an initial step toward brain-computer interfaces for restoring verbal communication in patients with acquired language impairments.

Disclosures: L. Schiffl: None. **L.M. Held:** None. **J. Hedemann:** None. **A. Wagner:** None. **B. Meyer:** None. **J. Gempt:** None. **S.N. Jacob:** None.

Poster

PSTR142: Language: Neural Circuits and Mechanisms

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Program #/Poster #: PSTR142.27/MM11

Topic: F.05. Brain-Machine Interface

Support: NIH U01-NS128612
NIH R01-MH122258

Title: The Speaking Island: From Local Architecture to Network Connectivity in Human Insular Speech Processing

Authors: *P. KEREZOUDIS[1], M. JENSEN[2], B. KLASSEN[3], G. A. WORRELL[1], N. GREGG[3], N. F. INCE[4], J. VAN GOMPEL[4], D. HERMES[5], K. J. MILLER[4];
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Abstract: Understanding speech and language representation in the human brain requires mapping the primary cortical areas and their interactions. The human insula, a multifunctional hub buried within the Sylvian fissure, has been implicated in speech motor control through neuroimaging and lesional studies; however, its precise role remains incompletely understood with conflicting results across studies. To address this gap, we quantified electrophysiological

changes from implanted depth electrodes in epilepsy patients performing various speech-related and basic movement tasks combined with single-pulse electrical stimulation (SPES) to map effective connectivity. We identified distinct spatiotemporal activation patterns within the insula corresponding to different stages of speech production. The middle short gyrus showed selective activation during the pre-articulatory period, while the posterior dorsal insula engaged during articulatory execution, overlapping with tongue movement representations. Intermediate insular regions were active during articulation but not isolated tongue movements, potentially reflecting speech-specific state estimation or sensory feedback processing. Covert speech elicited minimal insular activation, suggesting that insular engagement requires actual motor program execution rather than motor imagery or planning alone. SPES-derived effective connectivity revealed temporally-specific patterns: pre-articulatory insular channels showed preferential connectivity with frontal operculum, articulatory channels with parietal operculum, and robust interhemispheric connections between homologous regions. These findings delineate the hierarchical organization of speech motor control within the human insula, resolving previous conflicting results by demonstrating temporally-specific functional subdivisions. Our results also have significant implications for resective, ablative and neuromodulation therapies targeting this region.

Disclosures: P. Kerezoudis: None. **M. Jensen:** None. **B. Klassen:** None. **G.A. Worrell:** None. **N. gregg:** None. **N.F. Ince:** None. **J. Van Gompel:** None. **D. Hermes:** None. **K.J. Miller:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.01/MM12

Topic: J.03. Anatomical Methods

Title: Advanced Optical Clearing Techniques for Comprehensive Neural Network Imaging

Authors: *M.-C. CHENG[1], M. ISBRECHT[1], M. E. MCGLOTHLIN[2], D. CAI[3];
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Abstract: Mapping neural connectivity across entire organs requires high-resolution imaging techniques that can penetrate deep into intact tissues. Light scattering within dense biological structures presents a major obstacle to comprehensive neural network visualization, limiting conventional microscopy to superficial tissue layers. To overcome this challenge, we have developed innovative chemical and biological tissue clearing approaches that preserve native GFP fluorescence and cellular antigens while achieving optical transparency throughout diverse tissue types. Our optimized protocol addresses the complex refractive index mismatches encountered when imaging across heterogeneous tissues, from lipid-rich brain regions to dense cardiac and hepatic structures, as well as formalin-fixed human brain sections. The methodology

integrates strategic tissue permeabilization, protein cross-linking, hydrogel embedding, and controlled delipidation processes, each carefully calibrated to maintain structural integrity while achieving optical clarity. Critical to our success is the precise selection of gel monomers and crosslinkers, combined with optimized detergent concentrations that preserve native fluorescence in GFP-transgenic specimens. This approach ensures uniform transparency in deep tissues without compromising fluorescent signal quality or introducing artifacts from gel expansion. When coupled with automated microscopy and advanced computational image processing, our technique enables unprecedented resolution and scalability for neuronal network reconstruction across entire organs. These methodologies establish a foundation for expanding tissue clearing applications to larger, more complex organ systems across diverse species and experimental models.

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Poster

PSTR143: Tools and Methods for Circuit Tracing

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Program #/Poster #: PSTR143.02/MM13

Topic: J.03. Anatomical Methods

Support: UM1MH130994

Title: Uc irvine brain initiative cell atlas network brain procurement program for the center for multiomic human brain cell atlas project

Authors: *J. V. BERRY[1], M. A. KIM[4], T. C. HOLMES[5], B. TRAN[2], A. SEQUEIRA[2], F. MAMDANI[2], J. GAMA[6], E. S. MONUKI[7], N. GAMA[2], E. HEAD[3], X. XU[8], B. REN[9], M. BEHRENS[10], J. R. ECKER[11];
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Abstract: Obtaining neurotypical postmortem brain tissues from donors with broad backgrounds that reflect the general population is challenging but is of critical importance for large human brain mapping projects. In this paper, we introduce the UC Irvine Brain Initiative Cell Atlas Network Brain Donation Program and share our methods and protocols for neurotypical brain collection and sample preparations towards generating high quality human brain cell multiomic atlases. We have collected, analyzed, and characterized brain tissue samples from cognitively normal donors that represent the United States population to support the Brain Initiative Cell Atlas Network (BICAN) consortium to construct a human multiomic brain atlas. Here we describe our human postmortem brain procurement process and challenges encountered with

brain donations of cognitively normal donors between the ages of 2-65 years in Orange County, California. We have obtained donor brains with assistance from the OC Coroner's Office, UC Irvine Willed Body program, UCI Medical Center, and Children's Hospital of Orange County. Our early experience demonstrates both feasibility and challenges in collecting cognitively normal adult human brains from communities that accurately reflect the Southern California population. In spite of our goals, our data indicate sex, age, and race biases in our procurement pipelines. We plan to expand our collection pipeline and further engage in brain donation awareness and education with racially and ethnically broad communities to increase general representation in our brain donation program.

Disclosures: J.V. Berry: None. **M.A. Kim:** None. **T.C. Holmes:** None. **B. Tran:** None. **A. Sequeira:** None. **F. Mamdani:** None. **J. Gama:** None. **E.S. Monuki:** None. **N. Gama:** None. **E. Head:** None. **X. Xu:** None. **B. Ren:** None. **M. Behrens:** None. **J.R. Ecker:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

Location: SDCC Halls B-H

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Program #/Poster #: PSTR143.03/MM14

Topic: J.03. Anatomical Methods

Support: NIH BRAIN Initiative Phase I and Phase II SBIR (NS105500)
NIH NIAAA Phase I SBIR (AA030512)
NIH NIA Phase I SBIR (AG084801)
DARPA HR0011-16-C-0094

Title: Development, preclinical testing, and path to human use for the NeuralGlider Insertion System - placing implants into the brain with lower force, less damage, and better outcomes

Authors: *R. BAGWELL[1], J. GREASER[1], V. C. CUZON CARLSON[2], M. L. MULVIHILL[1], T. D. KOZAI[3], T. THAI[4], S.-H. LEE[5], R.-U. HAQUE[6];
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Abstract: A key of preclinical neuroscience research is modulation and measurement of neural activity using surgically-placed tools like microelectrodes (electrophysiology), optics (fiber photometry), and needles (delivery of chemogenetics). Despite efforts to minimize tissue damage from these tools through design optimization, the biological response continues to limit research. An alternative approach is to optimize the insertion process. We studied the reduction of force effect of micro-scale ultrasonic vibration of electrodes, infusion cannulas, and optical lenses during insertion, and whether minimizing mechanical forces during surgery improved physiological and experimental outcomes, such as chronic neural activity and reactive gliosis. Using an ultrasonic inserter (NeuralGlider® Neural Implant Inserter, Actuated Medical, Inc.)

with oscillation near 25 kHz, multiple tools were evaluated with brain tissue ex vivo and in vivo. Puncture force into the pial surface of ex vivo rodent and porcine brains decreased 70-80% relative to standard insertion, which in the case of small, high-density electrodes (Neuropixels 1.0) enabled shuttle-free placement without buckling. In vivo, acute recordings from porcine cortex using microelectrodes implanted with vibration demonstrated higher single unit yield compared to insertion controls, highlighting tissue effects caused during standard implantation. The impact of insertion angle of implants relative to tissue surface is also being investigated. Vibrated insertion of 0.5mm GRIN lenses and large diameter optical lenses (e.g. 1.0 mm) into ex vivo porcine brain tissue reduced pial puncture force by >50%, and resultant tissue compression compared to control ($p<0.01$, Student's T-test). The goal is to eliminate the cortical coring typically required for optical lens placement. Planned imaging experiments in rodents will provide insight on tissue compression and damage at the optical lens-tissue interface of chronic optogenetic and neuroimaging tools. Ex vivo testing demonstrated that infusion needle vibration reduced puncture force by >75% at speeds up to 500 µm/s compared to control and enabled puncture of porcine dura with 33G needles. In vivo testing showed that these smaller gauge infusion needles reduced aliquot backflow along needle tracks. Entrance and infusion sites also showed higher cellular density (less damage) with vibrated insertion after 6 weeks. Controlled ultrasonic vibration of neuroscience tools during insertion improves placement and study outcomes, and advances research in three areas - Penetrating Neural Implants, Optical Systems, and Needles for Delivery of Chemogenetics.

Disclosures: R. Bagwell: A. Employment/Salary (full or part-time): Actuated Medical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actuated Medical. **J. Greaser:** A. Employment/Salary (full or part-time): Actuated Medical. **V.C. Cuzon Carlson:** None. **M.L. Mulvihill:** A. Employment/Salary (full or part-time): Actuated Medical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actuated Medical. **T.D. Kozai:** None. **T. Thai:** None. **S. Lee:** None. **R. Haque:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.04/MM15

Topic: J.03. Anatomical Methods

Support: SBIR Grant R44MH119989

Title: Simple Tools for Neuroscientists to Produce Brain-Wide Cellular Resolution Snapshots of Neuronal Activity Using cFos and Npas4

Authors: *N. GUANZON[1], E. BLAES[1], C. REDD[1], Y. GALLEGOS[1], A. REKSOATMODJO[1], P. CHEUNG[1], I. F. SMITH[2], J. KELLY-ROMAN[3], C. F. VALENZUELA[3], Z. GONG[4], S. P.

GANDHI[5,1], D. G. WHEELER[1,6];
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Abstract: To look deep inside tissues, traditional histological methods rely on slicing specimens into thin sections. Tissue clearing, by contrast, provides access to the intricate anatomy of the whole, intact brain, offering neuroscientists an unbiased and comprehensive view of brain structure and function. Translucence Biosystems is developing an ecosystem of tools to support a dimensional shift from 2D to 3D histology. Using iDISCO-based clearing kits, a ZEISS Lightsheet Z.1 microscope with our Mesoscale Imaging System, machine learning-powered whole-brain object segmentation with our Voxels™ software, and novel statistical methods for anatomical analysis, our pipeline generates regionalized readouts of cellular patterns across hundreds of brain areas. The immediate-early gene (IEG) product cFos has been used for decades to monitor changes in neuronal activity. Although cFos expression is driven by calcium signaling downstream of neuronal firing, it can also be induced by cAMP signaling and other pathways activated by neurotrophins or other paracrine factors. In contrast, the IEG product Npas4 is neuron-specific and a more pure marker of increased activity-dependent calcium signaling. Our data show that cFos and Npas4 respond differently to behavioral and pharmacological stimuli and that co-staining both markers reveals distinct yet overlapping neuronal populations. To promote the adoption of this technology, the BRAIN Initiative funded the development of our iDISCO-based Neuronal Activity Kits and cloud-based Voxels™ whole-brain quantification software. The kits include validated anti-cFos and anti-Npas4 antibodies and does not require specialized equipment for whole-brain clearing and staining. Users with little to no experience in tissue clearing have successfully used the kits to generate rich, brain-wide snapshots of neuronal activity and have also labelled other markers, such as Amyloid plaques. By pairing kit-prepared samples with our Voxels-based quantification tools, we generated brain-wide readouts of cell counts, signal intensity, and Npas4/cFos colocalization. These findings demonstrate a user-friendly and scalable workflow for whole-brain analysis of cFos and Npas4, helping researchers map brain-wide activity patterns in response to experimental interventions. SBIR Grant R44MH119989 “Rapid Evaluation of Neuronal Activity in the Intact Whole Brain at Single Cell Resolution”

Disclosures: N. Guanzon: None. **E. Blaes:** None. **C. Redd:** None. **Y. Gallegos:** None. **A. Reksoatmodjo:** None. **P. Cheung:** None. **I.F. Smith:** None. **J. Kelly-Roman:** None. **C.F. Valenzuela:** None. **Z. Gong:** None. **S.P. Gandhi:** None. **D.G. Wheeler:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.05/MM16

Topic: J.03. Anatomical Methods

Support: NIH Grant ZIA MH002928

Title: A Novel Procedure Improving Stereotaxic Targeting in Nonhuman Primate Brain Surgeries

Authors: *P. HARMON[1], K. CAMERON[2], B. B. AVERBECK[3], R. AZADI[4];
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Abstract: Conventional MRI-guided targeting for neurosurgery in nonhuman primates (NHPs) typically relies on the use of MRI-visible earbars within stereotaxic frames. However, inconsistencies in head positioning between scans and surgeries can reduce the precision of this technique. To overcome this limitation, we developed a method that utilizes skull-implanted fiducial markers, allowing MRI data to be directly coregistered to stereotaxic coordinates based on the fixed position of the skull. Because fiducials designed for human use are often too large for NHPs, we implemented a novel solution using MRI-compatible cranial screws commonly used in NHP procedures. To assess the accuracy of this approach, we implanted 28 ceramic screws into a 3D-printed macaque skull, which was then placed in a gel containing MRI contrast agent. We measured the 3D coordinates of the fiducials from T1-weighted scans and within a stereotaxic frame, both before and after altering the skull's position. Coregistration was performed using a 3D affine transformation, and results demonstrated robust alignment even after repositioning. The mean localization error using all 28 fiducials was 0.35 mm. Additional analyses indicated that as few as six to eight screws yielded comparable accuracy, with an average error of 0.48 mm. Changes in skull positioning within the frame did not significantly impact alignment accuracy. This novel approach eliminates the need for earbar-based targeting and its inherent variability, offering a more consistent and precise method for localizing brain structures.

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Poster

PSTR143: Tools and Methods for Circuit Tracing

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Program #/Poster #: PSTR143.06/MM17

Topic: J.03. Anatomical Methods

Support: U24NS109113
U24NS119916

Title: Generating a repository of open-source molecularly defined recombinant antibodies for brain research

Authors: L. MACNIVEN[1], K. MITCHELL[1], D. HOUSTON[2], M. REGO[3], J. S. TRIMMER[1], ***K. D. MURRAY**[4];

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Abstract: We developed a widely-used collection of monoclonal antibodies (mAbs) termed NeuroMabs, targeting brain proteins validated in fundamental neuroscience research applications including immunoblots and immunohistochemistry (neuromab.ucdavis.edu). To maximize the impact of NeuroMabs we expanded the collection into an open-source molecularly defined repository of renewable reagents. First, all hybridomas producing NeuroMabs are available through the Developmental Studies Hybridoma Bank at the University of Iowa (DSHB, https://dshb.biology.uiowa.edu) and the UC Davis MMRRC (https://www.mmrrc.org) enabling low-cost production of mAbs at any scale. DSHB also develops ready-to-use versions of these antibodies. Second, to develop molecularly defined renewable versions of these reagents we established a pipeline to convert mAbs from hybridomas into recombinant mAbs (R-mAbs) which can be archived and disseminated as DNA sequence and in expression plasmids. After initially employing RT-PCR to generate heavy and light chain variable ("VH" and "VL") domain sequences we moved to a high-throughput Illumina-based sequencing platform working directly from hybridomas. To date over 10,000 hybridoma VH and VL sequences have been posted to an open access website called NeuroMabSeq (neuromabseq.ucdavis.edu). These VH and VL domain sequences are used to design gene fragments for R-mAb expression plasmid generation. Finally, validated R-mAb plasmids are made available through the non-profit plasmid repository Addgene (https://www.addgene.org/), where over 680 R-mAb plasmids have been deposited to date through their open access distribution system. Addgene also develops and distributes ready to use R-mAbs from these plasmids. A benefit of converting hybridomas to R-mAbs is the ability to design next generation antibody-based labeling molecules. We currentl utilize VH and VL domain sequences to engineer expression plasmids for miniaturized single chain variable fragments (scFvs), which have enhanced tissue penetration and enable higher resolution imaging relative to larger conventional antibodies. Expression plasmids expressing validated scFvs are also available through Addgene (over 150 deposited to date). This open-source resource is both affordable and renewable allowing greater access to molecularly defined antibodies that will expand their impact on neuroscience research. In addition, access to primary sequence information has the potential to foster user driven reagent development enhancing the utility of these antibodies in ways critical for moving the BRAIN Initiative and other neuroscience research efforts forward.

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Poster

PSTR143: Tools and Methods for Circuit Tracing

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Program #/Poster #: PSTR143.07/MM18

Topic: J.03. Anatomical Methods

Title: Unveiling trans-scale bioarchitecture through ionic glassy tissue

Authors: *Y. GAO[1], F. XIN[1], K. YUAN[2];
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Abstract: Biological structures across scales integrate seamlessly to perform essential functions. While various histological methods were developed to reveal these intricate structures, preserving the integrity of large-volume architectures while revealing microstructures with high resolution remains a major challenge. Here, we introduce VIVIT, a novel volumetric, trans-scale biostructure inspection method leveraging the unique chemical properties of ionic liquids. VIVIT transforms biological tissue into an ionic glassy state, which enables morphology-preserved optical clearing with ultra-high transparency, crystal-damage-free cryosectioning and long-term storage, and amplifies fluorescent signals from both genetically encoded and immunostained labels, thus yielding precise and reliable mapping of fluorescent signals within intact 3D architectures. Using VIVIT, we demonstrated the link between the modality of synaptic inputs to multisensory thalamic neurons and the targets of their brain-wide outputs, and identified unique aspects of inhibitory control in the human cortex. VIVIT thus offers unprecedented opportunities to elucidate the organizational principles underlying trans-scale biostructures.

Disclosures: Y. Gao: None. **F. Xin:** None. **K. Yuan:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

Location: SDCC Halls B-H

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Program #/Poster #: PSTR143.08/NN1

Topic: J.03. Anatomical Methods

Title: Optimized glyoxal-based fixation improves high-sensitivity immunostaining for challenging molecular targets in neural tissues.

Authors: *K. KONNO[1], M. YAMASAKI[2], M. WATANABE[3];
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Abstract: Precise molecular localization in neural tissues relies heavily on optimized chemical fixation strategies for immunohistochemistry. The conventional use of 4% paraformaldehyde (PFA) remains the gold standard; however, extensive protein cross-linking and tissue shrinkage frequently impede antibody penetration and epitope accessibility, particularly for membrane-bound proteins such as receptors and ion channels concentrated in synaptic clefts, postsynaptic densities, and axonal trigger zones. While various antigen-retrieval methods have been explored to mitigate these limitations, their efficacy remains variable. Here, we systematically evaluated glyoxal-based fixation—a dialdehyde with two carbon atoms—as an alternative approach for high-sensitivity immunostaining. Our recent work demonstrated that glyoxal fixation substantially enhances specific detection of molecular targets that are poorly visualized in PFA-

fixed tissues. In this presentation, we will summarize the methodological advantages, critical parameters for implementation, and potential caveats of glyoxal fixation, with an emphasis on its application for fine structural analysis in neuroscience. This approach offers a powerful tool to expand the capabilities of molecular imaging in complex neural architectures.

Disclosures: K. Konno: None. **M. Yamasaki:** None. **M. Watanabe:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

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Program #/Poster #: PSTR143.09/NN2

Topic: J.03. Anatomical Methods

Support: CRSNG
FRQNT

Title: Neuronal quantification in mouse brains fixed with solutions used in gross anatomy laboratories

Authors: *A. GÉRIN-LAJOIE[1], E.-M. FRIGON[1], D. BOIRE[1], J. MARANZANO[1,2]; [1]Anat., UQTR, Trois-Rivières, QC, Canada; [2]Neurol. and Neurosurg., McGill Univ., Montreal, QC, Canada

Abstract: Background: Brain banks usually provide neuroscientists small blocks of tissue fixed with neutral-buffered formalin (NBF), whereas gross anatomy laboratories have been underexploited for research and could become a new source of full brains. However, these brains are typically fixed with solutions better adapted for dissection and teaching, which could cause some molecular changes and therefore have an impact on the antigenicity, cellular morphology, and cell quantification of the tissue. Recent studies have shown that the antigenicity is preserved in mouse and human brains fixed with three solutions: 1) NBF, typical of brain banks, 2) a saturated salt solution (SSS), and 3) an alcohol-formaldehyde solution (AFS), both used in gross anatomy laboratories. The main goal of this study is to compare the effects of the 3 fixatives on the number and size of neurons, to assess whether the cells fixed with the solutions from anatomy laboratories are similarly preserved as the NBF-fixed ones and thus could be offered for research. **Methods**: 27 C57BL/6J mouse brains were fixed with one of the three solutions (NBF N=9; SSS N=9; AFS N=9) and cut in 40µm-thick slices with a cryostat to perform immunohistochemistry targeting neurons. Photomicrographs of 3 regions of interest (ROI; 100X) were taken in layer 3 of the primary motor cortex with a brightfield microscope (Olympus-BX51W1) for image analyses. The total neuronal count per ROI, and the diameters of 10 randomly selected cells were quantified using Neurolucida software (MBF-Bioscience). The surface of the 10 cells and the total cell surface per ROI were quantified using the Display software (MINC Tool Kit). All three fixatives were compared using an ANOVA or Kruskal-Wallis with SPSS. **Results**: We found no significant difference between the three fixatives for

the total neuronal count ($F_{2;24}$=131.269; p=0.569), the small diameters of 10 cells (H(2)=1.355; p=0.508), the surface of 10 cells ($F_{2;807}$=1.855; p=0.157), and the total cell surface ($F_{2;24}$=1.026; p=0.374). However, the large diameters of 10 cells were different between the fixatives (H(2)=9.165; p=0.010). We found that they were smaller in cells fixed with NBF than with SSS (p=0.031) or AFS (p=0.016). **Conclusion**: Despite their varied chemical composition, the three fixatives did not have a significant impact on the neuronal count or surface of the mouse brain cells. However, the difference in large diameters observed for the NBF cells might indicate a slight difference in the cell morphology compared with the SSS and AFS. These results are a promising start to determine the usability of brains fixed with gross anatomy solutions for quantitative neuroscientific research.

Disclosures: A. Gérin-Lajoie: None. **E. Frigon:** None. **D. Boire:** None. **J. Maranzano:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.10/NN3

Topic: J.03. Anatomical Methods

Title: Comparative transduction analysis of multiple AAV serotypes following intrathecal delivery via whole-mount tissue clearing and 3D imaging

Authors: *Z. ZUO, R. COMAPOSADA-BARÓ, G. HOUSER, S. JAGER, K. L. MADSEN, A. T. SÖRENSEN;
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Abstract: Intrathecal delivery of recombinant adeno-associated virus (rAAV) vectors enables direct and efficient access to the central and peripheral nervous system for gene transfer. In this study, we systematically evaluated the transduction profiles of 7 commonly used rAAV serotypes (AAV1, AAV2, AAV5, AAV8, AAV9, PHP.eB and PHP.S) following intrathecal administration, mapping their entire distribution throughout the dorsal root ganglia (DRG), spinal cord, and brain. To enable single-neuron tracing in the spinal cord and visualize transduced DRG, we delivered AAV vectors encoding the Cre recombinase sequence under identical expression cassettes driven by the human synapsin 1 promoter but packaged in different capsids. Six to seven-week-old Ai14 reporter mice were injected intrathecally with one of the AAVs using identical dosing. Five weeks post-injection, mice were perfused, and the brain and spinal cord were collected with the vertebral column and surrounding bone structures left intact. An optimized whole-mount tissue clearing protocol, tailored for intact spinal preparation, was applied in conjunction with volumetric imaging to achieve high-resolution, 3D reconstruction of the central and peripheral nervous system, including detailed visualization of the DRGs. Consistent with previous studies, we observed distinct differences in transduction profiles among the different AAV serotypes. Across the spinal cord, AAV9, PHP.S and PHP.eB demonstrated the highest transduction efficiencies, followed by AAV5 and AAV8. These serotypes showed

particularly clear expression in the fasciculus gracilis of the spinal cord white matter, with clear, continuous signal streams extending from the lumbar region to the brainstem. In contrast, AAV1 and AAV2 exhibited less expression, with weak signals in gray matter and only sparse labeling throughout the white matter. While nearly all capsids were capable of transducing DRGs, each serotype displayed preferential tropism for cervical and lumbar DRGs. In this project, we aim to provide a dataset to guide the selection of optimal AAV serotypes for targeting specific regions of the mouse spinal cord and DRGs. Additionally, our work highlights the utility of tissue clearing for visualizing rAAV transduction in large, intact tissue preparations.

Disclosures: Z. Zuo: None. **R. Comaposada-Baró:** None. **G. Houser:** None. **S. Jager:** None. **K.L. Madsen:** None. **A.T. Sörensen:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

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Topic: J.03. Anatomical Methods

Support: NIH Grant R00MH128891

Title: De Novo Design of High-affinity Neuropeptide Binders for Detergent-free Immunofluorescence

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Abstract: Detergent-free immunolabeling is essential for multiplexed fluorescent imaging of brain tissue, enabling correlated light and electron microscopy (CLEM) to resolve both cellular identities (via fluorescence microscopy) and the fine structures of neuronal networks (via volumetric electron microscopy). Although a variety of immunoprobes, including nanobodies, scFvs, and aptamers, have proven feasible for detergent-free tissue labeling, the utility of this method remains limited by the availability of suitable high-affinity binders and by the lengthy, labor-intensive process required to screen for effective binders using conventional antibody generation techniques. For small proteins like neuropeptides—which are crucial for neuronal function and commonly used as cell-type markers—generating high-affinity binders is particularly challenging due to their flexible structures, limited available surfaces for molecular interaction, and sensitivity to fixation-induced conformational changes. To address these challenges, we developed an integrated pipeline combining in silico antigen selection, de novo binder design with a diffusion model trained on intrinsically disordered protein regions, tissue-based validation, and partial diffusion optimization. Using this approach, we generated binders targeting Vip, Lamp5, Penk, and Sncg—cortical interneuron markers that previously lacked robust affinity reagents—with Kd values ranging from 10 nM to 100 nM. Immunohistochemistry demonstrated colocalization of these binders with target cell populations in fixed tissue. Owing

to their small size (17-21 kDa), these binders are well-suited for detergent-free immunolabeling in CLEM applications. Our workflow offers a general strategy for generating high-affinity binders against challenging targets in the brain, facilitating the integration of molecular analysis into volumetric electron microscopy to advance connectomics research.

Disclosures: X. Lu: None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

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Topic: J.03. Anatomical Methods

Support: NIH R34 NS116885
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Title: Transcriptomic cell-type specificity of local cortical circuits

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Abstract: The complex functions of the neocortex rely on networks of interconnected excitatory and inhibitory interneurons, each of which are composed of multiple neuron types. Prior studies have established rules of local connectivity between major subclasses of inhibitory and excitatory cortical neurons, but the advent of single-cell transcriptomic technologies has revealed a remarkable diversity in transcriptomic neuronal subtypes. Is there specificity of synaptic connections between cortical neurons classified at the level of transcriptomic subtypes, as might be expected if the different types mediate different functions? Here we present a novel method that ties together transcriptomic cell type and anatomical connectivity, “Single Transcriptome Assisted Rabies Tracing” (START). START combines monosynaptic rabies tracing and single-nuclei RNA sequencing to identify the transcriptomic cell types providing monosynaptic inputs to defined populations of neurons. We employed START in conjunction with Cre driver mouse lines to transcriptomically characterize monosynaptic input neurons to 5 different layer-specific excitatory cortical neuron populations in mouse V1. At the subclass level, we observed the results expected from prior studies that resolved neuronal subclasses based on antibody staining, Cre-expressing mouse lines, or morphological characterization. With improved neuronal subtype granularity achieved with START, we were able to demonstrate transcriptomic subtype specificity of inhibitory inputs to the different subclasses of excitatory neurons. These results establish a new set of local connectivity rules at the resolution of transcriptomic inhibitory cell types.

Disclosures: M. Patino: None. **M. Rossa:** None. **E.M. Callaway:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

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Title: PHP.eB peripheral delivery and central expression in Cre mice

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Abstract: Investigating the molecular and functional identity of specific neuronal populations is a critical component of neuroscience research. In the brain, local populations can be targeted using stereotactic injections of viral vectors that deliver recombinase-dependent tools, but this surgical approach cannot target widely distributed populations. While peripheral delivery is a potential strategy to access widely distributed populations, most viruses cannot cross the blood-brain barrier. Unlike other viruses, PHP.eB transduces cells across the central nervous system. However, neurotropic viruses often have tropism for specific subtypes of neurons, and it is unclear if PHP.eB transduces neurons equally across brain regions and subpopulations. To evaluate its sensitivity and tropism, we injected a PHP.eB vector that delivers Cre-dependent tdtomato (PHP.eB-FLEX-tdTomato) in a series of mice with and without a Cre-driver knockin (*Nps*-2A-Cre, *Lmx1b*-2A-Cre, *Foxp2*-IRES-Cre, *Hsd11b2*-IRES-Cre, and C57BL6/J). In all Cre-driver mice except for *Nps*-2A-Cre, we observed widely variable transduction efficiency across cell-types and brain regions. Additionally, we found non-specific expression in neurons and astrocytes (scattered throughout the cerebral cortex, striatum, cerebellum, and other brain regions), with a similar pattern in Cre-negative mice, indicating that a low rate of spontaneous recombination occurs throughout the brain. Collectively, our results confirm that peripheral delivery of PHP.eB can transduce widely distributed neuronal populations. However, wide variations in tropism and transduction specificity merit careful consideration for each specific neuronal population.

Disclosures: H. Zhu: None. **J.C. Geerling:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

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Program #/Poster #: PSTR143.14/NN7

Topic: J.03. Anatomical Methods

Support: STI2030-Major Projects (2022ZD0205202)

Title: Whole brain mapping of single-neuron transcriptionally-defined projectome

Authors: *H. MU, H. WANG;
Univ. of Sci. and Technol. of China, Hefei, China

Abstract: Cell type mapping through single cell RNA sequencing and spatial transcriptomics have dramatically expanded the boundary of our knowledge about cellular identity and organization in the brain. Parallelly, with sparse viral labeling and high resolution optical whole-brain imaging, brain-wide single neuron projectome mapping of thousands of neurons in many brain areas have been successful. However, direct mapping of brain-wide projectome of single-neurons with their molecular identity has been a long-lasting challenge. Here, we address this challenge by combining fluorescence *in situ* hybridization (FISH) with virus-based sparse labeling of neuronal morphology, and image both types of labels using our previously developed whole-brain 3D imaging method VISoR. We developed a pipeline including viral labeling, whole-brain sample hydrogel embedding and sectioning, VISoR imaging of whole-brain projectome, multi-round hybridization chain reaction (HCR-FISH) labeling and VISoR imaging of cell-type markers, and finally image reconstruction and registration. With this strategy and pipeline, we profiled 77 types of neurons across the whole mouse brain at single cell resolution based on their expression of 8 genes including neurotransmitter transporters, neuromodulator synthases, and neuropeptides. We further resolved the brain-wide single-neuron projection morphology of 216 VTA dopaminergic neurons and subtyped these neurons by transcriptional profiling of 5 marker genes. Such transcription-defined projectome analysis will enable in-depth correlative analysis of neuronal cell types, circuit architecture and functions.

Disclosures: H. Mu: None. **H. Wang:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

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Program #/Poster #: PSTR143.15/NN8

Topic: J.03. Anatomical Methods

Support: NIH T32
IRACDA

Title: Recapitulating functional wiring of the cortico-thalamic loop in vitro

Authors: *A. CISNEROS[1], M. MOAREFIAN[4], J. DURU[5], M. TEODORESCU[2], T. SHARF[3];
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Abstract: Three-dimensional stem cell-derived neural organoids provide a promising platform to investigate early stages of brain development, circuit formation, and interregional communication. While co-culturing region-specific organoids into assembloids has enabled the study of cortical and subcortical interactions, these models lack directional specificity and spatial control, limiting their ability to recapitulate canonical circuit formation. To address this, we propose a novel microfluidic platform that enables the construction of directional and tunable interregional circuits while preserving anatomical distinction. This system, which we refer to as "directoids," incorporates micropatterned polydimethylsiloxane (PDMS) structures to control uni- and bidirectional axonal growth between cortical and thalamic organoids. Our time lapse data demonstrates a fourfold decrease in speed for axons traveling in the inhibitory direction as compared to control and permissive channels. All microstructures confirmed a robust, directionally biased axon outgrowth with 100% successful biasing, which establishes a scalable and reproducible method for modeling structured and asymmetric connectivity in vitro. This approach offers a powerful tool to investigate the mechanisms underlying hierarchical circuit formation, regional specification, and functional integration in the developing brain.

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Poster

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Title: A Neurotomographic Approach for the Mesoscale Mapping of Convergent Neural Circuits

Authors: O. A. AYANSHINA[1], T. T. ADEYELU[2], M. L. OSBORN[4], K. L. MATTHEWS[3], *C. C. LEE[4];
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Abstract: Brain regions receive convergent inputs from multiple neural sources; this prolific connectivity enables these regions to integrate disparate information streams that are necessary

for higher-order neural computations. At the mesoscale level, these integrative computations are structurally supported by global interconnections among widely dispersed brain nuclei and areas. In this regard, the spatial separation of interacting brain regions poses a significant challenge for understanding the physiological functions of anatomically defined neural circuits. Ultimately, this understanding requires analyzing the physiological characteristics of each component of the connected neural ensemble, i.e. multi-site neural recordings from interconnected brain regions. However, such global recordings require *a priori* knowledge of the distribution of globally connected neurons that maintain these functional neural circuits. Therefore, we describe here a neurotomographic approach for mapping the mesoscale connectivity of globally connected neural networks based on assessment of mouse forebrain regions including primary somatosensory barrel cortex (S1BF), primary auditory cortex (A1), and hippocampus. We conjugated colloidal gold with a retrograde tracer, wheat-germ agglutinin (WAHG) tracer, which was stereotaxically injected into mouse brain S1BF, A1, and hippocampus unilaterally. Micro-computed tomographic imaging was employed to scan the brain *in vivo* and *ex vivo* with 3-D image reconstruction. The brain was then histologically processed using silver staining enhancement to reveal the extent of the colloidal gold-coupled tracer labeling of neuronal cells. Our data demonstrates the areal extent of convergent inputs to the injected areas from convergent forebrain sources. The virtual slices and histological slices comparatively maintained similar average labeling intensities. These data also demonstrate the applicability of this approach for identifying brain areas for multi-site electrode recordings and for the rapid connectional assessment of convergent neural circuits.

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Poster

PSTR143: Tools and Methods for Circuit Tracing

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Topic: J.03. Anatomical Methods

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Title: A viral and optical approach to single-neuron retrograde rabies tracing

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Abstract: Introduction. Understanding how a neuron's functional responses arise from synaptic inputs requires precise mapping of its presynaptic partners. An effective tool for such targeted mapping is monosynaptic retrograde tracing via G-deleted rabies virus (RVΔG). However, achieving single-neuron rabies initiation typically relies on *in vivo* electroporation of helper plasmids (encoding G and TVA), which is unreliable, low-yield, and limited to superficial neurons.
Methods. To circumvent this technical barrier, we combined intersectional, ultra-sparse viral labelling with optical ablation to achieve RVΔG initiation from isolated, genetically defined neurons in cortical Layer 5 (L5). First, we used a dual-recombinase strategy to restrict the co-expression of G and TVA to an ultra-sparse population of starter neurons. In transgenic mice (*Rbp4-Cre::Ai94*) expressing Cre recombinase and GCaMP6s in L5 neurons, we injected a low-titre adeno-associated virus (AAV) driving Cre-dependent Flp recombinase, alongside high-titre, Flp-dependent AAVs encoding N2c glycoprotein and TVA_{66T} receptor, each coupled to a distinct fluorescent reporter. Second, we sought to eliminate supernumerary starter neurons with two-photon laser photoablation. The final injection of EnvA-pseudotyped RVΔG initiated retrograde tracing from the remaining starter neurons.
Results. Our viral labelling strategy consistently produced ultra-sparse populations of starter neurons (<15 per injection site) co-expressing G, TVA, and their reporters within 2-3 weeks. We demonstrate successful refinement of starter populations toward single neurons by photo-ablating excess cells, a technique we newly adapted for use in deep cortical layers. Subsequent RVΔG injection led to bright retrograde labelling of presynaptic neurons from these pre-defined starters, hundreds of which could be functionally imaged *in vivo* within the cranial window. Post-mortem whole-brain volumetric imaging using serial two-photon microscopy revealed labelling of both local and long-range input neurons, including those from thalamic nuclei and the frontal cortex.
Conclusions. Our viral and optical method provides a robust approach for genetically-targeted, ultra-sparse RVΔG tracing initiation that eliminates the need for electroporation, and shows strong potential for single-neuron initiation. Integration of this technique with *in vivo* functional imaging allows direct investigation of how presynaptic ensemble activity shapes postsynaptic tuning. Ultimately, this tool enables a mechanistic dissection of connectivity architectures underlying neuronal computations.

Disclosures: T. Chang: None. **L.F. Rossi:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

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Topic: J.03. Anatomical Methods

Support: NIH/NINDS RF1NS023945-28
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Title: Modular Architecture of the Basal Forebrain Cholinergic System

Authors: *M. E. L. S. NUNES[1], I. T. KIM[1], L. ZABORSZKY[2];
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Abstract: The basal forebrain cholinergic system is implicated in a wide range of global and specific functions and serves as the primary source of acetylcholine (ACh) in the cortex. Recent work (Vasanyi et al., 2025) has shown that this system can be subdivided into three spatially and hierarchically organized networks. To characterize whether individual basal forebrain cholinergic neurons (BFCNs) innervate cortical areas that follow these spatial patterns, we employed an intersectional recombinase-based viral tracing strategy in ChAT::Cre+ Long Evans rats. In ongoing experiments visualizing projection-defined subpopulations of BFCNs, we find that these neurons primarily send collateral axons within their respective networks, rather than across networks. For example, BFCNs projecting to the primary motor cortex (M1) also send collateral axons to the primary somatosensory cortex (S1), but not to the primary visual cortex (V1). Moreover, the axonal collaterals are organized into supragranular and infragranular layers. To further explore the coordination and functional roles of cholinergic action in cortical areas within and across the three BFCN networks, we conducted fiber photometry recordings in freely moving rats, using two different indicators (GCaMP6s-axon and GRAB-ACh). In summary, our findings provide anatomical and in vivo imaging evidence of the spatial organization and impact of BFCNs on cortical areas.

Disclosures: M.E.L.S. Nunes: None. **I.T. Kim:** None. **L. Zaborszky:** None.

Poster

PSTR143: Tools and Methods for Circuit Tracing

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Program #/Poster #: PSTR143.19/NN12

Topic: J.03. Anatomical Methods

Title: Non-invasive single-neuron tracing: php.eb-syn-cre aav and light sheet microscopy unite

Authors: *P. RHOTON[1], S. LEWIS[2], M. KENWOOD[3], D. BETZ[4], A. NAWABY[5], D. M. RAMIREZ[6], M. P. GOLDBERG[7];
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Abstract: Understanding the intricate morphology, connectivity, and function of individual neurons is crucial for comprehending brain function, but current tools are limited. Reconstructing a neuron's full axonal and dendritic arborization over long distances through dense brain tissue remains a significant challenge due to microscopy and tissue sectioning limitations. Traditional CNS viral tracing methods require direct brain injection and have limited spatial reach. We

developed a method to characterize neuronal morphology and connections using the PhP.eB AAV (adeno-associated virus) which penetrates the blood-brain barrier in order to infect CNS neurons through intravenous injection. Injections at full viral titers lead to extensive neuronal expression, precluding assessment of single neurons. We assessed the effect of systemic administration of a neuron-specific PhP.eB AAV-Cre virus at low titers with a loxP-flanked-STOP Ai9 reporter mouse with intense Cre-dependent cellular fluorescence. We utilized a single retro-orbital injection of PhP.eB-Syn-Cre AAV (Addgene 105540) in B6.Cg-Gt(ROSA)26Sortm9(CAG-tdTomato)Hze/J reporter mice (Jackson Labs), followed by tissue clearing and light sheet microscopy two weeks after injection. syGlass software was used for data visualization. With sufficiently low titers (50 nl injection, 6 mice) we obtained sparse labeling with intense td-Tomato fluorescence visualizing axons and dendrites. This method allowed tracing of individual corticospinal axons in the brainstem and cervical spinal cord and detailed visualization of spinal neuronal morphology. We concluded that sparse neuronal labeling using systemic administration of PhP.eb AAV-cre, Ai9 reporter mice, and light sheet microscopy provides a non-invasive, straightforward, and highly effective method to visualize, reconstruct, and analyze the 3D morphology and connectivity of individual neurons within the mouse brain and spinal cord.

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Poster

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Program #/Poster #: PSTR143.20/OO1

Topic: J.03. Anatomical Methods

Support: NIH Grant U01AG076791

Title: Ventral hippocampal CA1 interneuron circuits revealed by monosynaptic rabies virus tracing

Authors: *Q. YE[1], C. LEE[2], D. ZHANG[2], S. Z. WANG[3], X. XU[4];
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Abstract: Approximately 301 million people in the world suffer from anxiety and fear-related disorders. Different states of anxiety and fear trigger subsequent behaviors that could save a person's life or induce severe negative mental health implications. Consequently, anxiety and fear serve as important emotions regulated by important neural circuitry. The ventral hippocampal CA1 (vCA1) has been implicated in playing critical roles in long-range projections responsible for anxiety and fear-inducing stimuli. Many populations of interneurons exist within

vCA1, including populations expressing parvalbumin (PV), thought to exhibit anxiety behavior, and somatostatin (SOM), thought to exhibit fear behavior. Utilizing monosynaptic rabies tracing in distinct PV and SOM-expressing transgenic mouse lines, we map presynaptic neural circuits of PV and SOM interneuron populations of vCA1 to understand neural circuitry differences in distinct interneuron types. Following injections, histological and data quantification processes, pre-synaptic regions projections to ventral CA1 are shown to exhibit different patterns of expression, which could contribute to distinct functions. As such, this project aims to identify novel characteristics of presynaptic neural circuits in distinct PV and SOM interneuron types of the vCA1 region to possibly further understand the pathology behind anxiety and fear regulation and recognition.

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Poster

PSTR143: Tools and Methods for Circuit Tracing

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Program #/Poster #: PSTR143.21/OO2

Topic: H.05. Mood Disorders

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Title: Anatomical and transcriptomic characterization of the paraventricular nucleus of the thalamus across human and mouse

Authors: *M. R. TETZLAFF[1], B. LEONARD[2], A. FLORIOU-SERVOU[4], C. KOOIKER[5], J. RASMUSSEN[3], M. A. YASSA[6], T. BARAM[7];
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Abstract: Rationale: The paraventricular nucleus of the thalamus (PVT) has emerged as an essential integrator of homeostatic states toward motivational regulation in the context of reward-seeking, arousal, and encoding of salient events. Our lab has previously shown that the PVT is selectively activated by early life adversity (ELA), and that adult modulation of these early-life activated cells can reduce deleterious reward-related behavioral outcomes caused by ELA. However, the type of cell altered by ELA and transcriptomic changes to the PVT resulting from ELA remain unknown. Most studies of the PVT to date take place in rodents, and there is limited knowledge regarding the molecular and anatomical characteristics of the human PVT. fMRI analysis have suggested that the human and rodent PVT share analogous networks and functions. Here, we assess the human PVT in health and disease (Major Depressive Disorder, MDD) and in

the context of ELA. **Methods** This study utilizes TRAP2 mice to selectively assess cells activated during the first week of life (P6-P7) and MERscope spatial transcriptomics to identify target cells by expression of select transgenes. We additionally implement MERscope spatial transcriptomics to consider the characteristics of the anterior and posterior PVT across several human individuals with MDD. We then compare the human PVT to known characteristics of the mouse. **Results:** Several potent signaling molecules, including DRD2, ADCAP1, CRH, and others, are shown to be present in PVT cells across species, though with differing relative abundances and anatomical positioning. Notably, the human PVT includes numerous GAD1/2-positive interneurons, which are largely absent from the mouse PVT. Ongoing analysis aims to identify which PVT cells are activated in early life in mice during early life adversity, and consider the relative incidence of analogous cells in the human PVT. **Conclusions:** The PVT contains several conserved characteristics across species, which may relate to analogous functions in health and disease. Here, we continue to interrogate the PVT across species as a node for encoding early life events and executing adult outcomes which relate to mental health conditions.

Disclosures: M.R. Tetzlaff: None. **B. Leonard:** None. **A. Floriou-Servou:** None. **C. Kooiker:** None. **J. Rasmussen:** None. **M.A. Yassa:** None. **T. Baram:** None.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.01/OO3

Topic: J.04. Physiological Methods

Title: Spectral Power Analysis of Delta Waves in Neonatal Electroencephalography: A Tool for Assessing Brain Maturation and Injury

Authors: S. SHIRAKI[1], H. HAYASHI[2], S. HAYASHI[3], H. RIN[4], C. ISHIKAWA[5], K. KASHIMA[6], D. ZAFER[7], ***Y. KITASE**[6];
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Abstract: Recent advances in neonatal intensive care have dramatically improved survival rates among extremely preterm infants, yet neurodevelopmental impairments such as cerebral palsy, epilepsy, and cognitive dysfunction remain highly prevalent. Quantitative evaluation of brain function is essential for guiding early interventions, but conventional EEG and amplitude-integrated EEG (aEEG) are often limited by subjective interpretation. Delta waves (0.5-4.0 Hz), which dominate neonatal EEG, reflect both maturation and injury-related cortical activity changes. We aimed to characterize the developmental trajectory and suppression patterns of delta waves using spectral power analysis. We retrospectively analyzed 399 EEG recordings from

neonates (gestational age: 23-42 weeks) obtained using the 10-20 system. FFT-based power spectral analysis was performed in 0.25 Hz bins. Developmentally, we found a significant increase in 0.0-1.0 Hz delta power in anterior-frontal-temporal and central-occipital regions from 24 to 30 weeks, reflecting maturational processes. Higher frequency delta components (2.0-4.0 Hz) decreased transiently in occipital areas from 28-34 weeks, then increased in frontal regions approaching term, suggesting region-specific trajectories of cortical development. To assess injury, EEGs were visually graded for suppression severity (Grades I-V). Spectral power was significantly reduced in suppressed EEGs, particularly within the 1.0-1.5 Hz band. Lower frequency delta waves (<2.0 Hz) were more sensitive to suppression, consistent across gestational ages. Spectral power strongly correlated with visual grading, indicating that frequency-specific reductions reflect functional cortical depression. This study supports the use of delta wave spectral power as a sensitive, objective biomarker for brain maturation and injury in neonates. Compared to amplitude-based techniques, spectral analysis provides granular, region- and frequency-specific data. Incorporating this approach alongside aEEG could improve early diagnosis of neonatal encephalopathy, guide neuroprotective interventions such as therapeutic hypothermia, and ultimately enhance long-term neurodevelopmental outcomes.

Disclosures: S. Shiraki: None. **H. Hayashi:** None. **S. Hayashi:** None. **H. Rin:** None. **C. ishikawa:** None. **K. Kashima:** None. **D. Zafer:** None. **Y. Kitase:** None.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.02/OO4

Topic: J.04. Physiological Methods

Title: Advanced EEG Telemetry Measurements in Mice: Applications in Quantitative EEG, Sleep Architecture and Seizure Phenotyping

Authors: *F. GAGNON[1], G. PEYON[2], E. ESNEAULT[3], G. CANTONI[1], S. BENMANSOUR[1]; [1]emka Technologies, PARIS, France; [2]Porsolt S.A.S, Le Genest Saint Isle, France; [3]Porsolt, Le Genest St Isle, France

Abstract: Electroencephalographic (EEG) recordings in rodents are essential for translational neuroscience research, particularly in the context of epilepsy, sleep regulation and neuropharmacology. The aim of this project was to evaluate the sensitivity and reliability of detecting modulation in brain activity, to major events in the mouse. We present the versatility of the easyTEL+ implantable digital telemetry system (emka Technologies) for EEG and activity tracking in mice, applied to three distinct experimental paradigms: (1) seizure assessment in a convulsive model, 2) long-term sleep architecture analysis and (3) acute spectral band quantification. In the first model, systemic administration of kainic acid (35 mg/kg, i.p.) was used to induce acute behavioral seizures. Mice were monitored and simultaneously recorded for EEG over a 2-hour window. Seizure severity was scored based on the occurrence and latency of

forelimb clonus, rearing, and rearing followed by falling. Seizure events were detected with high-amplitude rhythmic activity. Latencies and seizure duration, including behavioral events were temporally correlated with EEG abnormalities, confirming the sensitivity of the system for integrated seizure analysis. In the second model, EEG and activity signals were continuously recorded over 23 hours in freely moving mice, housed in groups, to evaluate the effects of diazepam (8 mg/kg, p.o.) on sleep-wake states. We distinguished between non-REM (NREM), REM, and wake periods using standard criteria. Diazepam significantly increased NREM sleep duration while modestly reducing REM sleep, consistent with its known sedative profile. In the third model, we recorded one hour of EEG following administration of fluoxetine (32 mg/kg, i.p.), a selective serotonin reuptake inhibitor. Quantitative EEG (qEEG) analysis revealed minor changes in power distribution induced by fluoxetine across the delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-32 Hz), and gamma (32-64 Hz) bands. A slight increase in delta was observed, while theta, alpha, and gamma spectral power showed a slight decrease during spontaneous wakefulness in some animals, with variability depending on brain region. Collectively, these data highlight the robustness and reliability of the easyTEL+ digital telemetry platform for investigating neuroactive compounds and neurological phenotypes in mice. Its ability to combine high-quality EEG acquisition with behavioral analysis, while group housing animals, makes it a powerful tool for preclinical neuroscience research.

Disclosures: F. Gagnon: None. **G. Peyon:** None. **E. Esneault:** None. **G. Cantoni:** None. **S. Benmansour:** None.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.03/OO5

Topic: J.04. Physiological Methods

Title: Enhanced Seizure Channel Detection Using ResWaveNet Architecture with Grey/White Matter Pre-filtering

Authors: *X. SHAO[1], R. MCGINN[2], R. MARTIN DEL CAMPO VERA[1], M. PARRA[3], C. LIU[1], S. KELLIS[4], B. LEE[1];
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Abstract: Accurate identification of seizure onset zones (SOZ) and propagation pathways in stereoelectroencephalography (sEEG) recordings is critical for successful epilepsy surgery outcomes in drug-resistant patients. Existing computational approaches lack incorporation of neuroanatomical constraints, failing to use the critical distinction between grey matter (seizure-generating) and white matter (seizure-propagating) tissue types. We developed a novel ResWaveNet architecture incorporating grey/white matter anatomical pre-filtering to enhance seizure channel detection. The system features: (1) a pre-filtering module prioritizing grey matter

channels using tissue classification, (2) a ResWaveNet backbone combining residual connections with dilated causal convolutions for temporal feature extraction. Time-series features including half-wave characteristics, line length, area, and frequency band powers were extracted using sliding windows. The model was trained on drug-resistant epilepsy patients (N=2 patients, 12 seizures) with Optuna hyperparameter optimization. Accuracy was evaluated by comparing the first N channels ranked by our model's seizure probability scores against the N channels identified by neurologist annotations, where N equals the number of clinically determined seizure channels for each patient. Results showed significant improvements in seizure channel detection accuracy compared to Wavenet architecture using the same data: Patient 1 (NSeizure=5) increased from 55%±21% to 80%±6% ($p<0.05$), and Patient 2 (NSeizure=7) improved from 69%±11% to 87%±8% ($p<0.001$). The anatomical pre-filtering effectively reduced white matter false positives while preserving grey matter sensitivity. This approach addresses critical limitations in seizure localization by incorporating neuroanatomical knowledge, potentially improving surgical planning and reducing subjective interpretation needs in clinical practice.

Disclosures: X. Shao: None. **R. McGinn:** None. **R. Martin Del Campo Vera:** None. **M. Parra:** None. **C. Liu:** None. **S. Kellis:** None. **B. Lee:** None.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.04/OO6

Topic: J.04. Physiological Methods

Support: ZIAMH002838
ZIAMH002898
ZIAMH002899

Title: Evoked cortical responses to transcranial light stimulation in marmosets and rats with broad opsin transduction

Authors: *L. V. IVES[1], D. ZALDIVAR[1], A. R. RIBEIRO GOMES[1], N. WRIGHT[3], S. KEARNEY[1], L. BAWEKE[1], D. A. LEOPOLD[2];
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Abstract: The targeted perturbation of cortical activity is a central paradigm for studying the operation of the brain and its connection to behavior. Optogenetic tools allow for the local excitation or inhibition of defined neural circuit elements with high spatial and temporal resolution. However, in non-transgenic models, such stimulation depends on the local viral delivery of opsins and light. Here, we present a minimally invasive paradigm for optogenetic

cortical perturbation that combines broad opsin expression through fetal injection and transcranial light stimulation. In both marmosets and rats, we used a recently described intrauterine injection procedure to achieve widespread transduction of either of two opsins, channelrhodopsin and ChRmine, across the cerebral cortex (Ribeiro Gomes et al.). In opsin-expressing marmosets and rats, as well as control animals, we combined transcranial light stimulation using blue, orange, and red light with EEG mapping (15 recording sessions in the marmoset and 20 in the rat). In both species, transcranial light stimulation of opsin-expressing animals led to time-locked, high amplitude (10-50 micro-Volts) EEG responses. At different positions across the skull surface, blue (473 nm) and orange (585 nm) light pulses evoked strongest responses near the site of optical stimulation and often elsewhere, such as the homotopic contralateral locations. Preliminary findings combining transcranial cortical light stimulation with functional MRI in the marmoset further demonstrate robust optogenetic-fMRI responses across the brain. The prospect of relatively noninvasive, but spatially and temporally precise control of brain activity in nonhuman primates opens new avenues to study the operational principles of brain circuits most relevant for human cognition. This will allow us to study brain-wide expression of opsins in cortical as well as subcortical regions.

Disclosures: L.V. Ives: None. **D. Zaldivar:** None. **A.R. Ribeiro Gomes:** None. **N. Wright:** None. **S. Kearney:** None. **L. Baweke:** None. **D.A. Leopold:** None.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.05/OO7

Topic: J.04. Physiological Methods

Support: NSTC 113-2313-B-492-002-MY3

Title: Innovative Brain Implant Method for Real-Time Electrophysiology in Freely Behaving Miniature Swine

Authors: *H.-C. PAN[1], C.-M. YEH[1], Y.-C. CHOU[1], T.-M. HUANG[1], J.-W. YANG[2], D.-T. JU[3], H. CHEN[4];
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Abstract: Electrophysiological monitoring in freely-moving animals provides critical insights into the relationship between neural activity and behavior. However, achieving reliable, long-term brain implantation in large animal models, such as miniature swine, poses challenges due to surgical complexity, infection control, and signal quality. In this study, we introduce a novel brain implantation technique that enables stable, low-noise, real-time electrophysiological recordings in freely-behaving Lanyu minipigs for up to 90 days. The method involves a precise

aseptic surgical approach, using customized multi-channel tungsten electrodes integrated with a lightweight, water-resistant wireless recording headstage implanted into the hippocampus and cortex. This minimally invasive technique ensures long-term implant stability and infection prevention, with low signal artifacts and clear recordings maintained throughout the 90-day period. Furthermore, continuous neuronal activity monitoring was achieved without restricting natural behaviors, allowing long-term recording sessions of over 8 hours.We validated this method through real-time electrophysiological recordings in minipigs performing behavioral tasks, such as open field and gait analysis tests. The results demonstrated high-fidelity, low-artifact recordings throughout the study. Importantly, the minipigs exhibited no signs of infection or behavioral disturbances, confirming the success of the aseptic procedures and the biocompatibility of the implants. This novel brain implantation method provides a robust, long-term solution for chronic electrophysiological studies in large animal models, opening new possibilities for exploring neural activity during complex behaviors and contributing to advancements in brain-computer interface research and neurological therapies.

Disclosures: H. Pan: None. **C. Yeh:** None. **Y. Chou:** None. **T. Huang:** None. **J. Yang:** None. **D. Ju:** None. **H. Chen:** None.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.06/OO8

Topic: J.04. Physiological Methods

Support: NIH NIGMS IDeA Program Grant #P20 GM103446

Title: Sparse EEG Channel Reconstruction via Variational Autoencoders

Authors: *A. BOUKARI[1], J. LIU[2];
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Abstract: Electroencephalogram (EEG) recordings can often be difficult or expensive to perform outside of advanced clinical settings. The equipment needed to record full 64-channel data can be prohibitively expensive, and the data is often subject to noise from radio frequency interference, poor electrode contact, or other artifacts. Recovering missing or malformed channel data can be highly beneficial for EEG data recording on the edge, enabling the usage of affordable EEG equipment for epileptic seizure detection, sleep analysis, brain-computer interfaces, and more. This research explores the usage of a Variational AutoEncoder (VAE) framework for EEG channel interpolation, enabling fast and precise reconstruction of full 64-channel recordings from sparse channel inputs. Various studies have applied deep learning techniques to extract latent representations of EEG signals using VAEs, Transformers, and other deep learning methods. The usage of these latent representations for EEG interpolation, however, remains underexplored. Our method explores the usage of a VAE structure for this task. Our

model architecture includes a sparse convolutional encoder to encode inputs into a latent vector representation, and then a decoder to decode this EEG representation back into a full 64-channel EEG signal. Experiments on the OpenMIIR dataset demonstrate a Pearson correlation coefficient (r) >0.85 between original and reconstructed signals from a 16 channel input, outperforming traditional interpolation methods.

Disclosures: A. Boukari: None. **J. Liu:** None.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.07/Web Only

Topic: J.04. Physiological Methods

Title: Eeg biomarkers of impulsiveness and personality traits in healthy adults

Authors: *C. SARACINI[1], M. RODRIGUEZ ULLOA[2], D. BARROS MUÑOZ[2], F. ARRIAGADA[3];
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Abstract: Biomarkers based on EEG may enable early, cost-effective screening for comorbid conditions. Prior studies have linked theta/beta ratio (TBR), alpha/theta ratio (ATR) and frontal alpha asymmetry (FAA) to impulsivity, anxiety, and personality traits. Increased frontal theta may reflect amygdala-prefrontal engagement, whereas alpha is linked to relaxation: decreased ATR in frontal regions associates with higher trait anxiety. However, it remains unclear which marker best distinguishes excitatory/inhibitory aspects in healthy adults. We evaluated resting-state (RS) TBR, and ATR as correlates of impulsivity, anxiety, depression, stress, and Big-Five traits in adults without psychiatric history. EEG was recorded during an 8 min RS protocol (4 min eyes open, 4 min closed) in 36 healthy volunteers (22 females) with a 128-channel BioSemi ActiveTwo (500 Hz). After preprocessing, we computed theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) power, frontal alpha asymmetry (FAA), ATR, and TBR at Fz, F3, and F4. Psychometrics included Barratt Impulsivity Scale, DASS-21, and BFPTSQ-Short. Partial Spearman correlations (controlled for age and sex) showed TBR significant correlation with cognitive impulsivity ($r = 0.476$, $p < 0.01$), while ATR correlated inversely with depression ($r = -0.538$, $p < 0.001$). Additionally, TBR also correlated with depression ($r = 0.464$, $p < 0.01$) and ATR with depression ($r = -0.386$, $p < 0.05$). Among Big-Five traits, Emotional Stability (low Neuroticism) correlated modestly with FAA ($r = -0.400$, $p < 0.05$). In healthy adults, both TBR and ATR serve as sensitive markers of impulsivity and depression, suggesting imbalanced attentional control and alertness. We discuss the results in the frame of behavioral Activation/Inhibition System.

Disclosures: C. Saracini: None. **M. Rodriguez Ulloa:** None. **D. Barros muñoz:** None. **F. Arriagada:** None.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

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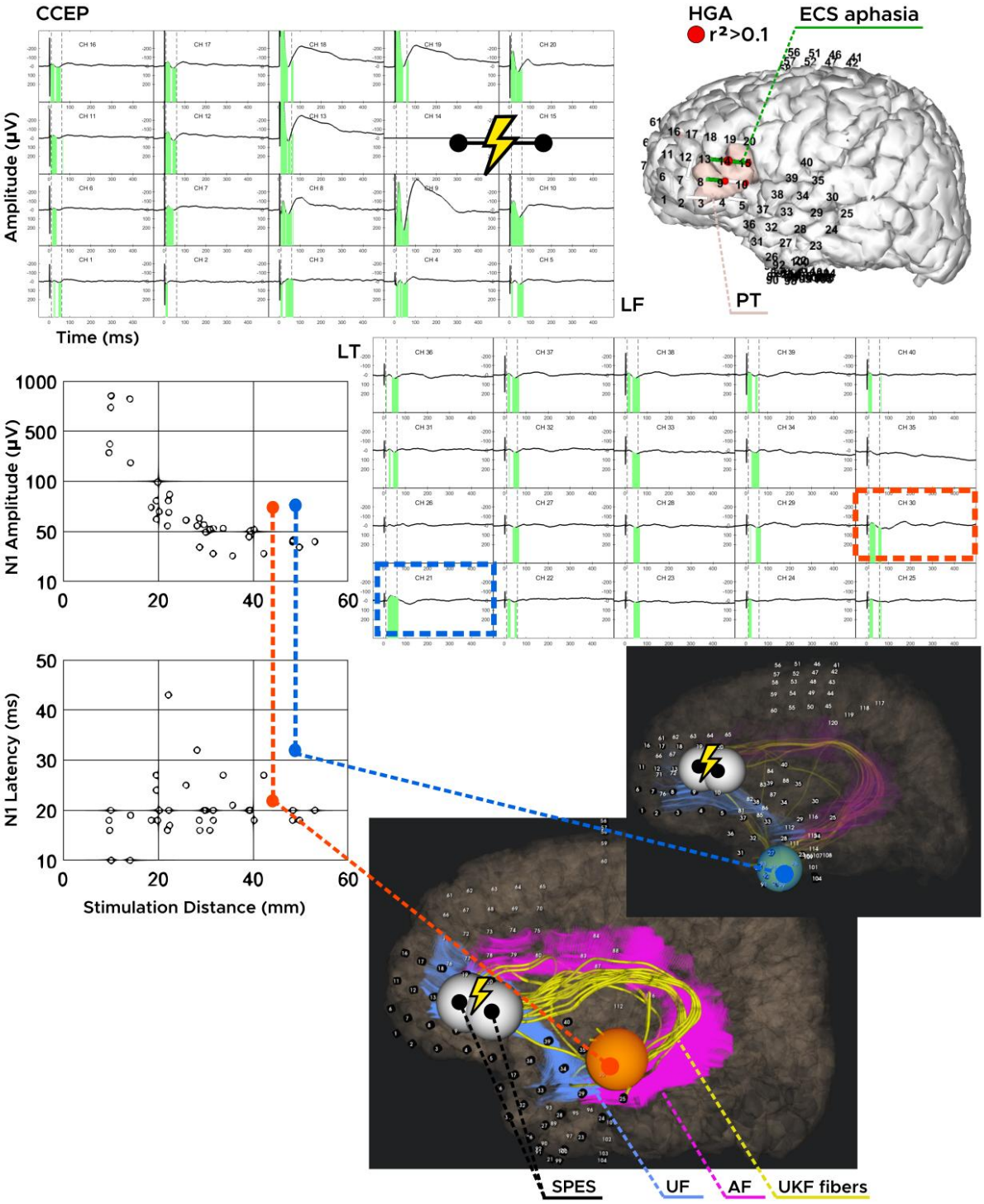
Program #/Poster #: PSTR144.08/OO9

Topic: J.04. Physiological Methods

Title: Multimodal Functional Mapping of the Language Network Using ECS, High Gamma Activity, CCEPs, and Tractography

Authors: *C. KAPELLER[1], K. KAMADA[2], K. MAYR[1], C. GUGER[1];
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Abstract: Electrocortical stimulation (ECS) remains the gold standard for language mapping. High gamma activity (HGA; 70-160 Hz) recorded via electrocorticography (ECoG) reflects cortical activation during task engagement. Cortico-cortical evoked potentials (CCEPs), generated through single-pulse electrical stimulation (SPES), offer a measure of connectivity. We present a multimodal approach combining ECS, HGA, CCEPs, and diffusion MRI tractography to localize language pathways during epilepsy surgery. A 24-year-old male with drug-resistant epilepsy underwent presurgical monitoring. Language mapping included ECS and HGA analysis during a picture-naming task. SPES was applied to the left pars triangularis (expressive language area), previously identified by ECS-induced aphasia and HGA during naming. Stimulation consisted of 60 monophasic pulses (300 μs duration, 15 mA). CCEPs were recorded at 2400 Hz and analyzed from -200 to 500 ms relative to stimulation. Diffusion MRI (3T) tractography was performed using a two-tensor unscented Kalman filter model. Parameters included one seed per voxel, FA ≥ 0.15, GA ≥ 0.1, and maximum fiber length of 250 mm. Spherical ROIs (10 mm radius) were placed to the stimulation and CCEP-responsive sites. ECS and HGA localized expressive language function to the left pars triangularis. SPES at this site elicited robust CCEP responses in two regions of the left temporal lobe. Posterior temporal CCEP responses (55 μV, 22 ms latency, 44 mm distance) corresponded to tractography-defined connections with 21 fibers (median length: 116 mm; range: 46-195 mm). Anterior temporal responses (58 μV, 32 ms latency, 48 mm distance) had 25 associated fibers (median length: 147 mm; range: 101-177 mm). These findings informed surgical targeting and language preservation. This case demonstrates the clinical utility of integrating ECS, HGA, CCEPs, and tractography for mapping of language networks. The multimodal strategy provided converging evidence for functional and structural connectivity, guiding surgical planning to minimize language disruption.



Disclosures: **C. Kapeller:** A. Employment/Salary (full or part-time): g.tec medical engineering GmbH. **K. Kamada:** None. **K. Mayr:** A. Employment/Salary (full or part-time): g.tec medical engineering GmbH. **C. Guger:** E. Ownership Interest (stock, stock options, royalty, receipt of

intellectual property rights/patent holder, excluding diversified mutual funds); g.tec medical engineering GmbH.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.09/OO10

Topic: J.04. Physiological Methods

Title: Changes in EEG Microstate Dynamics Between High and Low Homeostatic Sleep Pressure States

Authors: *R. PEREZ[1], A. SUBRAMONIAM[2], L. WHITEHURST[1], A. P. ZANESCO[3]; [2]Biol., [1]Univ. of Kentucky, Lexington, KY; [3]Ctr. For Mind and Brain, Davis, CA

Abstract: Electroencephalogram (EEG) microstates represent quasi-stable topographic patterns in the scalp electric field that reflect the activity of global functional brain networks. These microstates may provide a unique spatial-temporal perspective into understanding how moment-to-moment neural activity changes from pre to post sleep, including how neural dynamics change in the preparation for sleep and how neural coordination and synchrony during sleep impacts morning neural dynamics. Therefore, we aimed to examine how microstate dynamics differ between conditions of high and low homeostatic sleep pressure and how sleep macro and micro architectures influence next-day dynamics. We hypothesized that the four canonical microstate maps, specifically Microstate C and D, would differ from pre to post sleep, and that slow wave sleep and delta oscillations would predict these differences.38 healthy participants (mean age = 23.39; 20 males, 18 females) underwent five-minute eyes-open resting-state EEG recordings prior to an eight-hour sleep opportunity and immediately after morning awakening. Voltage topographies from 64-channel EEG were clustered into four canonical microstate maps. Multivariate analysis of variance models were used to investigate differences in microstate parameters between pre- and post-sleep conditions. Additionally, Pearson correlations were calculated to examine relationships between microstate dynamics and specific sleep stage features across the whole-night. Microstate A was more present during the night; greater mean duration (MD=0.63, p=.024), time coverage (MD=3.25, p=.018), and occurrence rate (MD < 0.01, p=.001). Microstate B also demonstrated a higher occurrence rate at night (MD<0.001, p=.001). Alternatively, while not significant, Microstate C and D were more present in the morning as demonstrated by GEV, mean duration, coverage, and occurrence rate. N2 sleep duration was positively associated with mean duration (p=.032), global explained variance (GEV) (p=.013), and time coverage (p=.033) of Microstate D in the morning. In contrast, N3 sleep duration was negatively associated with Microstate D mean duration (p = .029) in the morning. Total sleep time (p=.021) and sleep efficiency (p=.026) were positively correlated with Microstate B occurrence in the morning. N3 sleep duration was also positively associated with Microstate A occurrence rate in the morning (p=.046).These findings extend current sleep

models by demonstrating the active role of sleep in shaping network dynamics, further establishing sleep as a modulator of brain topology rather than merely a restorative state.

Disclosures: R. Perez: None. **A. Subramoniam:** None. **L. Whitehurst:** None. **A.P. Zanesco:** None.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.10/OO11

Topic: J.08. Methods to Modulate Neural Activity

Title: Centimani - a precision high-throughput implantation robot for flexible neural probes

Authors: *W. WANG[1], Y. WU[2], R. ALBOUY[3], C. XIE[2];
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Abstract: Flexible neural electrodes enable seamless integration with brain tissue and allow stable, long-term recordings from individual neurons without signal degradation. Distributed implantation of such electrodes facilitates the study of neural dynamics across a range of timescales—such as those underlying learning and memory—and provides valuable input for robust brain-machine interface systems. Despite the handling challenges posed by probe flexibility, prior work has demonstrated high-quality chronic recordings from up to 1024 channels using manual implantation of 64 shanks. However, these procedures are labor-intensive and lack stereotaxic precision, along with reliable control over key implantation parameters—such as insertion trajectory, speed, and position—as well as the ability to densely target large brain areas. These formidable challenges have limited the broader adoption of large-scale, distributed neural recording technologies. As a step toward automated precision implantation, Neuralink recently introduced a robotic system that uses a “sewing machine”-like mechanism for high-precision insertion of flexible probes. However, its strictly sequential strategy can lead to prolonged surgical times, increased tissue damage at higher speeds, and limited robustness to targeting errors. Here, we present Centimani, a minimally invasive, high-precision robotic system capable of implanting up to 32 flexible probe shanks with sub-100 µm accuracy at densities up to 500 µm. Centimani offers fully programmable control over insertion speed (ranging from micrometers per second to 10 mm/s) and site selection, enabling precise targeting of arbitrary brain regions while actively avoiding vasculature. It supports both simultaneous and sequential insertion modes, with total implantation times as short as one minute. We demonstrate that neural activity recovers following implantation, and that Centimani-implanted probes can simultaneously record from hundreds of channels. This enables tracking of monosynaptic neuronal connectivity and modulation of activity via microstimulation, providing a powerful platform for high-density, functional mapping of brain circuits.

Disclosures: W. Wang: None. **Y. Wu:** None. **R. Albouy:** None. **C. Xie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuralThread.

Poster

PSTR144: Advances in Electroencephalography and Telemetry

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.11/OO12

Topic: J.08. Methods to Modulate Neural Activity

Title: An electrotactile stimulation system that reproduces realistic tactile sensations using neural spike trains generated by tactile stimuli

Authors: *K. KIM[1], K. BAK[1], D. BAE[1], H. KIM[1], P. SUNGBAE[1], S. BAE[1], H. JUNG[2], Y.-J. KIM[2], S. CHUN[1];
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Abstract: Humans perceive tactile sensations through electrical signals of neural spike train generated by tactile afferents in the skin under tactile stimuli. To reproduce realistic tactile sensation, it is essential to convey tactile stimulation in the form of neural spike trains that human can perceive. However, there are few studies for neural spike train-based stimulation in artificial tactile feedback research. Here, we propose an electrotactile stimulation system with neural spike trains that were obtained by recorded response patterns of mouse nerves ex vivo to pressure stimuli to the hindpaw. We used a piezoresistive tactile sensor to collect tactile data. The output resistance data were converted into pressure values and then mapped to the neural spike trains. The specific spike trains were stimulated via a electrical stimulator to generate electrotactile sensations. Finally, the similarity between delivering pressure through electrical stimulation and delivering actual mechanical pressure was verified. The result shows that the neural spike train-based stimulation has the potential to approximate natural tactile perceptions, thus possible to reproduce realistic tactile sensation.

Disclosures: K. Kim: None. **K. Bak:** None. **D. Bae:** None. **H. Kim:** None. **P. Sungbae:** None. **S. Bae:** None. **H. Jung:** None. **Y. Kim:** None. **S. Chun:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.01/OO13

Topic: J.06. Computation, Modeling, and Simulation

Support: This material is based upon work supported by the U.S. Department of Energy, Office of Science, Office of Advanced Scientific Computing Research (ASCR) as part of the NSF/NIH/DOE/ANR/BMBF/BSF/NICT/AEI/ISCIII CRCNS Program. SNL is managed and operated by NTESS under DOE NNSA contract DE-NA0003525.

Title: Dendritic Dynamics for Compartment-Specific Learning

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Abstract: Spatial navigation requires the formation of coherent, map-like representations of the environment while simultaneously tracking current location, typically in a largely unsupervised manner. Extensive evidence from mammalian neocortex and subcortical structures suggests that primary sensory areas, intermediate regions such as the retrosplenial cortex (RSC), and the hippocampal formation interact bidirectionally to support flexible transformations between egocentric and allocentric codes.

Building on the theory of predictive learning, we propose a biologically plausible learning rule in which proximal inputs drive spiking activity, while distal dendritic inputs modulate burst activity. Learning then occurs on proximal dendrites based on a three-factor rule which combines the postsynaptic activity, presynaptic trace, and a longer-term trace of mean burst rate. This mechanism enables distal-guided learning of proximal synaptic weights. Implemented in an anatomically constrained sensory-RSC-hippocampal loop, this rule supports learning sensory-driven observations that align with internally generated expectations through contrastive learning of the feedforward firing rate with feedback expectations on distal dendrites.

We train this network in a simulated virtual environment and evaluate learned tuning curves with respective to behavioral variables. We find that single-compartment dendritic models qualitatively resemble experimental findings: allocentric and egocentric representations emerge in the expected order along the processing hierarchy, reflecting a population-level transformation from raw sensory input to egocentric codes. Population-level analyses show similar results, with increasing allocentric decodability along the processing hierarchy. However, these models suffer from catastrophic interference when exposed to novel environments and support only unidirectional transformations from sensory to allocentric representations.

We then extend the model to include neurons with multiple dendritic compartments. This branching architecture enables coordinate frame transformations to be learned at the level of individual neurons rather than relying on distributed population codes, by approximating matrix-matrix multiplication of inputs. Finally, we discuss how coordinate transforms of the level of individual neurons may enable separation of encoding and retrieval populations to mitigate catastrophic interference and enable bidirectional transformations.

Disclosures: G.W. Chapman: A. Employment/Salary (full or part-time): Sandia National Laboratories. **F. Wang:** None. **A.S. Alexander:** None. **F.S. Chance:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.02/OO14

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH NINDS 5F32MH132175
NIH NINDS/OD DP2 NS127291
NIH BRAIN/NIDA RF1 DA055667

Title: Dynisys: inferring low-dimensional dynamics and inter-area communication signals from multi-area neural datasets

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Abstract: While modern electrophysiological datasets routinely sample from multiple interconnected regions, most models are limited to inferring neural dynamics from individual brain areas. Since neural circuits do not operate in isolation, it is critical that we extend dynamical models to capture these coupled, interacting neural systems. Unfortunately, existing methods for inferring inter-area communication lack explicit dynamical models or are insufficiently expressive, limiting their ability to uncover computations distributed across the brain. We sought to extend existing single-compartment models to the domain of multi-site recordings, enabling both accurate prediction of population activity and direct interrogation of latent flow fields governing inter-area communication. We developed DynISys, a multi-compartment neural ordinary differential equation (NODE)-based dynamics model in which each compartment infers a single brain region's latent state and then uses these latents to predict spiking activity via an injective linear readout. Two factors determine the rules by which the activity of each compartment evolves: 1) the area's intrinsic dynamics and 2) low-dimensional inputs inferred from other dynamic compartments. This class of model is incentivized to invent superfluous features, which can make inferred dynamics and communication untrustworthy. To solve this problem, DynISys mandates injectivity by constraining its linear readouts from latent to neural activity to lie on the Stiefel manifold, obligating any invented features to degrade reconstruction performance. We applied DynISys to simultaneous dorsal premotor cortex (PMd) and primary motor cortex (M1) recordings collected while a monkey was performing a reaching task with a sequence of upcoming targets. We find that DynISys accurately reconstructs PMd and M1 population activity using low-dimensional dynamical compartments (avg bps ~ 0.1). Consistent with previous findings, DynISys also infers directed transmission of upcoming plans from PMd to M1 just before they manifest in observed M1 neural activity (R2 of next target prediction ~= 0.3). Crucially, DynISys allows us to probe the inferred dynamical flow field to identify dynamical structure associated with how inputs from PMd affect planning dynamics of

M1. DynISys bridges a critical gap in multi-region neural modeling, yielding both predictive power and mechanistic interpretability. This framework offers a scalable approach for dissecting inter-area computations in increasingly large, multi-site electrophysiological datasets enabled by advances in neural recording technology.

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Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.03/OO15

Topic: J.06. Computation, Modeling, and Simulation

Support: R01MH140020

Title: Nonlinear integration of synaptic and neuromodulatory inputs in astrocytes: a computational model of calcium-driven gliotransmission with diffusive dynamics

Authors: E. URDAPILLETA[1], R. AZAB[2], M. BOMPOLAKI[4], A. DRANOVSKY[5], M. DE PITTÀ[6], *S. DURA-BERNAL[3];
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Abstract: Astrocytes contribute actively to brain signaling through calcium-dependent mechanisms that mediate their bidirectional communication with neurons. Variations in astrocytic intracellular calcium can be initiated locally by synaptic activity or globally by neuromodulatory inputs, establishing a complex framework for information integration. These calcium signals regulate the release of gliotransmitters, which in turn influence synaptic transmission and neuronal activity across various brain regions. The convergence of localized and widespread signals—each capable of shaping astrocytic calcium dynamics—suggests a nonlinear mechanism for gliotransmitter release, especially when considering calcium's diffusive nature and the extracellular spread of gliotransmitters. Understanding how these processes interact in space and time requires computational modeling approaches that incorporate both detailed biophysics and cellular morphology. To explore these interactions, we present a computational model that incorporates astrocyte calcium signaling, cytosolic and extracellular diffusion, and gliotransmitter dynamics within a prototypal morphological framework. Leveraging the NEURON/NetPyNE simulation platform, the model integrates reaction-diffusion mechanisms for cytosolic calcium within astrocytes and gliotransmitter dynamics in the extracellular space. This allows for the analysis of a generic gliotransmitter concentration across

spatiotemporal coordinates, under varying input patterns and biophysical parameters. Simulations reveal that nonlinear interactions between local synaptic and global neuromodulatory inputs produce distinct gliotransmission signatures, shaped by the timing, intensity, and spatial distribution of stimuli. These emergent patterns underscore the importance of modeling astrocyte physiology at multiple scales to understand their integrative role in neural circuits. Our findings contribute to the theoretical framework for astrocyte-neuron communication and highlight the need for models that capture both the complexity and the emergent properties of glial signaling networks.

Disclosures: E. Urdapilleta: None. **R. Azab:** None. **M. Bompolaki:** None. **A. Dranovsky:** None. **M. De Pittà:** None. **S. Dura-Bernal:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.04/OO16

Topic: J.06. Computation, Modeling, and Simulation

Title: In Silico Electrophysiology and System Pharmacology: Coupling Between Dopamine Receptors and Ca^{2+} Channels in Subthalamic Neuronal Cells in Parkinson's Disease with Statistical Data Analysis

Authors: *C. MAHAPATRA;
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Abstract: Introduction: Parkinson's Disease (PD) is a neurodegenerative disorder characterized by disrupted motor function linked to abnormal activity in the basal ganglia, particularly the subthalamic nucleus (STN). Emerging experimental evidence suggests that dopamine D2 receptors (D2Rs) modulate N-type calcium (Ca^{2+}) channels, influencing the excitability and firing patterns of STN neurons. However, the mechanisms underlying this receptor-channel coupling remain poorly understood. This study aims to investigate the electrophysiological and pharmacological basis of D2R-Ca^{2+} channel interactions using an in silico modeling framework, supported by advanced statistical analysis.**Methods:** A detailed conductance-based model of an STN neuron was developed, incorporating key ion channels and membrane properties. Dopamine signaling was modeled via G-protein-coupled receptor (GPCR) pathways to simulate D2R activation and its inhibitory influence on N-type Ca^{2+} channel conductance. Pharmacological intervention was simulated using the D2R agonist Bromocriptine (10 μM). Neural spike sorting was performed using principal component analysis (PCA) and template matching to isolate action potentials. Statistical techniques—including hidden Markov models (HMM), point-process modeling, and time-series analysis—were applied to quantify changes in firing patterns and inter-spike interval distributions.**Results:** Simulation results showed that D2R activation led to a depolarizing shift in the half-activation voltage of N-type Ca^{2+} channels, reducing their conductance and decreasing the frequency of action potentials. Bromocriptine

treatment resulted in diminished window currents and lower excitability in STN neurons. Spike sorting confirmed a reduction in high-frequency firing events. HMM-based analysis demonstrated a significant drop in burst frequency, while point-process metrics indicated increased variability in inter-spike intervals. Time-series models further revealed shorter burst durations and suppressed firing rate modulation under dopaminergic conditions.**Conclusion:** This study presents a robust computational and statistical approach to analyzing the coupling between D2Rs and N-type Ca^{2+} channels in STN neurons. The findings suggest that D2R activation dampens neuronal excitability via calcium channel inhibition, contributing to the hypoactivity observed in PD. These insights support the potential for therapeutic strategies targeting ion channel dynamics, beyond traditional dopamine replacement, and offer a validated framework for future studies in neuropharmacology and systems neuroscience.

Disclosures: C. Mahapatra: None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.05/OO17

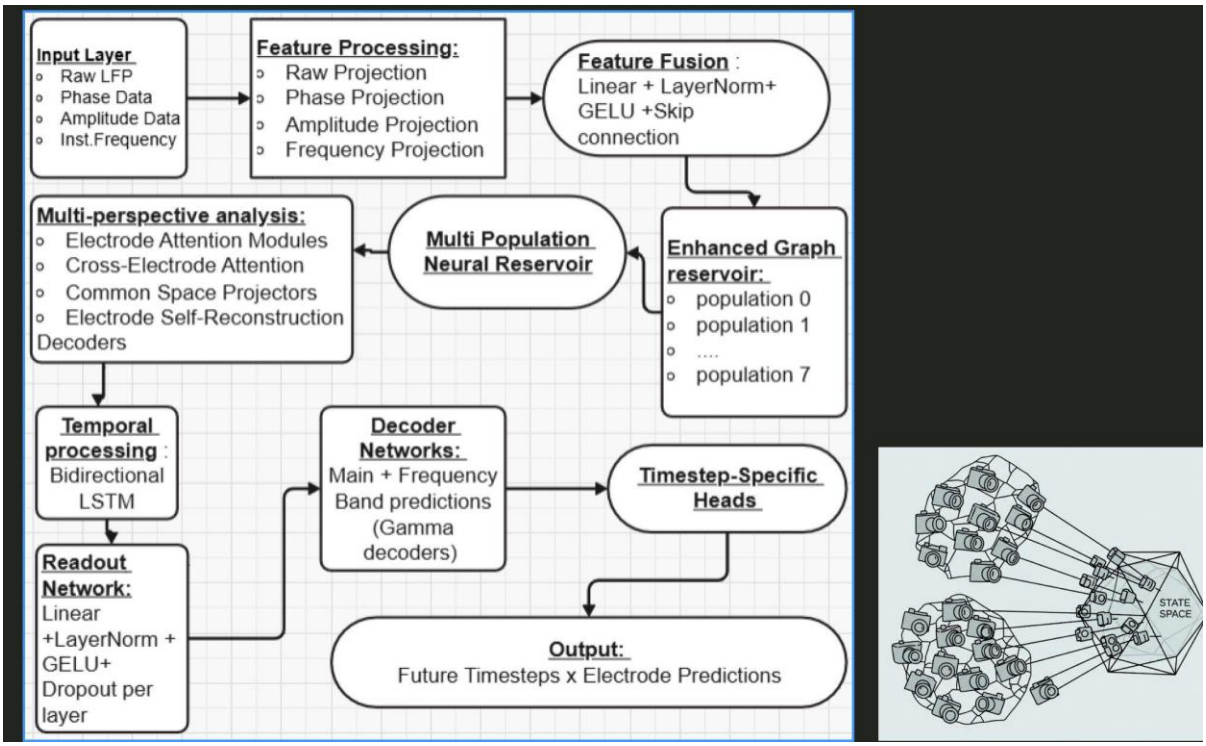
Topic: J.06. Computation, Modeling, and Simulation

Title: Graph-esns for cortical coordination: mapping neural perspectives in a shared embedding space

Authors: *A. PONNAMBALAM[1], K. VENKITESWARAN[2], A. BASU[3], R. SINGH[4], H. VORA[5];
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Abstract: Evidence suggests that the brain encodes information across a continuous, high-dimensional embedding space within neural activity. We examine how these neural "perspectives" appear within a high-dimensional plane where they can be compared to analyze how their information interacts.This approach is analogous to having multiple camera ensembles observe the same object: each camera must align with others to achieve optimal view while maintaining a common understanding of the object's spatial properties to interact effectively. In our analogy, cameras represent cortical populations, and the object represents state space.To model these dynamics, we propose a bespoke Graph-Echo State Network variant with multiple oscillatory components and individual components for each cortical population. This approach allows for modeling the perspectives of individual populations within a common state space, enabling the modeling of interactions between them. We demonstrate our architecture's robust performance across diverse species and tasks: Mus musculus LFP recordings from visual cortex during Gabor stimulus presentation (Neuropixels), human HD-ECoG during audiovisual film observation, human iEEG during object identification, and human resting-state activity

(Neuropixels). We demonstrate that neural cooperation can be modeled by projecting hidden states of each population's Graph-ESN bank into high-dimensional embedding spaces using UMAP, PCA, and PHATE. By analyzing the congruence of these hidden state populations within these embedding planes,we extract cognitively meaningful Inter-Population Engagement patterns, providing insights into underlying computational mechanisms. We justify this complex architecture by demonstrating superior validation losses and modular interpretability compared to mainstream approaches (LSTMs, Transformers,PINNs), which cannot achieve these capabilities. This modeling approach could facilitate deeper investigation into how cortical populations negotiate to construct cognitive processes we experience as thought.



Disclosures: A. Ponnambalam: None. **K. Venkiteswaran:** None. **A. Basu:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.06/OO18

Topic: J.06. Computation, Modeling, and Simulation

Support: NINDS F32NS129585

Title: Parameter inference in an oxygen reaction-diffusion model

Authors: K. KUMAR[1], R. MBOUZA[2], A. SRIVASTAVA[2], S. SAKADZIC[3], D. TARTAKOVSKY[2], *J. KRUEGER[2];
[1]Monta Vista High Sch., Cupertino, CA; [2]Stanford Univ., Stanford, CA; [3]Radiology, Massachusetts Gen. Hosp., Charlestown, MA

Abstract: All central nervous system (CNS) activities require energy. Oxygen is one of the essential metabolites involved in biochemical processes supplying such energy to the brain. Oxygen arrives through the vascular system and then freely diffuses through the CNS to its intended target sites. This diffusion is challenging to study in vivo leading to sparse experimental observations of oxygen concentrations, which in turn makes it difficult to estimate diffusion fields. To address this, we employed a computational approach involving a reaction-diffusion model for oxygen concentration in the brain that permits the inference of the underlying oxygen diffusion and reaction fields using sparse observations. A common approach to modeling oxygen dynamics is to assume a steady-state approximation. Previous work (Sakadžić et al 2016) estimated the ratio of oxygen consumption to diffusion using nonlinear least squares fitting that relies on point estimates within a Krogh cylinder model (KCM) framework. While this model aligns moderately well with experimental data, it provides limited uncertainty quantification for oxygen consumption estimates. Instead, here we use Ensemble Kalman filter, coupled with finite-element method-based forward models, to study the identifiability of the parameterized diffusion and reaction fields within the KCM framework and to estimate those parameters probabilistically using experimental data from rodent barrel cortex. Using KCM for partial pressure, we validated our model with synthetic data by contrasting it against the nonlinear least squares fitting and showed that our model is in agreement with the other approach while additionally providing uncertainty estimates of the reaction-diffusion ratio for oxygen. Moreover, incorporating the experimental data, our model has demonstrated considerable success in estimating the uncertain parameters, with the resulting diffusion and reaction fields lying within physically plausible regions, bolstering confidence in the estimates. Ongoing work is also focused on extending the forward model to include non-trivial geometry and multiple oxygen sources, enabling the use of observational data from such cases. This is expected to significantly increase the number of observations and help reduce uncertainty in the estimates. Furthermore, experimental data suggests that some of the reaction-diffusion dynamics might be better captured by a Michaelis-Menten based model and thus ongoing work is also exploring incorporating those dynamics to better reflect the underlying biological processes of oxygen reaction-diffusion.

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Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR145.07/PP1

Topic: J.06. Computation, Modeling, and Simulation

Support: R01 EY 033475
P30 EY 026877
Unrestricted Grant from Research to Prevent Blindness

Title: A Simulation Workflow for Modeling Foveal Photoreceptor Disruption in Vision Impairing Ophthalmic Conditions

Authors: *D. BUICKIANS[1], H. E. MOSS[2];
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Abstract: Visual dysfunction due to photoreceptor disruption is a common feature of many ophthalmic conditions, including retinal dystrophies and macular degeneration. It may also be a relevant mechanism in multiple sclerosis (MS), related to novel scattering features on the inner retinal surface that cast a shadow on the photoreceptors. However, it is challenging to isolate and analyze how specific photoreceptor disruption patterns impact visual perception and to what extent microsaccades can help to improve visual perception. To address this need we developed a simulation workflow built on the ISETBio (Image Systems Engineering Toolbox for Biology) framework, a MATLAB-based platform that models the front end of the human visual system, including scene creation with defined spatial and spectral radiance, optical modeling of the cornea and lens, simulation of a cone mosaic photoreceptor array based on human retinal architecture and movement of the ocular structures relative to the scene. The simulation models the impact of localized photoreceptor loss using inputs of visual scene luminance, cone mosaic geometry, cone mosaic disruption pattern and eye movements most of which are difficult or impossible to manipulate in vivo. The output of this model is a photon absorption map of the cone mosaic over time, representing the earliest stage of retinal encoding. This modular simulation allows precise isolation of variables supporting hypothesis-driven exploration of how disease-related disruptions to photoreceptors affect the retinal input signal. We present this workflow as a tool for the vision and neuroscience communities to model and visualize photoreceptor based visual deficits. Future efforts will incorporate downstream visual processing.

Disclosures: D. Buickians: None. **H.E. Moss:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.08/PP2

Topic: J.06. Computation, Modeling, and Simulation

Title: Integrating Biological and Chemical Graph Neural Networks for Small Molecule Blood-Brain Barrier Permeability

Authors: *G. AMANKWAH[1], S. PANDAY[1], R. DANEMAN[2], G. CHOPRA[1];
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Abstract: Blood-Brain Barrier (BBB) is a complex system of endothelial cells, astrocytes, and pericytes that regulates the passage of substances to the brain. This barrier is composed of receptors and transporters that regulate active and passive diffusion of compounds. BBB permeability is quantified using *in vivo* experiments measuring drug concentration in the brain against blood concentration (logBB), which is essential for the development of effective drugs for neurological disorders such as Alzheimer's disease. Over a decade, machine learning techniques have been used to predict the BBB permeability of compounds. However, such techniques have primarily relied on data related to the physical properties and chemical structures of drugs and often fail to account for the diverse molecular mechanisms, such as transcytosis, through which drugs cross the BBB. Here, we developed a robust learning framework using a bootstrapped graph neural network that incorporates the sub-graph features of molecular topology, the physicochemical descriptors of the compounds, receptor-ligand binding affinities, and the compound-sequence interaction probabilities with each selected receptor on the BBB for training. We incorporated the receptor-ligand binding affinities with several known receptors involved in transcytosis on the BBB. These include thiamine transporter, glucose transporter 1, MCT1, MFSD7A, MFSD2A, folate, and reduced folate receptor for transport mechanisms, highlighting interactions of the compounds with the receptors and transporters on the BBB. A dataset of 600 compounds with BBB permeability (358 BBB+ and 242 BBB-) was compiled from four different sources, where BBB+ and BBB- denote BBB-permeable and non-permeable compounds, respectively. Our transport-aware GNN model, with an F1 score of 0.92, a precision score of 0.92, and a Cohen’s kappa score of 0.80 for the test set, outperforms baseline models, such as traditional GNN model, SVM, KNN, and random forest. We conclude that our bootstrapped GNN learning framework identifies the molecular subgraph features and possible mechanisms for BBB penetrability.

Disclosures: G. Amankwah: None. **S. Panday:** None. **R. Daneman:** None. **G. Chopra:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.09/PP3

Topic: J.06. Computation, Modeling, and Simulation

Support: This work utilized computational resources support provided by the National Energy Research Scientific Computing Center (NERSC), a U.S. Department of Energy Office of Science User Facility

Title: Accurate inference of single-neuron biophysics from voltage responses with deep learning.

Authors: *K. CHAKRAVARTHULA[1], J. BALEWSKI[2], K. BOUCHARD[3], R. BEN-SHALOM[4];
[1]Computer Sci., Univ. of California, Davis, Davis, CA; [2]Natl. Energy Res. Scientific Computing Ctr. (NERSC), Lawrence Berkeley Natl. Lab. (LBNL), Berkeley, CA; [3]Helen Wills Neurosci.

Inst. & Redwood Ctr. for Theoretical Neurosci., Biol. Systems & Engin. Division, LBNL Scientific Data Division, LBNL, Berkeley, CA; [4]Neurol., UC Davis Med. Ctr., Sacramento, CA

Abstract: Inferring ion channel composition of individual neurons is essential to understand how electrophysiological diversity arises and how its disruption contributes to neurological disorders. However, experimentally determining conductance distributions in a given neuronal class is labor-intensive and has been achieved for only a few cell types, leaving a critical gap in our understanding of single-cell excitability. Conductance-based mathematical models, such as Hodgkin-Huxley (HH) models, simulate detailed neuronal morphologies and ion channel distributions to reproduce voltage dynamics across the neuron. Leveraging these biophysically detailed models, we developed a deep learning-based inverse modelling approach that predicts ion channel conductances from voltage responses to defined stimuli. Unlike conventional optimisation techniques like evolutionary algorithms, our inverse model requires only a single training pass to capture neuronal behavior across ion-channel parameter ranges and can then be deployed directly for inference, yielding greater efficiency.We created a data generation pipeline with complex HH models provided by the Blue Brain Project to produce large-scale training datasets. A convolutional neural network (CNN) was then trained with simulated spatio-temporal voltage traces as inputs, with corresponding ion channel conductances as targets, optimised to minimise error between predicted and ground truth conductances. CNNs trained on individual neuron morphologies achieved high accuracy in reconstructing both ion channel values and resultant voltage responses. This validation encompassed 170 neuronal morphologies spanning inhibitory and excitatory classes. However, these models exhibited limited generalizability with data from new morphologies. Because obtaining high-resolution morphological reconstructions experimentally can be challenging, we extended this strategy into a unified network, ONTRA (One Network To Rule Them All), trained on simulated data generated from diverse neuronal morphologies. Moreover, ONTRA models not only produce accurate predictions for familiar morphologies but also generalise well for unseen morphologies.We aim to translate this framework to experimental recordings, enabling inference of conductances and membrane properties from electrophysiological data, helping us to understand the relation between neurological disorders and their ion channel distributions. Moreover, this pipeline paves the way for constructing “digital twins” of neurons, facilitating extensive in silico pharmacological screening and advancing personalised therapeutic strategies.

Disclosures: K. Chakravarthula: None. **J. Balewski:** None. **K. Bouchard:** None. **R. Ben-Shalom:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.10/PP4

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant R01-NS124814
NIH Grant R01-NS094206

Title: Design of pathway-specific subthalamic deep brain stimulation for gait and balance impairment in Parkinson's disease

Authors: *M. FARSAD[1], Y. SEDDIGHI[4], Y. CHOI[2], M. BRYANTS[2], F. MIRBAGHERI[3], R. PATRIAT[4], C. D. MACKINNON[2], N. HAREL[4], S. E. COOPER[2], M. D. JOHNSON[3];
[1]Dept. of Biomed. Engin., Univ. of Minnesota, Minneapoils, MN; [2]Dept. of Neurol., [3]Dept. of Biomed. Engin., Univ. of Minnesota, Minneapolis, MN; [4]Dept. of Radiology, Ctr. for Magnetic Resonance Research, Univ. of Minnesota, Minneapolis, MN

Abstract: Motivation: While deep brain stimulation of the subthalamic nucleus (STN-DBS) is a successful treatment for many Parkinson's disease symptoms, postural instability and gait disorder respond inconsistently. This variability may stem from different pathway activation patterns across patients. In this study, we investigated the relationship between pathway activation between the pedunculopontine tegmental nucleus efferents to the globus pallidus internus (PPTg=>GPi) and pallidofugal afferents (GPi=>PPTg).
Methods: Patient-specific STN-DBS models were created for five individuals with bilaterally implanted stimulators (10 hemispheres). 7T MRI and post-operative CT were used to build finite element models to predict the extracellular potentials from DBS. The resulting tissue potentials were coupled with field cable models of reconstructed axon morphologies (PPTg=>GPi and GPi=>PPTg). In addition to these models, for each axon, a computationally-efficient modified driving function (MDF) was computed as a weighted sum of activating function values across all nodes. Across multiple pulse widths, we established mathematical relationships between field cable model thresholds and MDF calculations for internal capsule, PPTg=>GPi, and GPi=>PPTg pathways. This method was then integrated into a multi-objective particle swarm optimization (MOPSO) algorithm to identify patient-specific settings for targeting either PPTg=>GPi or GP=>PPTg pathways.
Results: We found a linear a relationship between log-transform of MDF maximum and NEURON threshold, improved R^2 compared to previous curve-fitting methods and reduced residual standard deviations while predicting the site of action potential initiation more accurately. The slope and intercept of the fits (constant for all patients and hemispheres) varied systematically with fiber diameter and pulse width. For each hemisphere, MOPSO was able to identify a pair of settings with maximum disparity between activation of the PPTg efferents versus afferents. These settings as well as the patient's usual clinical settings were compared over three visits, spaced over 6 weeks, with prolonged wash-in and wash-out of DBS effects.
Conclusions: This modified approach to computational modeling of DBS provides an efficient framework to prospectively identify STN-DBS parameter settings that maximizes disparity in pathway activation and then experimentally test specific hypotheses about how pathway activation relates to clinical outcomes on a patient-specific basis. This approach may enable more symptom-specific and personalized DBS programming.

Disclosures: M. Farsad: None. **Y. Seddighi:** None. **Y. Choi:** None. **M. Bryants:** None. **F. Mirbagheri:** None. **R. Patriat:** None. **C.D. MacKinnon:** None. **N. Harel:** None. **S.E. Cooper:** None. **M.D. Johnson:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.11/PP5

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH (P50-123109, R01-124814, R01-NS094206)
CMRR imaging

Title: Deep Learning-Based Prediction of Globus Pallidus Axonal Pathway Activation for Patient-Specific Modeling of Deep Brain Stimulation in Parkinson's Disease

Authors: *F. MIRBAGHERI[1], M. FARSAD[1], E. E. LECY[2], C. D. MACKINNON[3], T. PALNITKAR[4], R. PATRIAT[4], N. HAREL[4], Y. SEDDIGHI[4], S. E. COOPER[3], M. D. JOHNSON[1];
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Abstract: Computational models of deep brain stimulation (DBS) can help determine what axonal pathways to stimulate to affect individual symptoms. One approach, known as pathway activation modeling, includes detailed equivalent circuit models of ion channels and is thought to provide the most accurate relation between stimulus-induced transmembrane currents and DBS parameters for action potential generation. Another more computationally efficient approach uses a modified driving force (MDF) approximation to estimate transmembrane currents using a weighted activating function. However, this approach has challenges with axons that curve around a DBS lead or axons that begin or terminate near an active electrode. In this study, we added a neural network (NN) to the MDF calculations of myelinated axons to learn a data-driven relationship between log-normalized MDF values across all axonal nodes and pathway activation model thresholds. In five patients with globus pallidus DBS implants, we compared activation thresholds between the MDF and MDF-NN approaches across five axonal pathways. For this limited patient cohort, our method enhanced the root mean square error (RMSE) and R^2 values between the pathway activation model thresholds and the new MDF-NN prediction. For example, for three pathways, GPe=>GPi/STN/SN, GPe=>STN/SN, and GPi efferent, the RMSE improved by 71%, 75%, and 69% respectively. This novel approach refines a computationally efficient method to predict field cable model thresholds without the need for extensive biophysical model simulations. Our method generalizes the standard MDF approach to handle multiple axonal morphologies, multiple brain pathways, and different patient anatomies and lead placements within the globus pallidus. These advancements could increase the speed of computational modeling and DBS optimization.

Disclosures: F. Mirbagheri: None. **M. Farsad:** None. **E.E. Lecy:** None. **C.D. MacKinnon:** None. **T. Palnitkar:** None. **R. Patriat:** None. **N. Harel:** None. **Y. Seddighi:** None. **S.E. Cooper:** None. **M.D. Johnson:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.12/PP6

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH RO3 Award NS127192

Title: Diffcorank: a comprehensive framework for discovering hub genes and differential gene co-expression in brain implant-associated tissue responses

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Abstract: While brain implants offer significant potential for therapy and research, complex tissue responses often compromise their long-term stability. To address this challenge, differential co-expression analysis can be used to identify key molecular regulators involved in brain implant responses. We developed DiffCoRank, an integrated framework that improves differential co-expression analysis by integrating RNA-Seq data preprocessing, gene filtering, correlation-based module identification, and network analysis to discover differentially co-expressed gene clusters. A key innovation of our approach is false discovery rate (FDR)-based selection of strongly connected genes (SCGs), which improves detection of strong co-expression patterns that could otherwise be lost to spurious correlations. To enhance the identification of different modules, we employ a hybrid clustering technique that combines uniform manifold approximation and projection (UMAP) with density-based spatial clustering of applications with noise (DBSCAN). We propose a multicriteria hub gene ranking system incorporating network centrality metrics such as degree, closeness, betweenness, and eigenvector centrality to prioritize biologically relevant genes. Our method successfully identified important gene modules linked to stress responses, immunological regulation, and axonal pathfinding using RNA-Seq data from implanted rat brain tissue. Furthermore, we compared our results to existing co-expression analysis frameworks, showing that our method successfully identifies unique regulatory processes and consistent co-expression patterns. Our research offers novel insights into the molecular processes that explain implant-tissue interactions and possible approaches to improve the robustness and biocompatibility of brain interfaces.

Disclosures: A. Chakraborty: None. **E.K. Purcell:** None. **M.G. Moore:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR145.13/PP7

Topic: J.06. Computation, Modeling, and Simulation

Support: JSPS KAKENHI 24K22305
AMED Multidisciplinary Frontier Brain and Neuroscience Discoveries 24018835

Title: Inferring the excitation-inhibition balance underlying the synchronous network dynamics in human scalp EEG using a data assimilation framework

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Abstract: Modulation of the synaptic balance between excitatory and inhibitory neural ensembles (E/I balance) underlying the healthy brain network dynamics. Indeed, the E/I balance is associated with neuronal mechanisms underlying both transient and persistent changes in neuroplasticity and circuit-level dynamics in the brain. For example, perceptual learning is mediated by transient neuroplastic changes associated with shifts in the E/I balance. In contrast, the persistent changes in network dynamics, due to an imbalance in excitation/inhibition linked to amyloid-beta protein accumulation, would induce the development of dementia symptoms. Understanding the relationship between brain network dynamics and the E/I balance is crucial for deepening our knowledge of human neurophysiological mechanisms. However, quantifying the brain network dynamics and E/I balance changes in parallel is difficult to obtain from the intact human brain, even with state-of-the-art brain recording technologies. To address these issues, we recently developed a data assimilation (DA) method for tracking changes in E/I balance based on the single time series of EEG obtained from the human intact brain. Even though we found that our method was successful in detecting physiologically valid E/I balance changes during sleep from observed EEG, the DA method could not be applied to estimate brain network dynamics and E/I balance changes in parallel. Therefore, in this study, we proposed a novel EEG-DA method using a network-neural-mass-model (NNMM)-based estimation of brain network and E/I balance changes. The numerical validity of our method was confirmed by showing that it could estimate both brain network structure and E/I balance changes from synthetic multivariate EEG data generated by the NNMM with known parameter settings related to the network structures and E/I balance. It indicates that our method has the potential to quantify how changes in E/I balance influences changes in brain network dynamics. Finally, we will discuss the applicability of our proposed EEG-DA method in human neuroscience studies by showing the results of applying this method to observed human EEGs.

Disclosures: H. Yokoyama: None. **K. Kitajo:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.14/PP8

Topic: J.06. Computation, Modeling, and Simulation

Support: SECIHTI, CVU 11479

Title: In silico characterization of Capsaicin analogs: prediction of biological targets and molecular docking on the TRPV1 receptor.

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Abstract: The transient receptor potential vanilloid subtype 1 (TRPV1) is a transmembrane receptor with ion channel activity that facilitates the passage of cations, primarily calcium ions. TRPV1 is expressed in the central nervous system and sensory neurons and is involved in nociception and pain perception. To study the functions of TRPV1, agonism and antagonism have been proposed. Capsaicin and Anandamide are known agonists of the receptor, whereas AMG9810 acts as an antagonist. In this study, we conducted an *in silico* analysis to characterize potential biological targets of a set of 30 capsaicin analogs. The canonical SMILES representations of the molecules were retrieved from the *PubChem* database. The *Swiss Target Prediction* tool was used to forecast biological targets and made a frequency diagram. To identify possible biological activities, we performed a search using *PASS Online* and selected those with a probability score greater than 0.10. To explore protein-protein interaction networks associated with the predicted targets, we employed the *STRING* database. Furthermore, molecular docking simulations were carried out using the *Schrödinger* platform on the crystallized tetrameric structure of TRPV1 (PDB ID: 7MZ5), embedded in a POPC membrane model. As a result, we identified 40 biological targets with a probability greater than 30.8%, with TRPV1 being the most prominent. We identified 16 biological activities, with TRPV1 agonism being the principal. Correlation analysis between targets and predicted activities revealed four key functional groups: inflammation, lipid metabolism, neurotransmission, and cell proliferation and death regulation. The protein-protein interaction network showed 116 edges and an average node degree of 0.58. Docking score results were compared against reference ligands: Capsaicin (CID: 1548943) (-8.69), Anandamide (CID: 5281969) (-6.79), and AMG9810 (680502) (-8.37). Analysis of the binding pockets indicated that agonist binding involves hydrogen bonds with Thr550, Arg557, and Glu570. Moreover, Pi-Pi interaction with Tyr511 was found to enhance receptor affinity. Based on these criteria, we selected capsaicin analogs exhibiting docking scores lower (more negative) than -8.69 and demonstrating the specified interactions. The most promising candidates identified were Homocapsaicin II (CID: 11674147) and Methylcapsaicin (CID: 6440227).

Disclosures: C.A. Zerón Alvarado: None. **V. Alatriste:** None. **L. Martinez Mendieta:** None. **A. Carrasco Carballo:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.15/PP9

Topic: J.06. Computation, Modeling, and Simulation

Title: An End-to-End Model for Intracortical Decoding Motor Sequence

Authors: *Q. AN[1,2], C. LI[1], T. WANG[3], H. CUI[1];
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Abstract: Previous studies have shown that cortical preparatory activity conveys information about the sequential movements so that motor execution and motor planning occur simultaneously. Different from single-target movements, sequential movements involve interdependent elements across the sequence, and the decoding process should take into account interactive relationships within the data. In order to extract sequential information, we proposed an end-to-end multi-task model that jointly decoded sequential motor plans from neuronal population activity. In our recent study (Wang et al. Nat Commun 2024), we introduced a sequential double-reach task in which monkeys were trained to touch two targets in succession, while neuronal activity was recorded from two electrode arrays implanted in the dorsal premotor cortex (PMd) and primary motor cortex(M1). Based on these data, our decoder aimed to simultaneously predict neuronal activity and classify the two targets among 12 discrete conditions (2 targets, 6 positions, clockwise/counter-clockwise). The model employed shared self-attention representations to embed temporal features of population neuronal activity along with their positional encoding. The sequential feature was extracted via a stack of encoder layers, and a self-attention pooling mechanism is subsequently applied to compress the predicted neural activities. To better capture the motor plan of arm movement, we jointly trained two parallel output heads: a continuous regression head for generating neuronal activity and a discrete classification head for predicting target labels. Multi-task neural networks usually achieve faster inference and improved performance compared to single-task networks, but they are often difficult to train. Therefore, we automatically balance the training of deep multitask models by dynamically tuning gradient magnitudes, resulting in enhanced regression and classification performance. By decoding neural activities during movement execution, the model achieves 87.88% accuracy in a 12-class classification task. Crucially, during the motor preparation period, incorporating the regression head generated neuronal activity and improved decoding performance. The model achieves 59.5% classification accuracy and an r-square of 0.78 for generating neuronal activity, indicating that significant sequential information is present even before movement onset. These results demonstrate that our model can successfully extract both the representations and the dynamic characteristics inherent in sequential movement, providing novel approach for decoding sequential movements.

Disclosures: Q. An: None. **C. Li:** None. **T. Wang:** None. **H. Cui:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR145.16/PP10

Topic: J.06. Computation, Modeling, and Simulation

Support: Division of the Intramural Research Program (DIRP) of the National Institute of Mental Health (NIMH)
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Title: Machine learning models reveal scaling of cortical networks to holographic perturbation

Authors: R. SIDDIQUI, S. PAJEVIC, T. L. RIBEIRO, *D. PLENZ;
Sect Critical Brain Dynamics, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD

Abstract: Superficial cortical layers have been hypothesized to operate near a critical point, supported by statistical signatures of criticality observed across diverse recording modalities and species, including humans. Critical systems possess useful properties, such as optimal information transmission, that may underlie key aspects of neural computation. Understanding how criticality contributes to cortical processing and coding is important both clinically, for identifying potential dysfunction, and fundamentally, for advancing theories of brain function. A hallmark of systems at criticality is their sensitivity to small, local perturbations. We investigated this property in layer 2/3 (L2/3) pyramidal neurons in mouse primary visual cortex (V1) by recording the response of the ~150-300 neurons to holographically triggered action potentials using two-photon calcium imaging. In our field of view we selected 32 neurons as optogenetic stimulation targets and grouped them into local groups of size 1, 2, 4, and 8. In each trial, a random group was stimulated for 100 ms, with 100 trials conducted per group. We recast these perturbation experiments as a classification task, training machine learning models to decode stimulation location from the resulting population activity. Using model interpretability tools, we quantified how perturbation-related information is distributed across the network response for each group size. In addition, we constructed a cascading dynamics model that can be tuned to criticality and repeated the same stimulation and classification analysis across subcritical, critical, and supercritical regimes. We show that stimulation targets can be decoded from the activity of non-stimulated neurons, and that decoding performance increases with group size. SHAP-based model analysis reveals that the most predictive neurons tend to be spatially proximate to the target and strongly selective. Feature removal analyses further demonstrate information to be broadly distributed across the network and show that decoding remains robust even when highly predictive neurons are removed, also scaling with local group size. Similar analyses show improvements in classification performance in critical versus subcritical regimes in our simulation. These results suggest L2/3 V1 may exhibit dynamics similar to those in critical systems.

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Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.17/PP11

Topic: J.06. Computation, Modeling, and Simulation

Support: This work was supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – (DN. 1553 11.10.2022)

Title: Mapping cortico-subcortical connectivity with high-density probes

Authors: *F. NEGRI[1], D. VECCHIA[1], M. CARÈ[2], F. BARBAN[1,2], M. CHIAPPALONE[1,2]; [1]Univ. of Genova, Genova, Italy; [2]IRCCS Ospedale Policlinico San Martino, Genova, Italy

Abstract: Introduction. Cognitive and behavioral brain processes depend on the continuous interplay of widespread neuronal assemblies operating across cortical and subcortical regions. To dissect the functional architecture of both healthy and diseased neural circuits *in vivo*, it is fundamental to capture neural signals at high spatial and temporal resolution. This requires simultaneous recording of spiking as well as slow-wave activity across distributed brain areas, which can only be achieved using advanced technologies such as large-scale, high-density, high-count electrode arrays. **Objective.** This study aims at (i) demonstrating the capability of the high-density probes to perform stable recording from different brain regions simultaneously; (ii) evaluating the functional connectivity properties among those regions. **Methods.** We conducted experiments on healthy, anesthetized female and male Long Evans rats. High-density 512-electrode SiNAPS probes (7.75 mm long; Corticale SRL, Genova, Italy) were utilized to record spontaneous neuronal activity in cortical and subcortical brain regions. Recording lasting 20 minutes were performed with the Plexon acquisition system. Both intra-region and inter-regions functional connectivity were inferred via transfer entropy, after partitioning the probe electrodes among the recorded brain areas and performing spike detection and sorting. **Results.** In this study, we show that the 512-channel SiNAPS probe allows simultaneous and precise detection of both local field potentials and action potentials across multiple brain structures (i.e., cortex, hippocampus, and thalamus) in anesthetized rats. Its dense spatial configuration, combined with the ability to continuously record from all electrodes in parallel, enables robust isolation of single-neuron activity and fine spatial discrimination of neuronal sources. Furthermore, the comprehensive coverage provided by the array facilitates high-resolution mapping of functional connectivity across cortico-subcortical circuits, capturing both local interactions and long-range network dynamics. **Conclusions.** This enhanced experimental setup now enables detailed investigation of cortico-subcortical circuit loops and their connectivity at an unprecedented scale in healthy and diseased brains. Building on our previous work with low-density probes, this study leverages the advanced capabilities of high-density recording devices to explore the effects

of cortical ischemic lesions more comprehensively. This holds great promise for guiding the development of improved therapeutic strategies.

Disclosures: F. Negri: None. **D. Vecchia:** None. **M. Carè:** None. **F. Barban:** None. **M. Chiappalone:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR145.18/PP12

Topic: J.06. Computation, Modeling, and Simulation

Support: NSF Grant 2139319
NSF FGNM06 Career

Title: Graph Neural Networks Reveal Molecular Signatures of Disease Severity in Frontotemporal Dementia

Authors: *L. CORNELIS[1], R. SALONER[3], G. BERNARDEZ[2], K. B. CASALETTO[3], N. MIOLANE[2];
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Abstract: Recent advances in large-scale proteomics enable capture of thousands of proteins in human biospecimen samples, supporting discovery of disease-related biomarkers and drug targets. Traditional proteomic workflows model proteins as individual predictors of disease outcomes, failing to account for how relationships between proteins influence predictive performance.
In this work, we present a novel analytical framework applying a biologically-inspired graph attention neural network to cerebrospinal fluid proteomic data for predicting disease severity in 252 participants with frontotemporal dementia, a progressive neurodegenerative disease that lacks robust prognostic biomarkers. We construct disease-specific co-expression graphs where nodes represent proteins and edges encode pairwise correlations. Graph attention layers then extract hierarchical module-level features, which are then used alongside patient level demographic data for downstream predictions. The framework successfully forecasts cognitive decline and gold-standard markers of neurodegeneration, surpassing or matching traditional analytical methods including neural networks and LASSO regression.
Through systematic network interpretation using feature attribution techniques, we identify proteins with high importance for disease severity prediction that are not detected by other approaches. This includes targets such as TLR1 and C3, which are linked to neuroimmune signaling, and B4GALT3, which is associated with sugar metabolism. We integrate large language models (LLMs) as a second step in the explainability pipeline. After extracting the top

5-10 predictive proteins, we query LLMs to place these hits in context: What are these proteins' known functions? Do they have links to neurodegeneration, such as in Alzheimer's or Parkinson's research, or appear in animal studies? Human experts on our team verify all references before inclusion, but the automated search streamlines and enriches interpretation. Our study demonstrates how graph-based deep learning approaches can extract meaningful insights from high-dimensional proteomic data, advancing our understanding of the molecular underpinnings of frontotemporal dementia with potential applications for all neurodegenerative diseases.

Disclosures: L. Cornelis: None. **R. Saloner:** None. **G. Bernardez:** None. **K.B. Casaletto:** None. **N. Miolane:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.19/PP13

Topic: J.06. Computation, Modeling, and Simulation

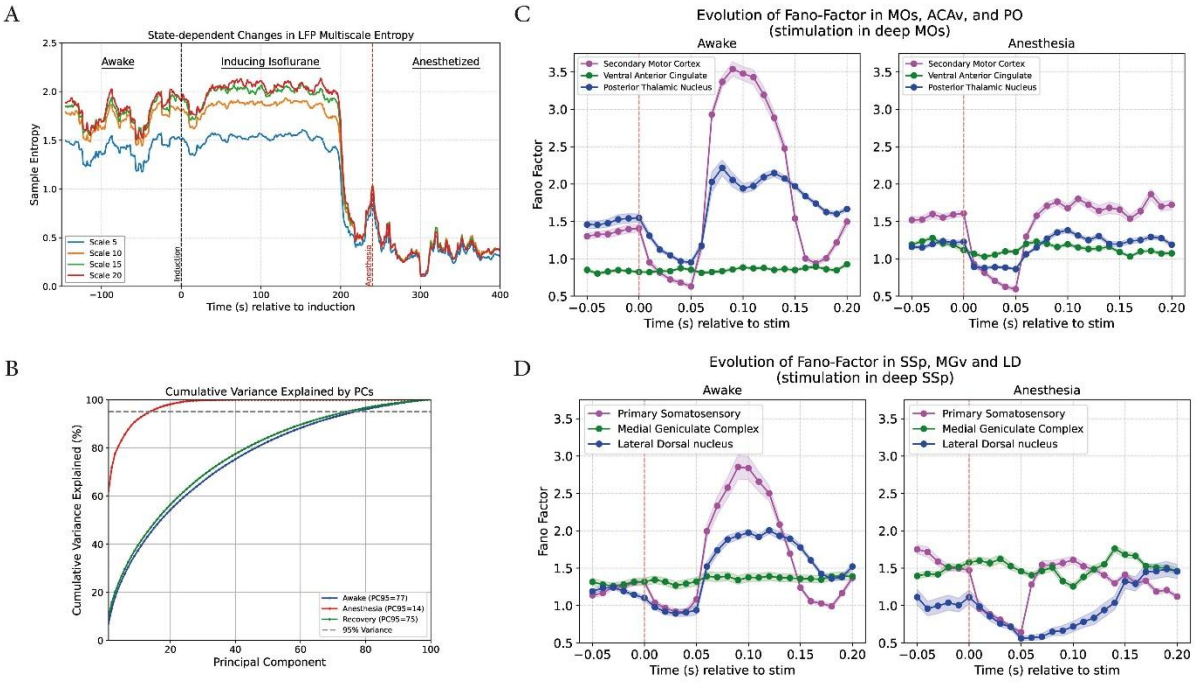
Support: ND is supported by NIH Grant R24MH117295

Title: Deep cortical layer stimulation reveals state-dependent changes in neural excitability

Authors: N. JOODI[1], ***N. DEHGHANI**[2];
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Abstract: Cortical information processing is fundamentally shaped by functional state, with transitions like those induced by anesthesia causing profound changes in excitability. Understanding how these state-dependent changes modulate the neural complexity is crucial for unraveling neural dynamics. To investigate this, we re-analyzed Neuropixels recordings (DANDI archive # 000458) from mice receiving electrical single-pulse stimulation in deep MOs (secondary motor) or SSp (primary somatosensory) cortices. We computed Multiscale Sample Entropy (MSE) on 4 coarse-graining scales of LFPs, quantified population spiking dimensionality via PCA, and measured the effect of electrical stimulation on spiking variability using Fano Factor. MSE showed distinct values across scales when awake but collapsed to a uniformly lower entropy under anesthesia (Fig.A). Population dimensionality collapsed under anesthesia (Fig.B), with principal components explaining ≥95% of variance falling 45% relative to awake state ($p<0.01$). Deep MOs stimulation suppressed variability in MOs and sensorimotor thalamic nuclei (SM-TH) in both states (Fig.C), while other cortical areas remained unchanged. Deep SSp stimulation produced suppression in SSp and SM-TH, but not in auditory thalamic nuclei or MOs (Fig.D). Critically, both SM-TH circuits and targeted regions showed pronounced post-stimulus rebound overshoot above baseline during wakefulness, which was blunted under anesthesia. These results demonstrate that deep cortical stimulation drives cortico-thalamo-cortical networks into transient low-variability states, but only awake networks robustly restore

variability. This highlights how brain state gates neuromodulatory efficacy and underscores the importance of high entropy and dimensionality during wakefulness.



Disclosures: N. Joodi: None. **N. Dehghani:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.20/PP14

Topic: J.06. Computation, Modeling, and Simulation

Support: JSPS KAKENHI Grant Number JP25H00448

Title: Towards constructive understanding of gut-brain axis: development of an integrated intestinal simulation

Authors: *S. HIRANO[1], S. YONEKURA[1], S. ISHIDA[2], Y. IMAI[2], Y. KUNIYOSHI[1];
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Abstract: Within the framework of the gut-brain axis, recent research has revealed the significant influence of gastrointestinal signals on cognitive and behavioral processes. A particularly crucial aspect is the enteric nervous system (ENS) and the pacemaker cells (interstitial cells of Cajal, ICC). It is understood that the gut can autonomously generate its own motility through the combined function of the ENS and ICC, even in the absence of brain

signals. However, existing intestinal models lack the integration of these biological components (ENS and ICC) with detailed physical representations of the intestine, including fluid dynamics and structural mechanics. This research aims to create such a comprehensive intestinal model. We expect this model will allow us to analyze the impact of ENS and ICC cooperation or dysfunction on the physical behavior of the intestine, providing insights into the mechanisms underlying both typical motility patterns and abnormal phenomena like backflow and obstruction.
The physical model consists of the intraluminal fluid simulated by the lattice Boltzmann method and the elastic intestinal wall by the finite element method. These two physical components are integrated using the immersed boundary method, as implemented in previous research (N. Takeishi et. al., 2019). The biological components include the ENS based on the leaky integrate-and-fire neuron model, and networks of ICC and smooth muscle cells (SMC). The ENS consists of sensory, inter and motor neurons, and is designed to generate peristaltic reflexes. The SMC's activity is modulated by inputs from both the motor neurons of the ENS and the ICC. The coupling between the physical and biological models is realized through bidirectional mechanisms: (1) SMC contraction is applied as displacement input to the FEM, and (2) stress and pressure computed by the FEM are provided as external current inputs to the sensory neurons.
This integrated model enables the simultaneous simulation of biological activity (ENS, ICC, SMC) and the physical behavior of the intraluminal fluid and the elastic intestinal wall. Furthermore, by enabling the ENS to sense the state of the intestine, it becomes possible for the ENS to autonomously generate motility patterns that correspond to the current intestinal state.
In conclusion, this study presents a novel intestinal model that integrates the biological components consisting of the dynamics of ENS, ICC, and SMC with fluid and structural simulations. We expect that this model will provide a constructive understanding of complex phenomena, such as the gut-brain axis, which are difficult to understand through physiological observation only.

Disclosures: S. Hirano: None. **S. Yonekura:** None. **S. Ishida:** None. **Y. Imai:** None. **Y. Kuniyoshi:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

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Program #/Poster #: PSTR145.21/PP15

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant R01 MH086638

Title: Simulation tool for prediction of ion and molecule propagation and distribution in detailed dendritic trees

Authors: *C. ROMARO[1], W. W. LYTTON[3], R. A. MCDOUGAL[2];
[1]Dept. of Biostatistics, Yale Sch. of Publ. Hlth., [2]Biostatistics, Yale Univ., New Haven, CT;
[3]Physiology/Pharmacology, DHSU, Brooklyn, NY

Abstract: Neurons are living cells, with complex interacting electrical and chemical dynamics. Many biological processes (e.g., spreading depolarization, intracellular calcium waves) are closely tied to this interaction which itself is often highly dependent on the details of neuronal morphology. These details increase the computational complexity of using simulations to plan or analyze experimental results. We present a method, leveraging the NEURON simulator (https://nrn.readthedocs.io) to use adaptive, varying grids for targeting computation effort on critical regions of interest while preserving numerical accuracy and robustness.
In the NEURON simulator, unbranched dendritic or axonal sections can be independently discretized using NEURON's standard voxelization algorithm, using NEURON's reaction-diffusion Region specification to accommodate per-Section grid size specification. Small voxels are either removed or added to create a join with minimal voxel overlap but always guarantee the absence of holes. Neighboring voxels of different sizes are connected to allow molecules to diffuse between the grids. A space partitioning tree was used for efficient cross-grid voxel alignment. For ease of use, the model specification is in Python; for performance, coupling between grids and all simulation is done in C++.
Mass is conserved when diffusing across the grid-size boundary, however subtle differences may arise in numerical results due to the changes in volume and surface-area voxel-size-dependent estimates; but the convergence is guaranteed even beyond the traditional numerical requirement $D * dt/dx^2 < 1/2$. Accuracy and performance are assessed for both simplified morphologies and detailed cell morphologies from NeuroMorpho.Org; initialization and simulation times may be equal or slightly slower than for the coarse grid, (but not for the finest grid) however the time cost may be 10% of the same accuracy using single grid size, or even 1% for the numerical required stability parameter ($D * dt/dx^2 < 1/2$) for single grid size.
This method has the potential to enable high-fidelity simulations combining chemical, electrical, and network activity with modest computing resources - providing clues to the real behavior of in vitro/vivo experiments; allows increased accuracy in small parts of the morphology or in regions of interest with moderate compute overhead.

Disclosures: C. Romaro: None. **W.W. Lytton:** None. **R.A. McDougal:** None.

Poster

PSTR145: Computational Approaches and Experimental Analyses I

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.22/PP16

Topic: J.06. Computation, Modeling, and Simulation

Title: Numerical Investigation of Nerve Stimulation Effects in the Vicinity of Orthopedic Implants

Authors: A. SHEN[1], L. YANG[2], M. DU[1], H. YE[4], N. KAULA, PHD[5], J. ZHENG[3], ***J. CHEN**[1]; [2]Dept. of Electrical and Computer, [3]Electrical and computer engineering, [1]Univ. of Houston, Houston, TX; [4]Biol., Loyola Univ. Chicago, Chicago, IL; [5]Cirtec Med., Arvada, CO

Abstract: Neurostimulator systems are increasingly employed to treat neurological and orthopedic conditions. However, for patient with passive orthopedic hardware, the hardware can distort local electric fields and potentially alter stimulation efficacy. Despite its clinical relevance, the interaction between neurostimulator systems and adjacent orthopedic implants remains insufficiently characterized. This study investigates how orthopedic implants affect the stimulation of nearby peripheral nerves. Numerical simulations were conducted in Sim4Life using the Yoon-sun model from the Virtual Population (a 26-year-old female with a BMI of 23.6), which includes over 74 tissue types with dielectric properties sourced from the IT'IS human tissue database. The Electro Ohmic Quasi-Static solver was used for the analysis. A 58.9 mm orthopedic plate was positioned along the radius bone, adjacent to a peripheral nerve stimulator targeting the radial nerve. The stimulator comprised four cylindrical electrodes (0.5 mm radius, 2 mm width, 1 mm spacing), each set to -1 V, with the implantable pulse generator (IPG) serving as the 0 V reference. The tangential electric field along the radial nerve was extracted for further analysis. A physiology axon model (MRG) was implemented in NEURON to estimate stimulation thresholds using a unipolar waveform at 30 Hz with a 0.3 ms pulse duration. For 5.7 μm fibers, the required stimulation voltage increased from approximately -2.3 V (without the plate) to -3.0 V (with the plate). For 16 μm fibers, the required stimulation voltage rose from -0.31 V to -0.45 V. On average, the required stimulation voltage/current was 41% higher in the presence of the implant compared to the no-implant condition. These findings indicate that metallic orthopedic implants can influence the required stimulation strength from the IPG, underscoring their potential to affect the efficacy and safety of electrical nerve stimulation.

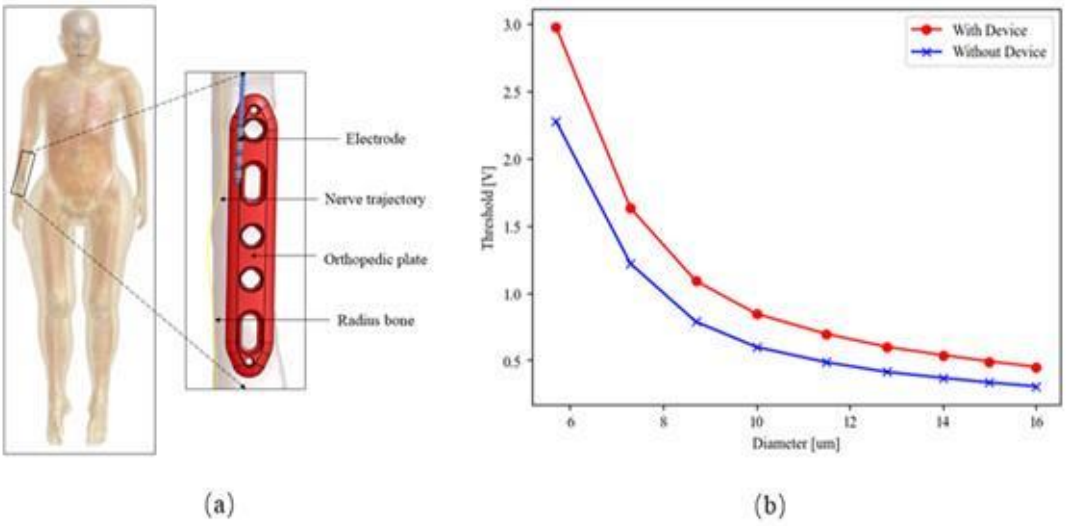


Figure 1. (a) Simulation setup; (b) Required stimulation strength vs. fiber diameter with and without orthopedic device.

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Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

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Program #/Poster #: PSTR146.01/PP17

Topic: J.07. Data Analysis and Statistics

Title: Meditation-journey: dataset and benchmarks for longitudinal study of different meditation techniques

Authors: *A. LI[1], A. SYED[1], M. ZHANG[2], B. COHEN[3], S. RAVISHANKAR[2];
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Abstract: Electroencephalography (EEG) is valuable for investigating meditation's neural correlates. However, publicly available, large-scale, longitudinal EEG datasets comparing distinct practices and tracking changes over extended training are scarce, yet crucial for understanding meditation-induced neural plasticity. To address this, we introduce "Meditation-Journey," a novel longitudinal EEG dataset and benchmark suite to study distinct neural effects and their evolution from various meditation practices over a 6-week training period.The dataset includes EEG from 30 healthy college students recorded pre/post a 6-week daily meditation schedule. Participants were randomized to three groups: SA-TA-NA-MA or Hare-Krishna mantras, or Breath Focus meditation. 64-channel EEG sessions included an initial eyes-closed resting state (ECR1), an assigned meditation with motion (M) period (e.g., mantra vocalization, alternate nostril breathing), a subsequent eyes-closed rest (ECR2), and a final silent meditation (SM) task (internal mantra for Japa groups, breath focus for Focused Attention). Standard preprocessing (filtering, ASR, ICA) was applied; data is BIDS compliant.The benchmark suite features classification tasks: (1) differentiating post-intervention SM vs. ECR1 states; (2) longitudinal (pre/post) SM change classification; (3) post-intervention ECR2 vs. ECR1 classification for immediate meditation effects; (4) meditation technique classification (post-intervention SM EEG); and (5) longitudinal (pre/post) baseline ECR1 change classification. Baselines were established using FBCSP, Shallow/Deep CNNs, and EEGNet, known for strong EEG classification.Preliminary results demonstrate the dataset's utility. For instance, Hare-Krishna meditation showed higher within-subject accuracy for immediate post-meditation effects (Task 3), and group-level meditation technique classification (Task 4) reached ~96% accuracy, with main misclassifications between mantra-based methods. The "Meditation-Journey" dataset, well-documented and preprocessed, will be a publicly accessible resource capturing EEG dynamics from three meditation practices over a 6-week intervention. It offers a valuable resource and standardized framework for new analytical methods in meditation research and EEG-based machine learning (e.g., neurofeedback for improved meditation). The complete dataset, preprocessing pipelines, and benchmark evaluation code will be released to accelerate understanding of their neuroplastic effects.

Disclosures: A. Li: None. **A. Syed:** None. **M. Zhang:** None. **B. Cohen:** None. **S. Ravishankar:** None.

Poster

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Topic: J.07. Data Analysis and Statistics

Support: National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT)(RS-2024-00357820)

Title: Spectral power differences across clozapine response subgroups in schizophrenia

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Abstract: Background: Schizophrenia is increasingly conceptualized as a spectrum disorder, where patients with similar symptom presentations may differ fundamentally in underlying neurobiological mechanisms. Despite ongoing efforts to identify electrophysiological biomarkers using EEG, most approaches have dichotomized treatment response into responder and non-responder categories. However, if identical pharmacological agents exert their effects through heterogeneous mechanisms, treatment responses may manifest in multiple distinct patterns. **Methods:**We analyzed resting-state EEG data from 14 patients with schizophrenia who underwent clozapine treatment. Based on changes in Positive and Negative Syndrome Scale (PANSS) scores, subjects were stratified into three data-driven subgroups: (1) *All Improved*, (2) *Positive Dominant*, and (3) *Increased*. EEG was recorded using a 32-channel 10-20 system (Comet-PLUS, Grass Technologies) at a 400 Hz sampling rate. High-pass filtered at 1 Hz, and underwent line noise removal using EEGLAB (https://eeglab.org). Noisy or flat channels were removed using the Clean_rawdata plugin and later interpolated using spherical interpolation. Signals were re-referenced to the common average. Independent component analysis (ICA) was performed with the AMICA algorithm, and non-brain or artifact components were removed using ICALabel. Components with residual variance <0.15 and brain probability >70% were retained. Continuous EEG was segmented into 2-second epochs. **Analysis:**For each subject, power spectral density was computed across canonical frequency bands (delta, theta, alpha, beta, gamma) at the channel level. Group-wise comparisons were performed within each session (Baseline and Post) and for the difference (Post - Baseline), focusing on identifying frequency- and region-specific patterns that may reflect distinct treatment-related neurophysiological mechanisms.**Result:**Spectral power analysis revealed a significant difference in the delta band at Fz between the Positive and Increased groups following clozapine treatment. Additionally, alpha band power at Pz, P3, P4, and CP1, and gamma band power at CP5, significantly differed

between these two subgroups. In contrast, no significant differences were observed in any frequency band or channel when the All Improved group was included in the comparisons. This suggests that spectral differentiation may be more detectable between narrowly defined response phenotypes.No significant spectral power differences were found between the **Positive** and **All Improved** groups at any site or frequency band.

Disclosures: J. Eo: None. **T. Youn:** None. **H. Park:** None.

Poster

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Program #/Poster #: PSTR146.03/PP19

Topic: J.07. Data Analysis and Statistics

Title: Electrophysiological Signatures Differentiate Bipolar and Unipolar Depression in Adolescents

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Abstract: Bipolar disorder (BD), characterized by alternating depressive and manic episodes, often presents with symptoms that overlap with unipolar depression, or major depressive disorder (MDD), complicating early and accurate diagnosis in adolescents. Misdiagnosing BD as MDD can lead to inappropriate use of antidepressants, exacerbating mood instability, and delaying effective management. This study aims to identify diagnostic neurophysiological markers that distinguish BD from MDD by employing a multifaceted electroencephalography (EEG) approach that integrates event-related potentials (ERP) and resting-state EEG (rsEEG) brain network features. A total of 86 adolescents participated in the study (24 BD, 30 MDD, 32 healthy controls (HC)). Notably, the MDD group included five diagnostically ambiguous cases who were initially diagnosed with MDD but transitioned to BD after a clinical follow-up of one year. These MDD-BD converters were included to assess the predictive potential of our method for the transition from MDD to BD. A three-stimulus oddball paradigm was used to record ERPs; N2 and P3 components were extracted from averaged waveforms. Resting-state EEG data were recorded under eyes-closed conditions and transformed from sensor- to source-space using inverse modeling. Brain network states were identified by clustering rsEEG epochs segmented with a sliding-window approach, and the proportion of time spent in each state was computed.Results indicated a graded increase in both N2 and P3 amplitudes across groups (BD < MDD < HC). Three distinct rsEEG brain network states were identified; proportions of States 1 and 3 showed group-level gradients, with State 3 differing significantly across all groups ($p < 0.001$). Importantly, the five MDD-BD converters showed ERP and rsEEG profiles more closely resembling those of the BD group at baseline, supporting the prognostic potential of the proposed features.In conclusion, integrating ERP and rsEEG-derived brain network features

reveals robust neurophysiological markers for distinguishing BD and MDD in adolescents. Validation with ambiguous clinical cases highlights the translational potential of this approach for early diagnosis based on baseline EEG data.

Disclosures: Y. Lei: None. **S. Liu:** None. **Y. Zhang:** None.

Poster

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Topic: J.07. Data Analysis and Statistics

Support: NIH Brain Initiative 5UH3NS119844

Title: Discriminating Tics from Voluntary Movements to Optimize Adaptive Deep Brain Stimulation in Tourette Syndrome

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Abstract: Tourette Syndrome (TS) is a complex neuropsychiatric disorder characterized by involuntary motor and vocal tics. Deep Brain Stimulation (DBS) targeting the centromedian (CM) nucleus of the thalamus and anterior globus pallidus interna (aGPi) has demonstrated therapeutic promise. This study investigates whether specific frequency features in local field potentials (LFPs) can reliably distinguish tics from voluntary movements to inform automatic adaptive DBS (aDBS) programming. We recorded neural activity from seven TS patients implanted with bilateral macroelectrodes in both CM and aGPi using Medtronic Percept neurostimulators. Simultaneous video, wireless EMG, and inertial sensors (Delsys) were used to annotate tic events and voluntary hand movements. For each subject, power spectra were compared across conditions to identify frequency ranges best discriminating tic-related activity. Across patients, low-frequency bands (centered at 7.81 ± 2.5 Hz) consistently showed higher power during tics than during voluntary movements, in 7 subjects, 6 of which experience therapeutic benefit. These features informed the personalization of adaptive stimulation thresholds and targets. While some subjects responded best to sensing and stimulation in the CM, others showed optimal outcomes with hybrid configurations (e.g., sensing in CM and stimulating in aGPi). Adaptive DBS was successfully implemented in all cases using patient-specific LFP thresholds for tic detection. Final outcomes indicate enhanced tic suppression, improved tolerability, and reduced stimulation time compared to conventional DBS. Crucially, differentiating tics from voluntary actions minimizes the risk of overstimulation during purposeful movement, potentially mitigating long-term side effects such as habituation, cognitive

burden, or interference with volitional motor control. These findings highlight the clinical relevance of individualized, frequency-based biomarkers for optimizing aDBS in TS.

Disclosures: J. Gomez: None. **G. Lowor:** None. **A. Gunduz:** None. **C.R. Butson:** None.

Poster

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Topic: J.07. Data Analysis and Statistics

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National Science and Technology Concil, Taiwan: NSTC 111-2823-8-A49-003
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National Science and Technology Concil, Taiwan: NSTC 111-2634-F-A49-014

Title: Electroencephalogram characteristics of Alzheimer's dementia using Holo-Hilbert spectral analysis

Authors: *Y.-R. CHEN[1,2], A.-C. YANG[1,2,3,4];
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Abstract: Background: Alzheimer's disease (AD), the most common cause of dementia, is marked by progressive cognitive decline and widespread brain dysfunction. Although EEG is a useful non-invasive tool for detecting neural changes in AD, conventional spectral analyses often fail to capture its complex, nonlinear signal characteristics. This study applies Holo-Hilbert Spectral Analysis (HHSA), a high-resolution method capable of capturing amplitude and frequency modulation patterns, to examine differences in electroencephalograms (EEGs) from individuals with Alzheimer's disease (AD), mild cognitive impairment (MCI), and healthy controls (HC). **Methods:** EEG data were obtained from a 19-electrode 10-20 system database.

Based on the Clinical Dementia Rating (CDR) score, participants (n=123) were categorized into four groups: healthy control (n=15), MCI (n=15), mild AD (n=69), and moderate-to-severe AD (n=24). For each participant, two 8-second segments of resting-state, eyes-closed EEG recordings were extracted. Holo-Hilbert spectrum analysis was applied, with carrier frequency (f_c), amplitude modulation frequency (f_{am}), and frequency modulation frequency (f_{fm}) segmented by powers of 2. Spectral energy across these frequency intervals was compared among groups. **Results:** After excluding low-quality data and those without clear event annotations, 101 participants remained for analysis. Compared to healthy individuals, moderate-to-severe AD patients exhibited a significant increase in DC and amplitude-modulated energy at f_c = 2-8 Hz. Similarly, individuals with mild or more severe AD showed a significant increase in DC and frequency-modulated energy at f_c = 1-8 Hz compared to healthy controls. Additionally, an increase in DC and frequency-modulated energy at f_c = 32-128 Hz was observed at the T3 and T4 electrodes. Similar trends were observed across different f_{am} or f_{fm} values within the same f_c range. However, HHSA results are sensitive to differences in signal decomposition results, indicating room for improvement in stability. **Conclusion:** HHSA results of f_{am} and f_{fm} can help distinguish between healthy individuals and AD patients. Notably, changes were prominent in temporal electrodes, aligning with known AD-related brain regions. While HHSA offers enhanced sensitivity to spectral modulations, its results can vary based on signal decomposition, highlighting a need for improved stability. Still, these findings support HHSA's potential as a non-invasive tool for characterizing AD-related neural dysfunction.

Disclosures: Y. Chen: None. **A. Yang:** None.

Poster

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Topic: J.07. Data Analysis and Statistics

Support: The Blavatnik Fund for Innovation at Yale
Internally Designated Funds

Title: A Deep Learning Neural Network for Reconstructing Fetal Brain Activity from Non-Invasive Abdominal EEG

Authors: *J. BURDE[1], E. BERI[3], J. A. CORTES[2], J. URRUTIA[2];
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Abstract: Fetal electroencephalography (fEEG) is a promising method for assessing fetal oxygenation levels during labor. However, vaginal fetal EEG (V-fEEG), the only currently available method, is invasive, requiring vaginal electrodes attached to the fetal scalp. Non-computerized, non-invasive abdominal fetal EEG has been proposed but is uninterpretable due to extensive signal artifact from non-EEG signals. This noise arising from the abdomen is caused

by muscle activity, maternal and fetal movement, and maternal and fetal electrocardiogram signal. Our method of computerized abdominal fetal EEG (cAb-fEEG) overcomes these challenges, utilizing a deep learning neural network (DNN) to identify and filter out non-fetal EEG signals. Deployed on non-invasive abdominal cAb-fEEG recordings, the DNN separates fetal EEG signals cleanly from the aforementioned signal artifacts, rapidly and accurately reconstructing brain activity. With a newly constructed cAb-fEEG belt we recorded 50 participants, obtaining evoked potentials with an auditory event-related potential (ERP) paradigm. We show that these cAb-fEEG signals contain enough information to exhibit a time-locked auditory ERP with a significant probability of not occurring by chance in the absence of stimulation. Altogether, our work establishes the ability of the DNN to extract fEEG signals drawn from the maternal abdomen, accurately remove artifacts, and reconstruct fetal brain activity in response to auditory stimuli. The results of this research will provide a non-invasive and novel method to directly measure fetal neurologic activity and have the potential to decrease the rates of preventable brain injury at birth.

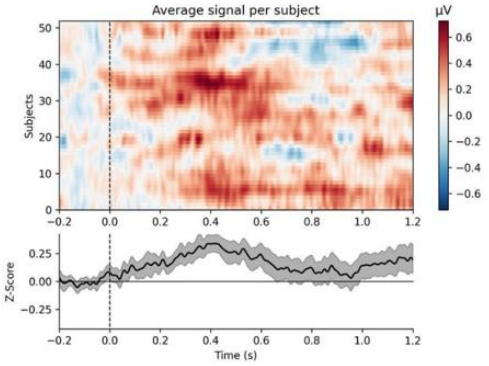


Fig 1.
Each row in the heatmap shows the reconstructed auditory ERP of an individual fetus (n=50), with the color scale representing amplitude (μV). The plot below displays the grand average across the entire sample, with the shaded area representing the standard error.

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Poster

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Support: Advancing Healthier Wisconsin MCW-Led Momentum Grants
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Title: A novel spike-sorting pipeline optimized for microwire recordings from humans

Authors: *T. BRAHMA[1], M. KHANI[2], F. J. CHAURE[3], C. HAUDER[4], S. MATHEW[1], A. S. DOMINGUEZ ZESATI[1], H. G. REY[1];
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Abstract: Efficient and accurate spike sorting is critical for isolating single neurons from extracellular recordings to distinguish neural activity of interest. However, while the electrodes and acquisition systems for non-human electrophysiology have been enhanced over the past decades to enable higher-yield single-neuron detections, those advances have not been translated into human electrophysiology. Single-wire electrodes are ubiquitously used, and although acquisition systems have augmented their signal-to-noise ratio over the last 15 years, we are still limited by their low electrode count. Moreover, unlike non-human recordings, human recordings often take place in hospitals where different noise sources and subject breaks can compromise the recording quality during experimental sessions. To bridge this gap, this work presents an automatic, open-source spike sorting pipeline that leverages contemporary computational capabilities and is tailored to single-neuron recordings from humans acquired via microwires. The pipeline is implemented in both MATLAB and Python, ensuring accessibility and compatibility across computational environments. Its modular and comprehensive structure supports customization and even opportunities for new developments as per the requirements of the user and the application. One feature is a data-driven automatic module to remove narrow-band interference, besides electrical line noise, which can be an essential tool while recording in clinical settings, particularly for online processing implementations. Following spike detection, the pipeline implements an artifact rejection module that separates waveforms that are unlikely to be associated with actual spikes. Additionally, we introduce a configurable feature-extraction, clustering, and benchmarking framework that not only allows flexibility in employing user-defined or conventional algorithms, such as wavelet transform with superparamagnetic clustering, but can also evaluate multi-method agreement among the different sorters. The pipeline also utilizes quality metrics like the presence ratio to support semiautomatic curation of the isolated clusters. Furthermore, we can integrate the customized pipeline with experimental tasks by removing task-unrelated waveforms, e.g., during a break in a task, and preventing over-clustering with the aid of Response Similarity Matrices computed across clusters. Thus, the presented pipeline addresses the three-pronged objectives of algorithm-adaptability, rigorous validation, and human single-neuron recording optimization to support clinical and cognitive neuroscience applications.

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Poster

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Program #/Poster #: PSTR146.09/QQ5

Topic: J.07. Data Analysis and Statistics

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Title: Connectivity analysis using partial correlation functions in patients with epilepsy

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Abstract: Epilepsy is the most prevalent neurological disorder, affecting approximately 1% of the global population. While antiepileptic pharmacotherapy achieves seizure control in roughly 75% of cases, the remaining 25% develop drug-resistant (refractory) epilepsy, for which surgical intervention may be indicated. Accurate localization of the epileptogenic zone and delineation of seizure propagation pathways are essential for effective surgical planning.We previously proposed a method for estimating seizure propagation by defining inter-channel connectivity among electrocorticographic (ECoG) signals using cross-correlation functions, followed by construction of a minimum spanning tree. However, conventional cross-correlation analysis is limited in that it cannot account for the confounding influence of other channels, potentially leading to spurious connectivity.In the present study, we introduce a refined analytical approach based on partial cross-correlation functions, which enables the estimation of direct functional connectivity by statistically controlling for the influence of all other channels. ECoG data were obtained from patients undergoing pre-surgical evaluation at the Department of Neurosurgery, Kinki University School of Medicine, with institutional ethical approval (Approval Nos. 21-135 and H26-1-1008).We applied both cross-correlation and partial cross-correlation analyses to ECoG recordings from two patients with generalized epilepsy and one patient with focal epilepsy. In cases of generalized epilepsy, linkages identified via cross-correlation were attenuated or absent in the partial cross-correlation analysis, suggesting that the former may reflect indirect coupling mediated by common sources. In the focal epilepsy case, although the EEG exhibited generalized features, clinical manifestations were consistent with focal onset—findings more accurately captured by the partial cross-correlation method.These results indicate that partial cross-correlation analysis provides a more precise characterization of seizure dynamics by isolating direct interactions, thereby enhancing the identification of epileptogenic networks. This approach holds promise for improving the accuracy of presurgical evaluation and optimizing surgical outcomes in patients with refractory epilepsy.

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Poster

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Program #/Poster #: PSTR146.10/QQ6

Topic: J.07. Data Analysis and Statistics

Title: Spatiotemporal Complexity Analysis of sEEG signals in Temporal Lobe Epilepsy: A Multifractal-based Machine Learning Approach

Authors: *N. S. JOHN, J. C. BULACIO, B. KRISHNAN, D. SERLETIS;
Epilepsy Center, Neurolog. Inst., Cleveland Clin., Cleveland, OH

Abstract: INTRODUCTION Patients with medically intractable epilepsy undergo extensive clinical testing to establish candidacy for potential epilepsy surgery. Finding mathematical biomarkers underpinning the dynamics of brain networks involved in seizure activity could lead to better outcomes following epilepsy surgery. Multifractal formalism introduces an invaluable framework for the investigation of nonlinear, scale-invariant features across multiple time scales in non-stationary time-series data. We sought to explore multifractal features defining temporal correlations in stereoelectroencephalography (sEEG) seizure recordings. **METHODS** We collected multi-channel sEEG data from 36 patients with refractory temporal lobe epilepsy treated at Cleveland Clinic, 28 of whom subsequently underwent a standard anteromesial temporal lobectomy, including amygdalohippocampectomy (ATL/AH) while the remaining 8 underwent a limited temporal lobe resection sparing hippocampus (LTR). All patients achieved at least 1-year of sustained seizure freedom. Multifractal Detrended Fluctuation Analysis (MFDFA) was used to test for fractal scaling in 155 sEEG-recorded seizures. Seizure data and electrode contact sites were annotated by experienced clinicians. Electrode contacts were systematically organized into anatomical groups. **RESULTS** We identified strong multifractal signatures in human sEEG data, demonstrating distinct spatiotemporal patterns across epileptiform states and between different anatomical networks. The designed workflow comprised of a K-means clustering analysis to characterize the feature variability across the pre-ictal, ictal and post-ictal epileptiform states for the anatomical regions clinically annotated, and a subsequent linear support vector machine classifier to differentiate surgical groups based on regional multifractal dynamics. A Mann-Whitney U-test with the Benjamini-Hochberg correction was conducted to assess the statistical significance of MFDFA-derived features with discriminative potential. Among the eleven MFDFA-derived features, the Hurst exponent emerged as a principal feature. Using this feature set, a linear support vector classifier (SVC) successfully distinguished between the ATL/AH and LTR surgical cohorts, achieving an accuracy of 96.9%, precision of 93.8%, recall of 100% and F1-Score of 95.8%. **DISCUSSION** Our results support the integration of multifractal spectral-based approaches and machine learning workflows into conventional sEEG interpretation and epileptiform network analysis, offering an exciting new tool for surgical decision-making in epilepsy patients.

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Poster

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Program #/Poster #: PSTR146.11/QQ7

Topic: J.07. Data Analysis and Statistics

Title: Surrogate map-based group-level analysis of human intracranial EEG data

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[1]Dartmouth College/UPenn MSTP, Philadelphia, PA; [2]Dept. of Psychological and Brain Sci., [4]Psychological and Brain Sci., [3]Dartmouth Col., Hanover, NH; [5]Med. Scientist Training Program, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Intracranial EEG (iEEG) is increasingly used to study cognitive processing, yet group-level inference remains challenging due to sparse electrode coverage within individuals and uneven sampling across participants. These constraints hinder the application of standard permutation-based methods for spatial null modeling, in part because the spatial structure of iEEG signals, particularly during cognitive tasks, is not well characterized. Researchers have typically relied on two main strategies, each with notable trade-offs: channel-level analyses offer limited spatial inference and are prone to multiple comparison issues, while atlas-based approaches impose rigid anatomical boundaries that may obscure distributed effects. To address these challenges, we introduce SMOOTH, a statistical framework that uses spectral resampling to generate topographically constrained surrogate maps that preserve the spatial autocorrelation of the empirical data. We validate this approach by showing that iEEG signals exhibit substantial spatial autocorrelation, making naive spatial shuffling unsuitable for cluster-based inference. Compared to conventional random sign-flipping, SMOOTH offers vastly greater permutation depth and reduces the inflation of null effects in sparsely sampled regions. We show that SMOOTH improves sensitivity of group-level effect detection, even in cognitively complex paradigms. Together, these advances position SMOOTH as a scalable, spatially principled solution for anatomically grounded, data-driven iEEG analysis that avoids reliance on predefined regions of interest.

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Poster

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Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.12/QQ8

Topic: J.07. Data Analysis and Statistics

Support: FINEP
UFRJ
UFPA

Title: Neuroplasticity in response to reading: a deep learning analysis of EEG in adolescents from diverse socioeconomic backgrounds

Authors: *P. V. CHAGAS;
Inst. of Biophysics Carlos Chagas Filho, Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil

Abstract: Adolescence is a critical period for prefrontal cortex (PFC) maturation, significantly influenced by socioeconomic status (SES). Lower SES often correlates with impoverished environments, potentially hindering cognitive development and reading competence. Reading is a potent tool for inducing neuroplasticity. This exploratory study investigated the effects of a systematic reading intervention as an environmental enrichment strategy on adolescent brain activity, particularly in those from lower SES backgrounds. Forty-six (46) adolescents and young adults (12-22 years) were recruited, and divided into three groups: Low SES/Poor Readers (LP; n=20), Low SES/Poor Readers with an 8-12 month reading Intervention (LPE; n=6), and High SES/Enriched Environment Readers (LAE; n=20). Resting-state EEG (22 channels) was recorded. EEG data were band-pass filtered into theta (4-8Hz), alpha (8-13Hz), and beta (13-30Hz) bands. For each subject, data from these bands were segmented into 1-second chunks. The EEGFuseNet, a deep learning model, was employed to extract rich feature embeddings from these multi-band EEG chunks. These embeddings were then used to train a multi-layer perceptron (MLP) classifier with subject-disjoint cross-validation. Our deep learning approach achieved high accuracy (approx. 90%) in a three-class classification distinguishing the LP, LPE, and LAE groups, suggesting distinct neural signatures across these developmental and environmental contexts. Visualization of the EEGFuseNet embeddings via t-SNE revealed clear clustering by group. Notably, the LPE (intervention) group occupied a distinct region in the embedding space, appearing to shift away from the LP group and, in some aspects, towards patterns observed in the LAE group, indicative of intervention-driven neural changes potentially linked to PFC maturation. The LP and LAE groups served as crucial controls, allowing us to assess the specific impact of the reading intervention. These findings demonstrate that systematic reading can act as a powerful environmental enrichment factor, measurably altering brain activity patterns in adolescents. Deep learning analysis of EEG provides a sensitive tool to capture these neuroplasticity changes, offering evidence for the potential of reading programs to mitigate cognitive disparities associated with socioeconomic inequality. This research underscores the importance of promoting literacy to foster positive brain development.

Disclosures: P.V. Chagas: None.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.13/QQ9

Topic: J.07. Data Analysis and Statistics

Support: Internal funding, Department of Neurological Surgery, University of Chicago

Title: The role of the centromedian nucleus in thalamocortical synchronization and cortical propagation of slow oscillations

Authors: *M. ALIPOUR, D. SATZER;
Neurolog. Surgery, Univ. of Chicago, Chicago, IL

Abstract: Slow oscillations (SOs; 0.5-1.5 Hz) are hallmark rhythms of non-REM sleep that support memory consolidation and regulate thalamocortical synchrony. While traditionally considered to originate in the cortex, emerging evidence suggests that the thalamus—particularly the centromedian (CM) nucleus—may play an active, causal role in initiating and shaping the propagation of these rhythms. To investigate the temporal dynamics of this thalamocortical interaction, we analyzed three nights of 24-hour simultaneous scalp EEG and stereo-EEG (SEEG) recordings from a patient with drug-resistant epilepsy. SOs were detected in both CM thalamic and scalp channels and classified into Frontal or Global subtypes based on their spatiotemporal propagation patterns. We then assessed latency and phase relationships between thalamic and cortical SOs using peak timing, Hilbert transform-derived phase angles, and phase-locking metrics. Our analysis revealed that CM SOs consistently preceded cortical SOs by approximately 50 ms, with a more pronounced temporal lead during Frontal SOs compared to Global SOs. Phase-locking analysis further confirmed a significant thalamic lead (mean direction: $-177.7° \pm 2.98°$, Rayleigh test $p < 0.0001$). Additionally, CM SOs associated with Global cortical SOs exhibited significantly greater amplitude and longer duration than those linked to Frontal SOs ($p < 0.01$, Cohen's $d = 0.325$), highlighting distinct thalamic contributions to different SO subtypes. Together, these findings support a leading and modulatory role for the CM thalamus in coordinating cortical SO dynamics. The observed differences in thalamocortical interactions across SO subtypes suggest that the CM nucleus may play a subtype-specific role in driving cortical SO propagation. Ongoing work aims to replicate these findings in a larger dataset, with the goal of informing future closed-loop neuromodulation strategies that leverage thalamic signals to predict and selectively influence cortical brain states.

Disclosures: M. Alipour: None. **D. Satzer:** None.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.14/Web Only

Topic: J.07. Data Analysis and Statistics

Support: NSERC RGPIN-2020-06342
NSERC-Alberta Innovates Supplements 232403195

Title: Characterizing higher-order interactions in EEG using information geometry

Authors: *E. ALBERS[1], P. MARRIOTT[2], M. TATSUNO[1];
[1]Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Statistics and Actuarial Sci., Univ. of Waterloo, Waterloo, ON, Canada

Abstract: Electroencephalography (EEG) analysis has traditionally relied on pairwise measures like coherence and correlation, which limit detection of higher-order neuronal interactions. This study applies a novel framework based on information geometry (IG) to assess first-, second-, and third-order interactions in EEG data during motor imagery tasks. Using a publicly available human EEG dataset (n=32, 19-29 years, mixed sex; Triana-Guzman et al., 2024) recorded during seated and standing postures with imagined sit-to-stand or stand-to-sit movements, we binarized the continuous EEG signals using three methods: two sign-based binarization methods (targeting phase dynamics) and power-threshold binarization (targeting amplitude coupling). Each trial included fixation, cue, imagery, and rest phases. IG measures were derived from binarized signals across EEG channels using the method proposed by Amari (2001) and Nakahara & Amari (2002), and mutual information (MI) was used to relate these measures to task labels. We found that MI was low during fixation but increased during cue and imagination phases. Power-threshold binarization captured both first- and second-order interactions effectively, whereas sign-based methods revealed minimal first-order but stronger second-order structure. Third-order information tended to be low across methods except in the delta frequency band. The analysis pipeline was also applied to white Gaussian noise to confirm the method induces minimal spurious MI. Ongoing statistical testing uses IG-derived test statistics corrected for multiple comparisons to identify regions of significant task-related information**.** In the search for tools that can identify higher-order dependencies in EEG data, this exploratory study validates IG as a promising option. By uncovering task-relevant, higher-order dynamics, this framework has potential implications for both neuroscience research and clinical applications.
Amari, S. (2001). Information geometry on hierarchy of probability distributions. *IEEE Transaction on Information Theory, 45*(5), 1701-1711.
Nakahara, H., & Amari, S. (2002). Information-geometric measure for neural spikes. *Neural Computation, 14*, 2269-2316.
Triana-Guzman, N., Orjuela-Cañon, A.D., Jutinico, A.L., Mendoza-Montoya, O., & Antelis, J.M. (2024). EEG data offline and online during motor imagery for standing and sitting. OpenNeuro Dataset ds005342.

Disclosures: E. Albers: None. **P. Marriott:** None. **M. Tatsuno:** None.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.15/QQ10

Topic: J.07. Data Analysis and Statistics

Support: NIH 1R01MH125934
NIH 1R01MH126700

NIH 5R01NS047293
NIH 5R24MH120037
The Swartz Foundation

Title: Streamlined Large-Scale EEG Analysis Using HED-BIDS Tools: A FAIR Approach to the Healthy Brain Network Dataset

Authors: *S. SHIRAZI[1], A. DELORME[2], A. FRANCO[3], M. P. MILHAM[3], S. MAKEIG[2]; [1]Inst. for Neural Computation, Univ. of California San Diego, San Diego, CA; [2]Inst. for Neural Computation, Univ. of California San Diego, La Jolla, CA; [3]Child Mind Inst., New York, NY

Abstract: Large-scale neuroimaging studies require standardized, reproducible analysis pipelines that can efficiently process thousands of datasets while maintaining scientific rigor. Traditional EEG analysis workflows often involve custom scripts and manual processing steps that limit reproducibility and scalability. We show integrating HED (Hierarchical Event Descriptors) and BIDS (Brain Imaging Data Structure) tools create a streamlined, FAIR-compliant pipeline for analyzing massive EEG datasets.We analyzed Release 3 of the Healthy Brain Network dataset (185 young subjects, 63 female, 10.0 ± 3.41 years; 128 scalp channels; six tasks: including resting, movie watching, memory, pattern matching, and SSVEP) available at NEMAR.org. The EEGLAB EEG-BIDS toolbox automatically constructed STUDY structures from the BIDS-formatted data, enabling batch processing across all subjects. The preprocessing pipeline included high-pass filtering (1-Hz cutoff), line noise removal channel and frame rejection, and AMICA to decompose the data into independent effective source components (ICs). We excluded 24 subjects from further analysis due to incomplete or poor quality data. We kept sources with > 70% likelihood of brain features as computed by ICLABEL. Clustering on source locations, scalp maps, and power spectra found 7 source clusters at the central, parietal, and visual areas with ICs from >50% of the subjects. We found two more clusters near the cingulate cortex with ICs from >45% of the subjects.We leveraged embedded HED-coded event information to extract visual presentation events containing abrupt contrast changes (movie shots, SSVEP stimuli) using HED-matlab-tools. Data were epoched from -0.6 to 1.5 seconds around contrast change boundaries. We computed time-frequency decompositions on the source-localized data to assess spectral power changes during visual processing. We used the EEGLAB STUDY framework to perform statistical comparisons across subjects and source clusters. The entire analysis required fewer than 300 lines of MATLAB code. Here, BIDS automatically handled dataset heterogeneity and metadata management, and HED streamlined event-related epoch extraction. EEGLAB STUDY functions facilitated seamless cross-subject analysis and statistical testing. This approach transforms large-scale EEG analysis from a labor-intensive workflow to automated operation of reproducible pipelines, enabling researchers to focus on scientific discovery rather than technical implementation and making large-scale data meta- and mega-analyses feasible using local or open high-performance clustering computation (NSGportal.org) resources.

Disclosures: S. Shirazi: None. **A. Delorme:** None. **A. Franco:** None. **M.P. Milham:** None. **S. Makeig:** None.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.16/QQ11

Topic: J.07. Data Analysis and Statistics

Support: Gift from The Swartz Foundation

Title: Ai-enhanced tools for hierarchical event descriptor (hed) annotation of neuroscience time series data

Authors: *S. MAKEIG[1], S. SHIRAZI[2];
[1]Swartz Ctr. for Computat. Neurosci., La Jolla, CA; [2]Swartz Ctr. for Computat. Neurosci., Univ. of California San Diego, San Diego, CA

Abstract: Accurate annotation of experimental events and stimuli is fundamental to neuroscience research, enabling reproducible analyses and cross-study comparisons. Hierarchical Event Descriptors (HED) is an INCF-endorsed FAIR facility for annotating experiment events in a both machine-readable and human-understandable format. HED uses hierarchical vocabulary trees to systematically describe participant experience and behavior, experiment conditions, and/or data events - thereby facilitating data archiving, sharing, meta-analyses, and automated processing across studies. HED schemas are extensible beyond its base vocabulary, in particular through specialized term library extensions, currently including HED-SCORE for EEG epilepsy annotations and HED-Lang for language annotation. A complete HED system specification and a powerful HEDtools toolbase are now available, but HED adoption has been limited by the need for HED annotators to master HED syntax. We have therefore developed three AI tools to automate HED annotation generation and validation. HED-BOT employs multi-agent architecture to convert natural language event descriptions (e.g., paper Methods sections) into valid HED annotations. The system includes an Annotation agent creating initial tags, a Validation agent checking HED compliance using online HED validation tools, and an Evaluation agent providing iterative refinement feedback. The agentic annotation-validation-evaluation cycle continues until a validation passes, followed by an Assessment agent to assist annotators in comparing generated HED tags against the original event descriptions so as to identify still-missing elements or dimensions.HED-VLM represents vision-language models fine-tuned for direct image-to-HED annotation. We fine-tuned Google Gemma 3 (4B parameters) using HED descriptions from 1000 Natural Scene Dataset (NSD) images, enabling automated visual stimulus annotation without intermediate text descriptions.HED-MCP implements a Model Context Protocol (MCP) server integrating HED tools with large language models. This leverages existing HED Python libraries and online validation services, enabling users to create baseline annotations, validate existing annotations, and request automated error corrections through natural language interactions.These tools collectively address major HED adoption barriers by automating annotation creation from multiple input modalities while ensuring compliance with HED standards.

Disclosures: S. Makeig: None. **S. Shirazi:** None.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.17/QQ12

Topic: J.07. Data Analysis and Statistics

Support: Coleman Fung Foundation
Charley Sinclair Foundation

Title: Using alternative EEG pre-processing pipelines can significantly influence study conclusions regarding cortical excitation/inhibition ratio

Authors: *F. S. RACZ[1], D. A. MAC-AULIFFE[3], P. MUKLI[4], J. G. MILTON[1], J. CABRERA FERNÁNDEZ[5], J. MILLAN[2];
[1]Dept. of Neurol., [2]Electrical and Computer Engineering; Neurol., The Univ. of Texas at Austin, Austin, TX; [3]Chandra Dept. of Electrical and Computer Engin., Univ. of Texas at Austin, Austin, TX; [4]The Univ. of Oklahoma, Oklahoma City, OK; [5]Univ. Politécnica de Madrid, Madrid, Spain

Abstract: Recent evidence suggests that cortical excitation/inhibition (E/I) ratio is correspondent to the spectral slope, β , i.e. the rate at which the power of brain waves decreases as frequency increases. While methodology for estimating β is mostly consistent in the literature, there is a lack of standardization among data processing protocols for slope analysis. Here we show that by applying different pre-processing steps to the same electroencephalography (EEG) data, conflicting conclusions related to the E/I ratio can arise. We analyzed resting-state EEG recordings using two distinct spatial filtering schemes: common average referencing (CAR) and small Laplacian filtering (SL). EEG was collected from eyes-open (EO) and eyes-closed (EC) states, with the latter considered a physiological state with stronger inhibitory tone. We hypothesized a decrease in E/I ratio (i.e., steepening of slope) when transitioning from EO to EC, predominantly over parietooccipital regions. Spectral slopes were estimated from representative prefrontal (PF) and parietooccipital (PO) scalp locations using the Irregular-Resampling Auto-Spectral Analysis (IRASA) technique, independently for low- (1-4 Hz, β*lo*) and high-frequency (20-45 Hz, β*hi*) regimes. For robustness, we carried out the complete analysis on two independent datasets (18 and 20 young, healthy volunteers, respectively). Our analyses demonstrated in both cohorts that the choice of spatial filtering scheme in an otherwise identical analytical pipeline can significantly alter study inferences. Specifically, using CAR indicated a decrease in E/I ratio both over the PF and PO cortices when transitioning from EO to EC ($p<0.007$, Cohen's $d>0.71$ for both). In contrast, when applying SL an increase in E/I ratio could be inferred only over the PO ($p<10^{-4}$, Cohen's $d=0.75$) but not the PF cortex, in line with expectations. Furthermore, while the commonly observed β*lo*<β*hi* bimodality pattern (steeper spectrum in high-frequency regime) was ubiquitously observed in the CAR pipeline ($p<10^{-4}$, Cohen's $d=1.84$ both regions) in EC, this pattern reversed (β*lo*>β*hi*) over the PF (but not PO) cortex when using SL ($p<10^{-4}$, Cohen's $d=1.65$). Finally, we observed comparable outcomes in terms of CAR vs. SL when obtaining β from broadband (1-45 Hz) data, as well as when using a different tool instead of IRASA (the SpecParam Toolbox) for slope estimation. This empirical evidence indicates that various data manipulations can have substantial effects on study

outcomes, and therefore calls for the development of a standardized data processing protocol for EEG-based analyses of the E/I ratio.

Disclosures: F.S. Racz: None. **D.A. Mac-Auliffe:** None. **P. Mukli:** None. **J.G. Milton:** None. **J. Cabrera Fernández:** None. **J. Millan:** None.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.18/QQ13

Topic: J.07. Data Analysis and Statistics

Support: NSF GRFP (2234657)
NIH NINDS JSTPN T32NS131178
Boston University Department for Mathematics and Statistics
Boston University Center for Systems Neuroscience

Title: Neural power spectral decomposition methods suffer from model misspecification, which leads to estimation bias and misinterpretation

Authors: *P. F. BLONIASZ[1], E. P. STEPHEN[2];
[1]Grad. Program for Neurosci., [2]Mathematics and Statistics, Boston Univ., Boston, MA

Abstract: Power spectra of neural voltage recordings (e.g., local field potentials, LFP; electroencephalography, EEG) are widely considered to track physiological changes in various behaviors and brain states through narrowband (rhythmic) and broadband (aperiodic, spanning a large frequency range) information. Broadband effects have gained interest because they are thought to be associated with asynchronous population activity and the relative dominance of dynamic processes with different timescales (e.g. excitatory/inhibitory synaptic activity). To study broadband effects, several power spectral decomposition methods have been developed to algorithmically decompose a signal into rhythmic and broadband components, resulting in numerous robust findings across brain states such as sleep or anesthesia-induced unconsciousness. However, many existing decomposition approaches have critical model misspecifications which can lead to systematic errors in the estimation and interpretation of observed power spectral effects. We use statistical theory and simulation to demonstrate how two types of model misspecification can lead to misinterpretations of neural power spectra; we provide a solution to each. First, under the well-accepted standard model, LFPs are well-modeled by a linear-additive superposition of biophysical processes. In contrast, several decomposition methods implicitly assume a multiplicative superposition. Second, time-domain LFPs are typically modeled by Gaussian processes—so the empirical power spectra would be Gamma distributed, with variance scaling with power. However, many decomposition methods use a Gaussian model for neural power spectra and assume homoscedasticity in variance. We address each issue and demonstrate that correct model specification leads to more accurate

decompositions. Likewise, we demonstrate that by coupling decomposition with a statistically well specified forward modeling framework (Filtered Point Processes, FPPs), broadband decompositions can be directly interpreted as the population firing rate and the rhythmic power of the rate process of each modeled biophysical process. Based on these results, we recommend that researchers take caution in interpreting the results of existing spectral decomposition techniques, specifically regarding the presence/height of rhythmic components and the height/slope of broadband components. Interpreting the power spectrum of neural voltage recordings in biophysical terms requires biophysically grounded statistical models with empirical validation; we provide several tools to assist researchers with spectral decomposition.

Disclosures: P.F. Bloniasz: None. **E.P. Stephen:** None.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.19/QQ14

Topic: J.07. Data Analysis and Statistics

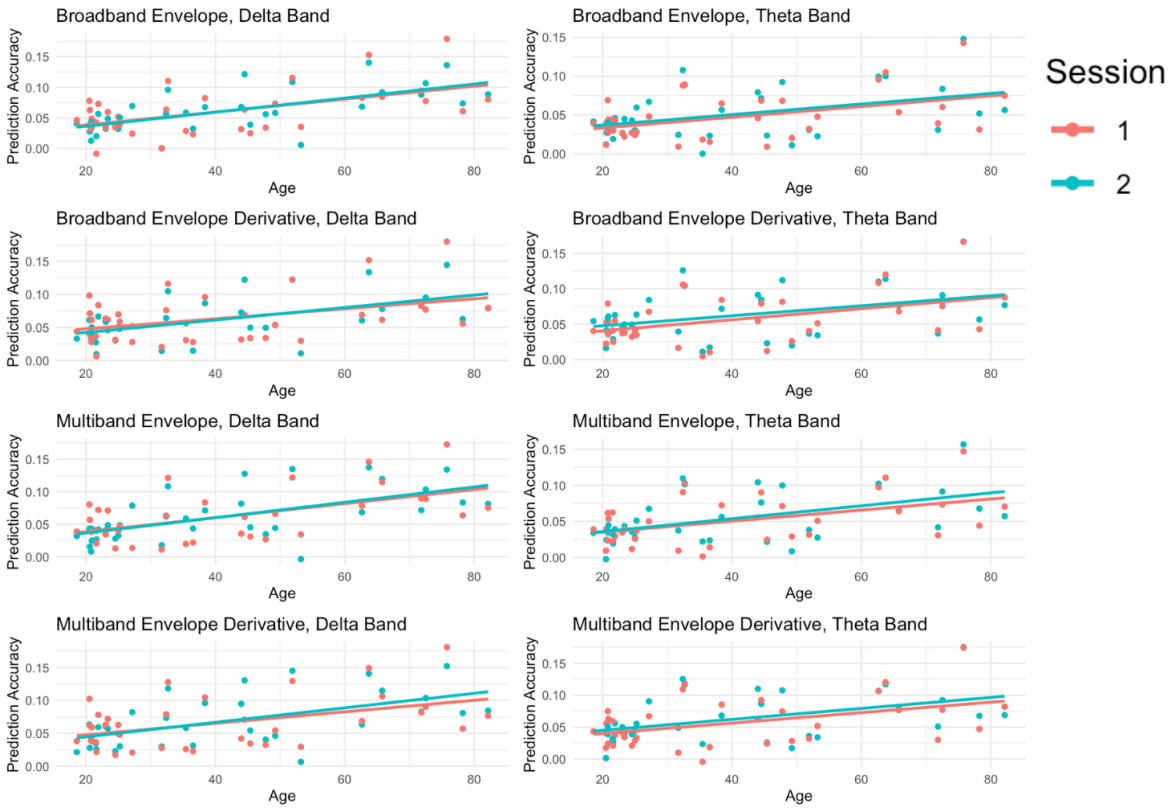
Support: NIH/NICHD R25HD106896
NIH/NIDCD R21DC021497

Title: Test-retest reliability of temporal response function measures across the lifespan

Authors: *C. DOXAKIS[1], H. DIAL[1], G. GNANATEJA[2];
[1]Univ. of Houston, Houston, TX; [2]Univ. of Pittsburgh, Oakland, PA

Abstract: Temporal Response Function (TRF) modelling is an ecologically valid tool used to assess cortical processing of continuous speech across the lifespan. However, the test-retest reliability for different envelope models and EEG frequency bands has not been assessed as a function of age. In this study we assessed test-retest reliability for different stimulus features (multiband envelope and its derivative, broadband envelope and its derivative) and EEG frequency bands (delta: 1-4Hz, theta: 4-8Hz). Participants (n = 36, age M = 40.3, range = 18.6 - 82.1, SD = 18.7) listened to a professionally recorded audiobook written at a 6th grade level while EEG was recorded on two separate sessions. TRF modelling was used to estimate a function to map stimulus features to the EEG for each frequency band. To assess test-retest reliability, prediction accuracy (Pearson's correlation between the TRF-predicted and observed EEG) was used as the outcome measure for a linear mixed-effects regression with main effects of age and session, their interaction, and a random intercept for participant. The model was run separately for each electrode (62 channel 10-20 system), although only channel Cz is reported for brevity. Session and the session-by-age interaction were the effects of interest for assessing test-retest reliability. Across models, neither session nor the session-by-age interaction were statistically significant (see fig. 1). This indicates that TRF-prediction accuracy was reliable across sessions and that reliability did not differ according to age. Taken together, this suggests

that TRF-derived measures of cortical tracking of broadband and multiband envelopes and their derivatives are reliable across the lifespan.



Disclosures: C. Doxakis: A. Employment/Salary (full or part-time): University of Houston. **H. Dial:** A. Employment/Salary (full or part-time): University of Houston. 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/NIDCD (R25HD106896). **G. Gnanateja:** A. Employment/Salary (full or part-time): University of Pittsburgh. 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.; Wisconsin Alumni Research Foundation, College of Letters and Sciences at the University of Wisconsin-Madison.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.20/QQ15

Topic: J.07. Data Analysis and Statistics

Support: AS-HLGC-113-04

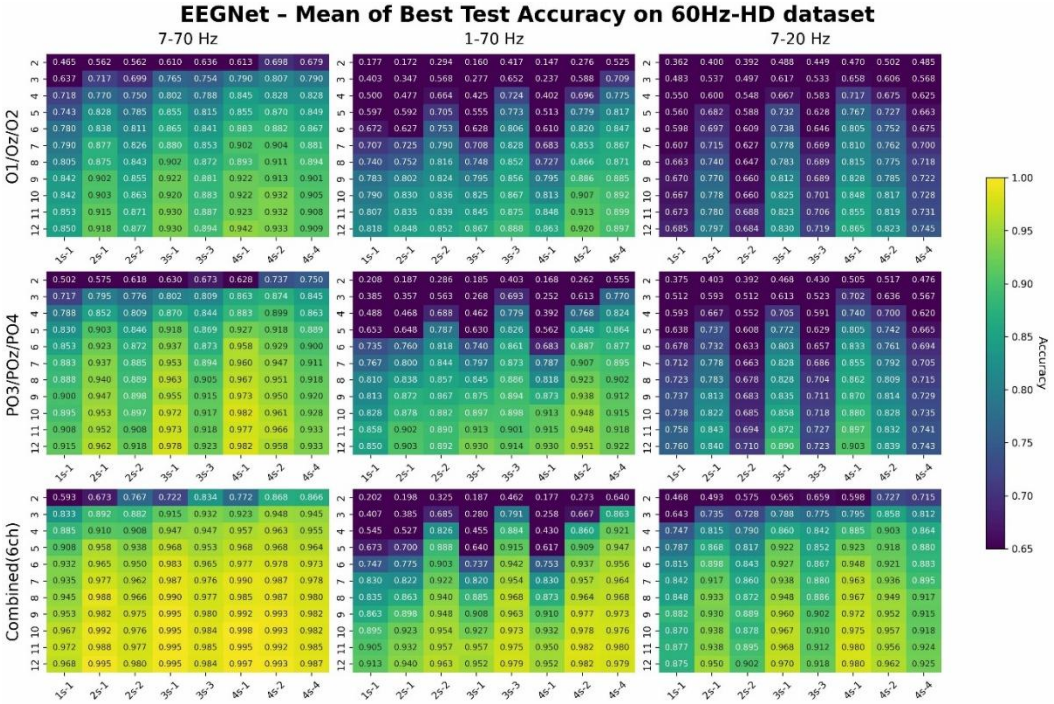
Title: Factor Analysis of SSVEP-Based Biometric Authentication: A Pilot Study

Authors: Y.-C. HSU, *Y.-T. WANG;
Academia Sinica, Taipei, Taiwan

Abstract: Electroencephalography (EEG)-based biometric authentication leverages individual neural signatures, offering high resistance to forgery. Steady-state visual evoked potentials (SSVEPs) are well-suited for such applications due to their high signal-to-noise ratio and minimal training needs. However, the influence of electrode selection and EEG data processing pipelines on system performance remain unclear.

This study examined how EEG channel selection and filter design affect person classification in SSVEP-based systems. Using two public datasets (YSU-CS and 60Hz-HD), we compared occipital (O1, Oz, O2), parieto-occipital (PO3, POz, PO4), and combined (all six channels) configurations under different bandpass filters (1-70, 7-70, and 7-20 Hz). Three convolutional neural networks (EEGNet, ShallowConvNet, DeepConvNet) were evaluated using 5-fold leave-one-block-out (LOBO) cross-validation.

Results show that parieto-occipital electrodes outperformed occipital-only configurations in most cases across models and datasets (see Figure 1 for EEGNet example), suggesting these regions may carry stronger subject-specific features. Additionally, while wider bandpass filters preserved classification performance, narrow filtering (e.g., 7-20 Hz) degraded the classification accuracy. These findings highlight spatial and spectral factors that shape SSVEP-based person authentication, providing more robust EEG-based biometric systems for BCI systems.



Disclosures: Y. Hsu: None. **Y. Wang:** None.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.21/QQ16

Topic: J.07. Data Analysis and Statistics

Support: Internal Departmental Funds

Title: Non-linear dimensionality reduction using manifold learning: validating source-localized magnetoencephalographic signal features and characterizing neurophysiological subgroups with umap

Authors: ***E. D. BERI**[1], J. BURDE[2], J. URRUTIA[2], J. A. CORTES[2];
[1]Psychiatry, Yale Sch. of Med., New Haven, CT; [2]Yale Univ., New Haven, CT

Abstract: Magnetoencephalography (MEG) offers a transformative window into brain dynamics, capturing millisecond-scale fluctuations in neural activity with unparalleled temporal precision. Unlike other neuroimaging modalities, MEG leverages how magnetic fields pass freely from brain to sensor, enabling accurate source localization of brain activity. These attributes position MEG as a powerful tool for decoding complex brain network functions and probing the neural underpinnings of neuropsychiatric disorders. Schizophrenia (SCZ)—a heterogeneous disorder marked by positive symptoms (e.g., hallucinations), negative symptoms (e.g., blunted affect), and cognitive deficits (e.g., attention and memory impairments)—remains poorly understood at the systems level. One of the key challenges in MEG-based psychiatric neuroscience is navigating the high-dimensional data space (n_subjects, n_trials, n_brainRegions, n_times). To address this, we introduce a novel framework that integrates advanced feature extraction with nonlinear dimensionality reduction to distill meaningful patterns from complex MEG datasets. In the present study, we collected MEG and structural MRI data from 48 individuals (33 SCZ, 15 non-SCZ) performing a spatial working memory task. Using Linearly Constrained Minimum Variance (LCMV) beamforming, we localized MEG signals to 75 regions of interest and extracted neurophysiological features across task phases—encoding, maintenance, and response. This anatomical grounding enhances interpretability by linking dynamic activity to specific brain regions while reducing cross-talk from non-relevant sources. To evaluate the discriminative power of these features, we applied Uniform Manifold Approximation and Projection (UMAP), a cutting-edge nonlinear dimensionality reduction technique. UMAP revealed distinct low-dimensional embeddings that clustered according to neuropsychological subgroup, indicating that features of the neural power spectra and functional connectivity patterns are informative markers of disease state. Our findings demonstrate the feasibility of using source-localized MEG features, combined with modern machine learning, to uncover latent neurophysiological structures that distinguish clinical populations. This work charts a path toward lightweight, interpretable, and precise biomarkers for psychiatric disorders—paving the way for a new era of precision psychiatry and individualized neuroscience.

Disclosures: E.D. Beri: None. **J. Burde:** None. **J. Urrutia:** None. **J.A. Cortes:** None.

Poster

PSTR146: Data Analysis and Statistics: Human Encephalography

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR146.22/QQ17

Topic: J.07. Data Analysis and Statistics

Support: ATLA JPJ004596
JSPS KAKENHI 21K07269
JSPS KAKENHI 24K15691

Title: Phase-locked activities of resting-state networks that transiently occur in human resting-state brain activities

Authors: *Y. TAKEDA[1], N. HIROE[2], O. YAMASHITA[1];
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Abstract: Spontaneous brain activities at rest are organized into resting-state networks (RSNs), such as the default mode network (DMN). The DMN has been reported to serve as a cortical hub that interacts with other networks, such as the visual and sensorimotor networks. Therefore, its activity is assumed to play a role in integrating different types of information distributed over the brain, such as visual and motor information. However, it is not clear how the DMN interacts with these networks at a fine temporal resolution. In this study, we reveal this process from human resting-state magnetoencephalography (MEG) data at millisecond-scale temporal resolution. From 617 subjects' resting-state MEG data, we used our recently proposed method, BigSTeP, to estimate the spatiotemporal patterns that repeatedly occur in resting-state brain activities. Within 100-300 ms, the spatiotemporal patterns had multiple frequency components, each of which transiently exhibited spatial patterns resembling well-known RSNs of fMRIs, such as the DMN. To detect the interactions across RSNs, we examined their timing relationship in the spatiotemporal patterns. As a result, in the alpha band component, the DMN and the visual network were alternately activated with a lag of about 25 ms, which is about 1/2 π rad in the alpha oscillation. In the beta band components, the DMN and the sensorimotor network alternately activated with a lag of about 13 ms, which is also about 1/2 π rad in the beta oscillation. These results suggest that the DMN interacted with the visual/sensorimotor network due to the phase-locked activities in the alpha/beta band with a lag of about 1/2 π rad. These orthogonal activities in the multiple frequencies may reflect the brain's strategy to achieve both the integration and separation of visual and sensorimotor information. Furthermore, we revealed how these activities consecutively moved between the DMN and the visual/sensorimotor network in tens of milliseconds. They moved in different ways depending on their direction (e.g., from DMN to visual network or from visual network to DMN), suggesting that different mechanisms generated the movements in different directions.

Disclosures: Y. Takeda: None. **N. Hiroe:** None. **O. Yamashita:** None.

Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR147.01/QQ18

Topic: J.04. Physiological Methods

Title: Transcranial direct current stimulation exerts therapeutic effects on balance function and locomotion activity in a rat model of brain tumor

Authors: *W.-Y. YEH[1], T.-H. HSIEH[2];
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Abstract: Abstract: Glioblastoma (GBM) is the most common and aggressive primary brain tumor, characterized by poor survival despite multimodal treatments such as surgery, radiation, and chemotherapy. While current therapies focus on prolonging survival, strategies to improve motor function remain insufficient. Given the ongoing need for alternative supportive therapies, transcranial direct current stimulation (tDCS) is a promising non-invasive neuromodulation technique known to facilitate neuroplasticity and motor recovery in neurological disorders, but its potential therapeutic benefits in GBM are not fully understood. To investigate the therapeutic effects of tDCS, we employed a rat brain tumor model established by implanting C6 glioma cells into the left telencephalon of male Sprague-Dawley rats. Animals were randomly assigned to receive either sham stimulation or anodal tDCS (0.8 mA/cm², 20 minutes/day, 7 days/week for 3 weeks). Behavioral assessments were performed using an open-field test to evaluate locomotor activity, a beam-walking test to measure motor coordination, and a novel object recognition test to assess cognitive function. Our results showed that rats receiving tDCS exhibited a significant delay in motor decline compared to the sham group, suggesting that tDCS intervention effectively postponed the deterioration of motor abilities in this GBM model. However, no notable improvements were detected in cognitive function following tDCS treatment. In conclusion, tDCS demonstrates potential in delaying motor dysfunction progression in a rat model of GBM. These findings support the use of tDCS as a complementary neuromodulatory strategy and provide translational insights into developing supportive therapies for GBM patients.

Disclosures: W. Yeh: None. **T. Hsieh:** None.

Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR147.02/QQ19

Topic: J.04. Physiological Methods

Title: Contribution of phase amplitude coupling to event related potentials

Authors: *K. RAJENDRAN[1], S. T. FIX[1], D. BUTLER[1], V. R. STEELE[3], S. AVIYENTE[4], E. BERNAT[2];
[2]Psychology, [1]Univ. of Maryland, College Park, MD; [3]department of psychiatry, Yale school of medicine, New Haven, CT; [4]Michigan State Univ., Okemos, MI

Abstract: Cross-frequency coupling (CFC) has been widely implicated in cognitive processes such as learning, memory, goal-directed behaviour, and reward-related processing(Jensen & Colgin, 2007). One specific type of CFC is Phase amplitude Coupling (PAC), which quantifies how the phase of a lower-frequency oscillation influences the amplitude of a higher-frequency oscillation (Onslow et al., 2011). PAC is increasingly recognized as a mechanism of functional connectivity, providing insight into how different neural populations communicate(Marzetti et al., 2019). Whereas traditional measures of connectivity focus on activity within a single frequency band or between two electrodes, PAC captures interactions across frequencies. In our study, we explore how PAC contributes to event-related potentials (ERPs), specifically the P3 component, which is implicated in response inhibition within a Go/No-Go paradigm(Aron et al., 2003; Wessel & Aron, 2015).
We applied our time-frequency PAC approach to a Go/No-Go dataset involving 170 participants(85 men, Mean age = 35.57 years, SD = 10.16) . Analyses were conducted separately for the Go and No-Go conditions and for two electrode sites: CPZ and FPZ. PAC was computed between the phase of frequencies from 1 to 12 Hz and the amplitude of frequencies ranging from 1 to 50 Hz. To examine the relationship between oscillatory neural features—including amplitude, inter-trial phase synchrony (ITPS), inter-channel phase synchrony (ICPS), and PAC—and the P3 ERP, we conducted shared and unique variance analyses. Compared to traditional measures, PAC uniquely accounted for additional variance in P3 mean amplitude across several conditions. Specifically, PAC explained an additional 10.31% of the variance for CPZ Go trials, 21.39% for CPZ NoGo trials, 20.79% for FPZ NoGo trials and -0.24% for FPZ Go trials. These findings suggest that PAC captures unique neural dynamics not reflected by traditional measures, especially during No-Go trials, where cognitive control demands are higher and PAC contributes more robustly to explaining P3 variability.
To further understand the relationship between PAC and other measures such as ICPS, ITPS, and time-frequency amplitude, we also examined the shared variance between these measures. We found that these measures share a modal variance of 4.5% (range = [−1.76, 62.67] depending on electrode site, task condition, and frequency). Assessing this shared variance could provide insight into the role of PAC in generating these other conventional neural measures. For example, future work should focus on the time course of PAC relative to other measures, i.e ICPS, ITPS and time-frequency amplitude.

Disclosures: K. Rajendran: None. **S.T. Fix:** None. **D. Butler:** None. **V.R. Steele:** None. **S. Aviyente:** None. **E. Bernat:** None.

Poster

PSTR147: Stimulation Methods

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR147.03/QQ20

Topic: J.04. Physiological Methods

Support: Turkish National Science and Research Council (No. 122R056)

Title: Visual and Auditory 40 Hz Gamma Entrainment Alters Oscillatory Brain Activities of Healthy Middle-Aged Adults

Authors: *B. GÜNTEKIN[1], F. ERDAL[2], A. AKAN[1], S. ÖZDEMIR[1], H. YIRIKOGULLARI[1], E. ÜNSAL[1], R. KAHVECI[1], Y. BALCI[3], S. ALPTEKIN[1], G. KARADAG[1], Y. VAROLGÜNES[1], B. BAS[1], T. AKTÜRK[4];
[1]Istanbul Medipol Univ., Istanbul, Turkey; [2]Istanbul Medipol University, Marmara Univ., Istanbul, Turkey; [3]Yeditepe Univ., Istanbul, Turkey; [4]Maastricht Univ., Maastricht, Netherlands

Abstract: In recent years, there have been growing findings that 40 Hz visual and auditory gamma entrainment enhances Alzheimer's disease symptoms in animal models. Together with this, it is another question how 40 Hz visual and auditory gamma entrainment affects healthy middle-aged people. For investigating this question, in this work, we compare oscillatory brain activities of healthy middle-aged participants in spontaneous EEG. Healthy middle-aged participants, who were between 44-65 years old, included either 40 Hz visual and auditory gamma entrainment (Entrainment, $n = 15$), or 40 Hz transcranial alternating current stimulation (tACS, $n = 12$), or control groups (Control, $n = 16$). In the entrainment group, participants received 40 Hz visual and auditory stimulation for 60 minutes per day across 10 days. In the tACS group, participants received 40 Hz tACS for 20 minutes per day across 10 days, with stimulation applied to the TP7, FT7, CP3, and O1 electrode locations. In the control group, participants did not receive any stimulation. Spontaneous EEG recordings in eyes-opened (EO) and eyes-closed (EC) conditions of participants were recorded before the applications (Pre), after the first application (Post-1), and after the last application (Post-10) for all groups. Results of the spontaneous EEG analysis revealed that the alpha dominant peak frequency power of entrainment group ($M = .69$, $SE = .11$) was higher than control ($M = .36$, $SE = .10$), $p = .02$ and marginally higher than tACS groups ($M = .40$, $SE = .11$), $p = .058$ in EO. Also, for the beta dominant peak frequency power, entrainment group ($M = .12$, $SE = .01$) was higher than tACS ($M = .08$, $SE = .01$), $p = .043$, and control groups ($M = .07$, $SE = .01$), $p = .006$ in EO. Furthermore, gamma dominant peak frequency power of entrainment group ($M = .037$, $SE = .003$) was higher than tACS ($M = .024$, $SE = .003$), $p = .003$ and control groups ($M = .021$, $SE = .003$), $p < .001$ in EO. Lastly, in EC, gamma dominant peak frequency power of control group ($M = .019$, $SE = .003$) was lower than entrainment ($M = .030$, $SE = .003$), $p = .003$ and tACS groups ($M = .028$, $SE = .003$), $p = .014$. The results of our study showed that 40 Hz visual and auditory gamma entrainment enhanced not only the gamma dominant peak frequency power but

also alpha and beta frequencies. In future research, these effects on the performance of middle-aged participants should be examined.

Disclosures: B. Güntekin: None. **F. Erdal:** None. **A. Akan:** None. **S. Özdemir:** None. **H. Yirikogullari:** None. **E. Ünsal:** None. **R. Kahveci:** None. **Y. Balci:** None. **S. Alptekin:** None. **G. Karadag:** None. **Y. Varolgünes:** None. **B. Bas:** None. **T. Aktürk:** None.

Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

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Program #/Poster #: PSTR147.04/RR1

Topic: J.08. Methods to Modulate Neural Activity

Support: FA9550-23-1-0724
FA9550-20-0061
P20 GM103650

Title: Electrical preconditioning with nanosecond pulses lowers stimulation threshold in adrenal chromaffin cells

Authors: J. MORENO DURAN, N. BUENAVENTURA, *J. ZAKLIT;
Univ. of Nevada, Reno, NV

Abstract: Preconditioning to modulate cellular excitability is a well-established strategy in neuromodulation, used in transcranial magnetic stimulation and transcranial direct current stimulation, where subthreshold stimulation alters neuronal responsiveness to subsequent stimuli. This concept extends beyond the nervous system. In cardiovascular research, electrical preconditioning has been explored as a strategy to enhance cellular resilience to ischemic injury. Our group is developing a novel electrostimulation modality using nanosecond-duration electric pulses (NEP) to modulate adrenal medullary chromaffin cells (CC), the body's primary source of catecholamines. NEP offer the potential for deep, targeted, and non-invasive stimulation and have been shown to activate various excitable cells, including neurons, cardiac myocytes, and peripheral nerves. In CC, we have previously demonstrated that a single 5 ns applied at a threshold electric (E)-field (defined as the lowest field intensity at which 100% of cells respond) of 10 MV/m pulse triggers Ca2+-dependent catecholamine release, mimicking physiological activation. However, widespread application of NEP is limited by the requirement for high E-field strengths. To address this, we explore subthreshold NEP preconditioning to enhance CC excitability and reduce the required stimulation E-field threshold. Using real-time fluorescence Ca2+ imaging, our preliminary data showed that a test stimulus delivered at a lower E-field of 6 MV/m failed to evoke Ca2+ responses in all cells, activating only two out of six cells. However, when CC were preconditioned with a subthreshold train of four 5 ns pulses at 5 MV/m applied at 2 Hz, which alone produced no detectable Ca2+ response, all cells subsequently exhibited a transient rise in [Ca2+]i in response to the same 6 MV/m. Of note is that E-field

intensities were computed in Sim4Life software. These findings indicate that subthreshold NEP preconditioning enhances cellular excitability, effectively lowering the stimulation threshold and enabling lower-intensity NEP to trigger physiological-like responses. Ongoing work aims to optimize conditioning parameters (pulse amplitude, duration, frequency, and number) to further lower the E-field intensity. Experiments using voltage-sensitive dyes and electrophysiological recordings will assess changes in membrane potential to elucidate underlying mechanisms of cell excitability. These studies will provide new insights into how subthreshold NEP preconditioning alters cellular excitability and may enable the development of more energy-efficient and safer neuromodulation protocols using NEP.

Disclosures: J. Moreno Duran: None. **N. Buenaventura:** None. **J. Zaklit:** None.

Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR147.05/RR2

Topic: J.08. Methods to Modulate Neural Activity

Support: KHIDI Grant HI22C0520
NRF Grant RS-2024-00458451

Title: Real-world effects of home-based transcranial direct current stimulation in depression: a randomized controlled trial of 3-week vs. 6-week protocols

Authors: *W. KIM;
Yonsei Univ., Yongin-si, Gyeonggi-do, Korea, Republic of

Abstract: *Background*: This study evaluated the clinical effectiveness, cognitive impact, and safety of home-based transcranial direct current stimulation (tDCS) in patients with major depressive disorder (MDD). Two stimulation protocols were compared: a 3-week active plus 3-week sham protocol (3WA) and a 6-week active protocol (6WA). *Methods*: In this randomized controlled trial, 197 participants with MDD were assigned to either 3WA (n=89) or 6WA (n=108). Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI) and Montgomery-Åsberg Depression Rating Scale (MADRS), while cognitive performance was measured using the Digit Symbol Substitution Test (DSST). Adverse events were monitored, and associations with psychotropic medication were analyzed using logistic regression. *Results*: Both groups showed significant reductions in depressive symptoms. Linear mixed-effects models revealed a significant main effect of time on BDI ($F=33.671$, $p<.001$) and MADRS ($F=34.499$, $p<.001$), but no significant group (BDI: $p=.365$; MADRS: $p=.511$) or group-by-time interaction effects (BDI: $p=.862$; MADRS: $p=.662$), indicating comparable efficacy across protocols. DSST scores improved significantly over time ($F=55.754$, $p<.001$), with no significant group differences ($p=.617$) or interactions ($p=.354$), indicating similar cognitive benefits. A total of 76 adverse events were reported, mostly mild and dermatologic (e.g., stinging: n=40; itching: n=11).

Non-medicated participants had a lower risk of adverse events (OR=0.187, 95% CI: 0.039-0.900, p=0.037). Tianeptine was the only drug significantly associated with increased adverse events (OR=6.073, 95% CI: 1.533-24.059, p=0.01); no associations were found for other medication classes. *Conclusions*: Home-based tDCS led to significant improvements in depressive symptoms and cognitive function. The 3- and 6-week protocols yielded comparable outcomes, suggesting shorter treatments may suffice. These results support the practicality of at-home tDCS and underscore the need to consider pharmacotherapy when evaluating safety.

Disclosures: W. Kim: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Ybrain Co., Ltd..

Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR147.06/RR3

Topic: J.08. Methods to Modulate Neural Activity

Title: Directional dependency of injected currents in temporal interference stimulation

Authors: *H. SOROUSHI, Y. LEI;
Dept. of Kinesiology & Sport Mgmt., Texas A&M Univ., College Station, TX

Abstract: Temporal Interference Stimulation (TIS) offers a promising noninvasive approach to modulate deep brain regions by leveraging the interference of high-frequency electric fields. In this study, we investigated the impact of current vector orientation on TIS efficacy, specifically targeting both superficial (primary motor cortex, M1) and deep (thalamus) brain regions. Individualized T1-weighted MRI scans were used to optimize targeting and personalize stimulation parameters for each subject. Healthy participants were recruited, and experimental conditions were designed to compare orthogonal versus parallel current injection orientations. To assess changes in cortical and subcortical excitability, we employed transcranial magnetic stimulation (TMS) and EEG both before and after TIS, quantifying neurophysiological modulation through motor evoked potentials (MEPs) and sensory-evoked potentials (SEPs). Our results revealed a clear distinction in neural excitability patterns between the two injection configurations, supporting prior hypotheses about TIS's directionality sensitivity. These findings underscore the importance of current vector orientation in optimizing stimulation outcomes and contribute to the growing understanding of TIS mechanisms in human applications.

Disclosures: H. Soroushi: None. **Y. Lei:** None.

Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

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Program #/Poster #: PSTR147.07/RR4

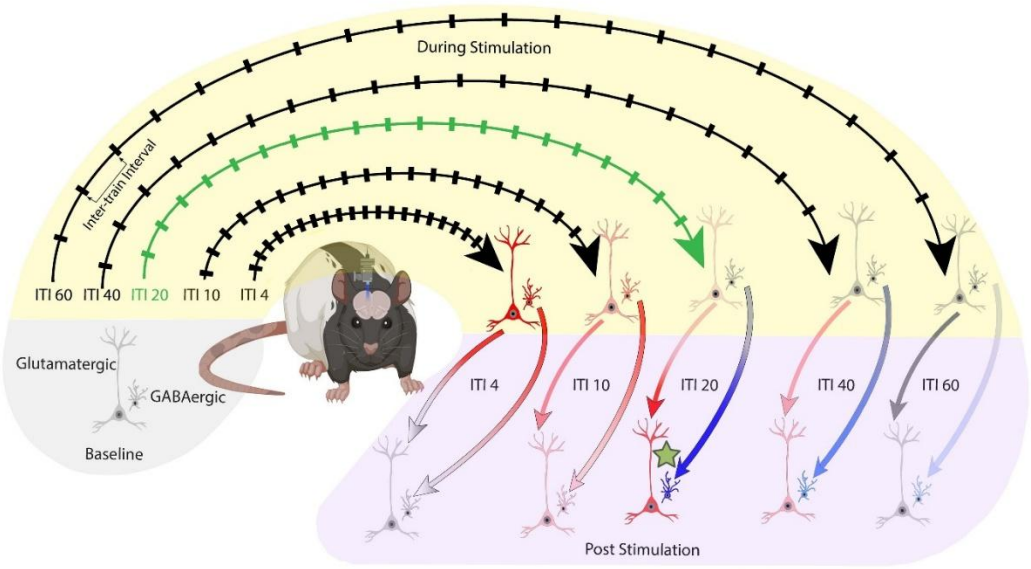
Topic: J.08. Methods to Modulate Neural Activity

Support: Burroughs Wellcome Fund 1015644
National Institute of Mental Health R01MH123650
Hope for Depression Research Foundation 30063773

Title: Extended-interval theta burst stimulation: a novel protocol for enhanced and sustained cortical plasticity

Authors: *M. SALIMI[1,3], J. MISHLER[4], J. RODGER[5], J. MISHRA[2], D. RAMANATHAN[6]; [1]Univ. of California San Diego, San Diego, CA; [2]Psychiatry, Univ. of California San Diego, La Jolla, CA; [3]VA San Diego Healthcare Syst., San Diego, CA; [4]Ctr. of Excellence for Stress and Mental Health, VA San Diego Med. Center, San Diego, CA, United States, SAN DIEGO, CA; [5]Univ. of Western Australia, Crawley, Australia; [6]Psychiatry, UC San Diego, La Jolla, CA

Abstract: Theta Burst Stimulation (TBS) is a widely used neuromodulation technique known to induce rapid synaptic plasticity in both experimental and clinical settings. Despite widespread adoption, variability in outcomes has limited the consistent clinical effectiveness of standard TBS protocols. In this study, we introduce and validate a novel TBS paradigm Extended-Interval Theta Burst Stimulation (eTBS) that significantly surpasses conventional protocols by eliciting stronger and more enduring modulation of cortical plasticity. We employed in-vivo calcium imaging using a miniaturized Inscopix microscope and electrical stimulation in rat medial prefrontal cortex, systematically varying inter-train intervals (ITIs) during TBS from 4 to 60 seconds. We identified that extending the ITI to 20 seconds (eTBS) selectively amplifies and sustains glutamatergic neuronal excitability while robustly suppressing GABAergic interneuron activity both during and post-stimulation. Crucially, this excitatory-inhibitory balance was uniquely optimized at the 20s interval, significantly outperforming the standard TBS protocol (10s ITI). Post-stimulation analyses confirmed that eTBS generated significantly more stable cortical responses, greatly reducing outcome variability. Moreover, histological verification with markers c-Fos and GAD-65 clearly supported these physiological observations, distinguishing eTBS from shorter intervals by demonstrating minimal inhibitory overdrive and reduced GABA production in parvalbumin-positive interneurons. Our discovery positions eTBS as a superior neuromodulation protocol, offering critical implications for refining brain stimulation therapies targeting neuropsychiatric disorders. By overcoming the limitations of conventional TBS, eTBS represents a significant advance in clinical and experimental neuromodulation practices.



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Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

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Program #/Poster #: PSTR147.08/RR5

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH SPARC 75N98022C00019
NIH NINDS-1R01NS136685-01A1

Title: Spatiotemporal activation of vagus nerve fibers via intermittent interferential current stimulation

Authors: *P. SCHNEPEL[1], N. ROSSETTI[1], W. SONG[2], N. JAYAPRAKASH[2], K. QANUD[2], T. DATTA[2], V. MIHAJLOVIC[1], S. ZANOS[2];
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Abstract: Vagus nerve stimulation (VNS) is gaining recognition as a promising treatment for various chronic conditions. However, the challenge of precisely controlling fiber activation to enhance desired outcomes while minimizing side effects hinders its clinical application. To address this, we present a VNS technique involving intermittent, interferential current stimulation (i^2CS) delivered via multi-contact epineural cuffs. In this study conducted on anesthetized swine, i^2CS generated distinct nerve potentials and organ responses in the lungs and laryngeal muscles, differing from those produced by non-interferential sinusoidal stimulation.

Post-experiment resection and micro-CT imaging of the stimulated nerve revealed that i^2CS responses are due to differential activation of specific organ-related fascicles within the nerve. Physiological responses in swine and single-fiber activity simulations in anatomically accurate, physiologically validated biophysical models of the vagus nerve suggest that i^2CS reduces fiber activation at the interference focus. Both experimental and modeling data show that current steering, along with beat and repetition frequencies, can predictably shape the spatiotemporal pattern of fiber activation, enabling improved control of nerve and organ responses. Compared to equivalent sinusoidal stimulation in the same animals, i^2CS results in lower levels of side effects from larger laryngeal fibers while achieving similar desired effects from smaller bronchopulmonary fibers.

Disclosures: P. Schnepel: None. **N. Rossetti:** None. **W. song:** None. **N. Jayaprakash:** None. **K. Qanud:** None. **T. Datta:** None. **V. Mihajlovic:** None. **S. Zanos:** None.

Poster

PSTR147: Stimulation Methods

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Program #/Poster #: PSTR147.09/RR6

Topic: J.08. Methods to Modulate Neural Activity

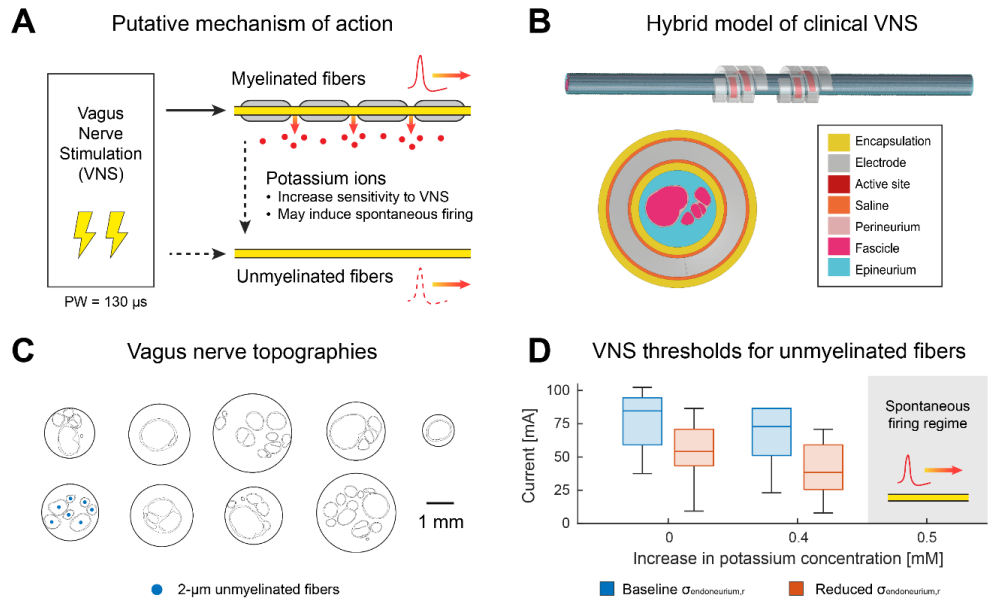
Support: NIH Project REVEAL (U54AT012307)
Bertarelli Foundation

Title: Activation of unmyelinated fibers by vagus nerve stimulation may be facilitated by extracellular potassium perturbations

Authors: *C. VERARDO[1], C. ANSALDO[1], V. MACEFIELD[2], S. MICERA[3,1], S. ROMENI[4]; [1]Scuola Superiore Sant'Anna, Pisa, Italy; [2]Monash Univ., Melbourne, Australia; [3]EPFL, Lausanne, Switzerland; [4]San Raffaele Hosp., Milano, Italy

Abstract: Vagus nerve stimulation (VNS) holds promise for a wide range of therapeutic applications, but its efficacy is limited by a poor understanding of its mechanisms of action. Preclinical and clinical evidence points to the activation of myelinated axons as the main causal link, with in-silico studies confirming that clinical stimulation protocols excite primarily myelinated, rather than unmyelinated, fibers. However, Patros et al. (2024) reported that microneurographic recordings from the vagus nerve of awake subjects during VNS exhibit hallmarks typical of the synchronous activation of unmyelinated fibers. Here, we hypothesize that VNS-induced activation of myelinated fibers may lead to an increase in extracellular potassium concentration sufficient to enhance the excitability of unmyelinated fibers, thereby triggering their firing. As first step toward testing this hypothesis, we implemented state-of-the-art hybrid models of clinical VNS. We considered realistic vagus nerve topographies derived from human samples available on the SPARC Portal and coupled them with digital twins of clinical VNS leads. Unmyelinated fibers were simulated using recently validated compartmental

models from Thio et al (2024), and their activation thresholds upon administration of VNS were investigated across different levels of extracellular potassium concentration. At small perturbations of potassium concentration, VNS current thresholds were reduced yet remaining outside clinically relevant ranges. However, larger potassium concentrations - but still within physiological ranges - yielded firing responses in fibers, confirming that increased potassium concentrations should receive attention as possible causal link for the activation of unmyelinated fibers during VNS. These findings prompt future experimental and in-silico studies aimed at elucidating the VNS-evoked effects on the ionic composition of the extracellular environment, paving the way for thorough testing of our hypothesis and advancing our understanding of the mechanisms underlying VNS therapies.



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Poster

PSTR147: Stimulation Methods

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Program #/Poster #: PSTR147.10/RR7

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH, 1RF1NS129520
NIH, 1R01NS115797-01
NIH 5R44MH118155-03
NSF, 1955981-CIF

Title: Deep Brain Stimulation desynchronizes the STN network and improves STN regulation of gait

Authors: *L. STEINER[1], S. ZHOU[2], X. HAN[2];
[2]Biomed. Engin., [1]Boston Univ., Boston, MA

Abstract: Deep Brain Stimulation (DBS), while effective for reducing Parkinsonian rigidity, tremor, and dyskinesia, results in mixed effects on gait and sometimes worsens gait. The subthalamic nucleus (STN) is a common DBS target for Parkinson's disease (PD). However, it is unclear how the STN regulates gait, contributes to PD gait impairment, and responds to DBS. Therefore, we performed large scale extracellular recordings in the STN of voluntarily locomoting mice, while delivering intracranial DBS and monitoring gait. Using a custom probe with 19 microelectrode sites spanning the entire dorsal-ventral axis of STN with electrical stimulation sites positioned alongside the recording site, we mapped the response of STN neural dynamics in healthy and dopamine depleted PD conditions. Our analysis revealed heterogeneous movement-related response profiles of STN neurons, with many exhibiting temporal precising firing during individual limb movement. STN local field potentials (LFPs) showed intrinsic oscillations across delta, theta, beta and high-gamma bands, which were also coupled to stepping movement. Dopamine depletion through intracranial infusion of neurotoxin 6-OHDA to the Medial Forebrain Bundle impaired gait, reduced STN neuronal firing, and increased STN movement correlation. DBS restored dopamine depletion mediated gait deficit and reduced STN network synchrony, while individual STN neurons exhibited diverse response profiles to DBS. Together, these results demonstrate that STN plays an important role in gait regulation in healthy and PD conditions, and DBS desynchronizes STN networks and rescues gait deficits.

Disclosures: L. Steiner: None. **S. Zhou:** None. **X. Han:** None.

Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

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Program #/Poster #: PSTR147.11/RR8

Topic: J.08. Methods to Modulate Neural Activity

Support: FWO Funding G0B4520N
NIH Funding 1R01MH123508-01
China Scholarship Council at CSC202006380043

Title: Hippocampal Rhythm Modulation via Frequency-Tuned Trigeminal Nerve Stimulation

Authors: L. CHEN[1], A. MAJDI[2], B. ASAMOAH[3], ***M. MC LAUGHLIN**[4];
[1]Neurosci., KU LEUVEN, LEUVEN, Belgium; [2]KU Leuven: Katholieke Univ. Leuven, Leuven, Belgium; [3]Neurosci., [4]KU Leuven, Leuven, Belgium

Abstract: Background: Trigeminal nerve stimulation (TNS) is a non-invasive method for modulating brain activity via peripheral afferents. While typically delivered using pulse-based protocols, little is known about how sinusoidal alternating current stimulation of the trigeminal nerve (TN-ACS) affects hippocampal network dynamics. **Objective:** We aimed to examine how TN-ACS at 8 Hz (theta) and 40 Hz (gamma) modulates neuronal activity in the rat hippocampus. **Methods:** We applied 3mins of TN-ACS at different frequencies in rats and recorded neural activity from hippocampus using multi-channel electrophysiology. We analyzed spike-phase entrainment in CA1, spike rate, power spectral changes in local field potentials (focusing on off-frequency stimulation effects), and spike-field coherence between CA3 LFPs and CA1 spikes. **Results:** We found that TN-ACS modulated hippocampal dynamics in a frequency-specific manner. 40Hz stimulation enhanced spike-phase locking in CA1, while 8 Hz did not. At the single neuron level theta-band coherence between CA3 LFPs and CA1 spikes showed a wide range of effects. At the group level theta coherence decreased during 8 Hz stimulation and increased during 40 Hz stimulation. Spike rates remained stable across all conditions. **Conclusion:** Our findings show that TN-ACS can entrain hippocampal spike timing and modulate interregional coherence without altering firing rates. These results suggest that TN-ACS can selectively shape deep brain rhythms and 40Hz TN-ACS could be developed as a good intervention candidate to manipulate memory-related processes.

Disclosures: L. Chen: None. **A. Majdi:** None. **B. Asamoah:** None. **M. Mc Laughlin:** None.

Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

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Program #/Poster #: PSTR147.12/RR9

Topic: J.08. Methods to Modulate Neural Activity

Title: Toward precision neuromodulation: evaluating high-definition and conventional tDCS and tACS on M1 excitability

Authors: *H. MENG[1], M. HOUSTON[2], A. RAO[4], Y. ZHANG[3], S. LI[5];
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Abstract: Introduction: Transcranial direct current stimulation (tDCS) is a widely used technique for modulating brain activity. In contrast, transcranial alternating current stimulation (tACS) operates through a different mechanism by entraining neural oscillations. However, whether its modulatory effects on motor behaviors are comparable to those of tDCS remains unclear. Furthermore, simulation studies have demonstrated that high-definition transcranial electrical stimulation (HD-tES) montages produce more focal and stronger electric fields. However, there is limited empirical evidence on whether these improved montages result in

enhanced modulatory effects on motor behavior compared to conventional montages. Therefore, the aim of this study is to investigate the neuromodulatory effects of HD-tDCS, HD-tACS, conventional tDCS (c-tDCS), and conventional tACS (c-tACS) on corticospinal excitability and motor unit activity in healthy adults. **Methods:** 16 participants underwent five 20-minute interventions in a randomized order, separated by a 2-day washout period. The interventions included HD-tDCS, HD-tACS, c-tDCS, c-tACS, and sham stimulation, all centered on the primary motor cortex (M1) at the flexor digitorum superficialis (FDS) hotspot. Corticospinal excitability was assessed using motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS). Motor unit activity was assessed using HD-sEMG over the FDS during a 20-second isometric contraction. A series of two-way repeated measures ANOVAs were conducted to analyze the effects of Intervention (HD-tDCS, HD-tACS, c-tDCS, c-tACS, and sham), Montage (HD vs. conventional), and tES type (tACS vs. tDCS) across Time (Pre vs. Post) on MEPs and motor unit activities. **Results:** A significant main effect of Time was observed ($p = 0.018$). Post hoc analysis revealed significantly increased FDS MEPs after both HD-tACS and HD-tDCS interventions, but no changes following c-tDCS, c-tACS or sham. Further analyses showed that the tES with HD montage significantly increased MEP amplitudes ($p = 0.039$), but there was no difference between two modalities (tACS vs. tDCS). Motor unit decomposition data are currently under analysis and will be reported upon completion. **Conclusion:** These findings provide compelling evidence that the modified HD-tES montage enhanced modulatory effects on corticospinal excitability compared to conventional tES. Our study did not show any difference in neuromodulatory effects between tACS and tDCS (HD or conventional montage). Further analysis of motor unit firing characteristics will offer additional insights into modulatory effects at the spinal level.

Disclosures: H. Meng: None. **M. Houston:** None. **A. Rao:** None. **Y. Zhang:** None. **S. Li:** None.

Poster

PSTR147: Stimulation Methods

Location: SDCC Halls B-H

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR147.13/RR10

Topic: J.08. Methods to Modulate Neural Activity

Support: Indiana University Grand Challenge in Addiction Grant
IUB Sharon Stephens Brehm Fellowship Program

Title: Temporal interference stimulation of the orbitofrontal cortex alters functional connectivity in humans

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Abstract: Temporal interference neurostimulation (TI) offers a novel opportunity to noninvasively stimulate deep brain regions without modulating overlying cortex. This key advantage over other noninvasive brain stimulation methods (e.g., transcranial magnetic stimulation, transcranial direct current stimulation) presents a unique tool for causal manipulation of deep brain structures within large-scale networks. However, the effects of TI on whole-brain functional connectivity remain largely unexplored. To address this gap, we conducted a psychophysiological interaction (PPI) analysis using functional MRI data from 20 human participants who received active TI stimulation of the mid-orbitofrontal cortex (OFC) at a 20 Hz beat frequency as well as sham stimulation delivered in four alternating 8-minute blocks. Results revealed a significant functional connectivity effect of TI, with a significant PPI interaction term between the OFC and the left parahippocampal gyrus ($p < 0.001$) during stimulation, suggesting network-level modulation involving regions linked to affective and contextual processing. This is the first study to demonstrate changes in functional connectivity induced by TI stimulation of the orbitofrontal cortex. These findings support the potential of TI as a precise and scalable method for investigating and manipulating causal dynamics within distributed brain networks, offering new avenues for connectivity research in both basic and translational neuroscience.

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Poster

PSTR147: Stimulation Methods

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Program #/Poster #: PSTR147.14/RR11

Topic: J.08. Methods to Modulate Neural Activity

Support: BMBF AI.D / 16ME0541

Title: Exploring neuronal response dynamics to intracortical electrical microstimulation in human cognitive association cortex

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Abstract: Intracortical electrical microstimulation (ICMS) can modulate neural activity and reveal causal contributions of single neurons and neuronal populations to behavior. ICMS has been successfully used to influence sensory perception, motor actions, and decision-making in

animals and humans. However, its effects on single-neuron spiking remain poorly understood, particularly in the human frontoparietal association cortex—a region critical for complex cognitive functions and uniquely expanded in humans. Here, we applied ICMS in a subject with stroke-induced language impairments (aphasia) through planar microelectrode arrays (64 electrodes each) chronically implanted in the inferior and middle frontal gyri (IFG, MFG) of the right hemisphere. Implantation targeted regions homotopic to the left language network to explore the potential of targeted neuromodulation with cellular resolution. To balance resting-state and task engagement, we used a passive fixation task minimizing behavioral confounds while maintaining stable attention. After 1000 ms of stable fixation, ICMS was delivered as a single pulse or a train lasting 500-800 ms, followed by a 3200-3500 ms post-stimulation period. Stimulation parameters included five current amplitudes (1, 5, 10, 20, 40 μA) and five frequencies (single pulse, 4, 8, 20, 76 Hz). Sham trials (no stimulation) were included, and all conditions were pseudorandomized. Stimulation artifacts were removed using local polynomial fitting, allowing precise analysis of post-stimulation spiking activity. In a representative session alternating stimulation between two MFG electrodes, 70 multi-units were detected across 48 electrodes. Stimulation responses were quantified relative to baseline (fixation epoch) firing rates. Stimulation trains combining high frequency (76 Hz) and high amplitude (20, 40 μA) elicited widespread inhibition on 47 electrodes within 100 ms of stimulation offset. For single pulses and trains with lower frequency or amplitude, modular responses appeared throughout the post-stimulation epoch. Across multiple months of concurrent stimulation and recording, signal and noise characteristics remained stable as measured by RMS and microelectrode impedances. Cumulative charge did not correlate with impedance or RMS changes. No adverse clinical events occurred. These observations support the safety of the stimulation protocol and the stability of long-term intracortical recordings. We believe our findings will contribute to laying groundwork for future investigations into the causal roles of defined populations of human neurons to higher brain functions, particularly language.

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Poster

PSTR147: Stimulation Methods

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Program #/Poster #: PSTR147.15/RR12

Topic: J.08. Methods to Modulate Neural Activity

Support: F31NS131020-01
Neuroscience Scholars Program

Title: Does electrical stimulation modulate the magnitude and generalization of neurophysiologic effects of prism adaptation?

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Abstract: BACKGROUND: Right-shifting prism adaptation (PA) is a well-studied sensorimotor behavioral phenomenon that induces a leftward visuospatial-motor behavioral aftereffect. Although the behavioral aftereffects of upper limb adaptation post PA are well-known, the underlying cortical plasticity mechanisms related to the behavioral effects of PA, and the extent of their generalization, are poorly understood. Somatosensory electrical stimulation (SES) is used as a therapeutic adjunct to motor training, and may accentuate the effects of PA as well as modulate the behavioral generalization.Purpose: We investigated whether PA combined with SES induces corticomotor excitability changes that generalize across limbs. Specifically, we evaluated whether stimulation to the left upper limb during PA affects the left lower limb, and whether stimulation to the left lower limb affects the left upper limb. METHODS: In two within-subjects experiments, healthy young adults participated in a single session of right-shifting PA, paired with either SES or Sham SES. Before and after PA, corticomotor excitability, intra-cortical inhibition, and intra-cortical facilitation were evaluated in the left first dorsal interossei (LFDI), tibialis anterior (LTA), and soleus (LSOL) muscles via motor-evoked potentials (MEPs) elicited in response to single and paired-pulse transcranial magnetic stimulation (TMS). Experiment 1 applied SES to the left upper limb of 15 healthy young adults during PA and measured TMS-evoked MEPs in the LFDI and nonstimulated LTA and LSOL. Experiment 2 applied SES to the left lower limb of 10 healthy young adults during PA, and measured MEPs in the LTA, LSOL, and nonstimulated LFDI. RESULTS: The results for Experiment 1 show that both PA+SES and PA+Sham led to significant sensorimotor behavioral aftereffects, showing a leftward shift during visuo-proprioceptive and proprioceptive pointing ($p < 0.001$). Neurophysiologically, PA+SES induced significant increases in MEP amplitude in the LFDI ($p < 0.001$), with some generalization to the LSOL ($p = 0.014$). Experiment 2 data collection is ongoing. Preliminary findings will assess whether lower limb SES combined with PA modulates cortical excitability in the upper limb. DISCUSSION: In summary, PA+SES showed similar behavioral effects to PA+Sham, with the potential added advantage of increased cortical excitability in the left upper and lower limbs, suggesting that combination of PA and SES may elicit greater and more generalized neurophysiological effects compared to PA alone.

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Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant 5R01NS129542-03

Title: Electrical stimulation of hippocampal areas selectively disrupts verbal memory in epilepsy patients

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Abstract: Verbal memory impairment is a major risk following hippocampal resection in mesial temporal lobe epilepsy (MTLE), yet current clinical tools have shown to inadequately preview functional memory deficits at the spatial precision of modern surgical techniques, such as the Wada test. Electrical stimulation (ES) has long been used for mapping out neocortical functions but has not been systematically employed for disruption of hippocampal subregions to guide memory prognosis. In this study, we evaluated whether focal ES of the left hippocampus, delivered via stereotactic electroencephalography (SEEG) depth electrodes during a four-alternative forced-choice (4AFC) verbal recognition memory task, can temporarily disrupt memory performance in a location-dependent manner. Five adult MTLE patients with left hippocampal SEEG implants encoded 10 common objects per condition (with auditory cue and verbal repetition), followed by a 15-minute consolidation period and a 4AFC retrieval task. Memory performance was assessed at non-stimulation baseline and under three ES conditions under epileptologist supervision: stimulation of the hippocampal head, tail, and simultaneous head and tail (50 Hz delivered at 0.5-1.5 mA, during both encoding and retrieval periods). The greatest effect of ES on performance was observed during simultaneous ES of the head and tail, exhibiting an average 31.5% worse performance in the 4AFC task when compared to baseline, whereas head-only and tail-only stimulation resulted in slightly worse performance than baseline, 8.5% and 14.4% respectively. These findings demonstrate that broader hippocampal ES leads to greater impairment of verbal memory than focal stimulation, with simultaneous subregional ES producing the most pronounced and clinically meaningful disruption. Our results suggest that subregional ES of the hippocampus can selectively disrupt memory and may provide a more precise functional readout to guide surgical planning than current memory disruption approaches, including the Wada test. This methodology has potential to enhance risk stratification and inform decision-making for patients undergoing MTLE surgery.

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Poster

PSTR147: Stimulation Methods

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Topic: J.08. Methods to Modulate Neural Activity

Support: NRF Korea Grant RS-2024-00337573
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KIST internal program 2E33682

Title: Comparative evaluation of non-invasive brain stimulation modalities using phantom and simulation-based approaches

Authors: *S.-H. PARK[1,2], K.-R. LEE[1], S. JEONG[1], H. CHO[1], S. LEE[1,3];
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Abstract: Non-invasive brain stimulation (NIBS) techniques—such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial interferential stimulation (tIS)—are increasingly applied to modulate brain activity for both clinical and research purposes. However, a clear understanding of their electric field characteristics, particularly in relation to deep brain penetration, remains incomplete. Accurate assessment of these fields is critical for optimizing stimulation protocols and interpreting neuromodulatory effects. In this study, we constructed a human head-sized phantom designed to replicate the electrical conductivity and geometry of biological tissues. Each of the three stimulation modalities (tDCS, tACS, and tIS) was applied using standardized electrode configurations, and electric potentials were recorded from multiple internal positions within the phantom using high-impedance recording electrodes embedded at cortical and subcortical analog sites. Empirical measurements revealed consistent distinctions in the spatial distribution and amplitude profiles across stimulation types. Overall, recorded potentials in deeper regions showed measurable attenuation compared to surface sites, but all three modalities generated detectable fields throughout the phantom. Notably, the tIS configuration resulted in a more spatially distributed field pattern at depth, while tDCS and tACS produced more surface-concentrated profiles. Complementary simulations using SimNIBS and finite-difference time-domain (FDTD) methods showed good concordance with experimental results. Simulated electric field vectors closely matched recorded voltage gradients in both spatial orientation and relative intensity, validating the phantom-based measurement approach and supporting the accuracy of the computational models. Our findings underscore the importance of combining empirical and modeling approaches to evaluate NIBS-induced fields. This study provides a reproducible framework for assessing and comparing electric field characteristics across stimulation modalities. The results highlight key considerations for stimulation depth, field orientation, and electrode configuration, offering foundational insights for optimizing NIBS protocols aimed at both superficial and deeper brain targets.

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Poster

PSTR147: Stimulation Methods

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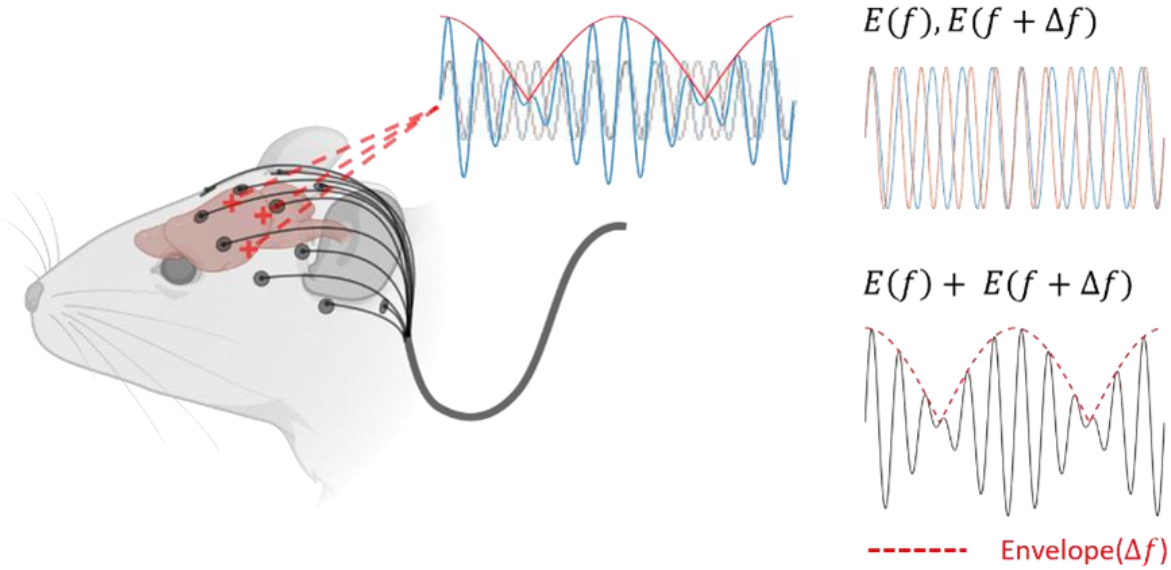
Program #/Poster #: PSTR147.18/RR15

Topic: J.08. Methods to Modulate Neural Activity

Title: High-precision and multi-point deep brain stimulation using multiple temporally interfering electric fields

Authors: *K. JO;
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Abstract: Neuromodulation plays an important role in the study and the treatment of the nervous system. Ultimately, neural stimulation must be applied precisely and non-invasively only to the desired areas. To this end, we propose optimized multiple Temporal Interference Stimulation (omTIS) that performs high-precision and multi-point simultaneous stimulation using optimized current amplitude and multiple carrier frequencies via multiple electrodes. Multiple electrodes enable we can target any region of the brain, including the deep brain with high focality. Multiple carrier frequencies implement independently controlled multi-point stimulation. The stimulus parameters such as amplitude, phase, and frequency of the current for each electrode are obtained by optimization process with finite element method (FEM) to stimulate the desired targets. We validated omTIS through finite element simulations, tissue phantom stimulation. Also, it was demonstrated through in-vivo experiments, proving its feasibility in real animals. omTIS, which is capable of high- precision and multi-point stimulation, will be a platform to promote the treatment of brain diseases and future research



Disclosures: K. Jo: None.

Poster

PSTR147: Stimulation Methods

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Topic: J.08. Methods to Modulate Neural Activity

Support: Republic of Korea, MSIT 2019M3C7A1031278
Republic of Korea, MSIT RS-2023-00266075

Title: Temporal interference stimulation modulates hippocampal activity in the rhesus monkey: an fMRI study

Authors: Y. KWAK[1], S. LIM[4], C. KIM[2], Y. LEE[5], C.-H. IM[1], H. LEE[1], *D. JANG[3,2];
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Abstract: Temporal Interference Stimulation (TIS) is a non-invasive neuromodulation technique that targets deep brain structures by generating low-frequency amplitude-modulated fields through the interaction of high-frequency currents. Although its potential has been demonstrated in several preclinical and clinical studies, direct validation of its neural effects in non-human primates remains limited, in part due to side effects and challenges in precise neural targeting. To investigate whether TIS can activate the hippocampus in non-human primates, we employed functional magnetic resonance imaging (fMRI) to assess BOLD responses in rhesus monkeys. Finite element simulations were used to determine optimal electrode placement and current intensity to focus a 6 Hz beat frequency within the right hippocampus, using 1200 Hz and 1206 Hz carrier frequencies. Electrode positioning was verified with MRI-guided navigation. As a control, 6 Hz transcranial alternating current stimulation (tACS) was applied at the same location and intensity. TIS and control conditions were delivered in a pseudo-randomized order during fMRI scanning. TIS significantly increased BOLD activity in the right hippocampus (FDR-corrected $p < 0.05$) compared to the control condition, with additional activation observed in the contralateral hippocampus. These results provide the first fMRI-based evidence that non-invasive TIS can modulate hippocampal activity in primates, demonstrating its potential as a tool for deep brain stimulation without surgical intervention. This work offers translational insights for neuromodulation approaches targeting limbic circuits in cognitive and psychiatric disorders.

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Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: Swiss National Science Foundation Grant 10001282

Title: A closed-loop reinforcement learning framework for real-time control of in vitro neuronal network dynamics

Authors: *B. MAURER[1], V. VASILIAUSKAITE[1], S. IHLE[2];
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Abstract: Current therapeutic electrical stimulation approaches suffer from limited understanding of optimal stimulation parameters and lack real-time adaptive control mechanisms. To study these fundamental control principles, in vitro patterned neuronal networks provide a more controlled model system where network parameters, environmental conditions, and stimulation protocols can be precisely manipulated while obtaining spiking activity of individual neurons. These networks, consisting of hundreds of neurons in patterning structures, however, still exhibit complex firing patterns.
We present a custom electrophysiology platform (Inkube [1]) that enables real-time, adaptive control of cultured neuronal networks through a reinforcement learning (RL) framework. Our system implements a closed-loop paradigm where stimulation timing is dynamically adjusted based on network response patterns, learning optimal control strategies with respect to a freely selectable reward function. The platform features 240 independent electrodes controlled by an FPGA-based system-on-chip architecture, achieving round-trip latency between spike detection and stimulus delivery below 15ms. The RL algorithm continuously optimizes stimulation timing to achieve desired network states, treating the cultured network as a dynamic environment for policy learning. Preliminary validation demonstrates that the RL agent can optimize reward signals through systematic exploration of stimulation timing parameters. The platform maintains stable operation and culturing conditions during extended recording sessions. The implemented protocol applies coordinated 4Hz stimulation across electrode subsets while dynamically adjusting temporal offsets to maximize network response metrics.
The platform provides a novel tool for network studies and offers a new experimental paradigm for understanding optimal neural control principles. All software and hardware are published under an open-source license, enabling broader adoption of RL-based neural control paradigms. This tool could benefit both fundamental neuroscience research and therapeutic neuromodulation applications.
References [1] Maurer, B., Fassbind, S., Ruff, T., Duru, J., Spacone, G., Rodde, T., Vörös, J., & Ihle, S. J. (2024). Inkube: An all-in-one solution for neuron culturing, electrophysiology, and fluidic exchange. bioRxiv 2024.12.06.627248. https://doi.org/10.1101/2024.12.06.627248

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Poster

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Program #/Poster #: PSTR147.21/RR18

Topic: J.08. Methods to Modulate Neural Activity

Title: Exploring electrophysiological biomarkers of vagus nerve stimulation as tools for personalized neuromodulation

Authors: *A. M. BOLLINGER[1], Z. S. BYNUM[2], S. A. HAYS[3], M. P. KILGARD[2], E. C. MEYERS[3];
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Abstract: While rehabilitation significantly improves recovery and quality of life for individuals with neurological impairments, many continue to suffer from residual disabilities, such as those resulting from stroke, spinal cord injury, traumatic brain injury, and post-traumatic stress disorder. Targeted plasticity therapy using vagus nerve stimulation (VNS) has demonstrated the ability to enhance rehabilitation outcomes in both preclinical models and clinical populations. However, about half of individuals do not respond to VNS, potentially due to suboptimal stimulation parameters. Recently, transcutaneous auricular vagus nerve stimulation (taVNS) has emerged as a potential non-invasive alternative. This study investigates acute physiological responses associated with taVNS, aiming to identify individualized stimulation parameters for optimized targeted plasticity therapy. Using non-invasive physiological monitoring including pupil responses, electroencephalography (EEG), and electrocardiogram (ECG) to study both healthy individuals and those with neurological impairments, applying randomized, interleaved, and time-locked (phasic) stimulation protocols. General population participants received sham and taVNS stimulation, while neurologically impaired participants received sham, taVNS, and will eventually receive invasive VNS. Current results from general population data (n=5), processed using EEGLAB and custom MATLAB scripts, show that oddball P300 wave amplitudes and latencies remain unchanged with taVNS, but behavioral responses improve significantly, with faster click latency and click release. No significant changes were observed in global band power metrics during resting state. Preliminary pilot results also indicate significant pupil dilation responses to taVNS stimulation, supporting the hypothesis of enhanced noradrenergic activity. Ongoing analyses are evaluating heart rate and respiratory dynamics as additional biomarkers of autonomic and physiological responses to stimulation. Further data collection is ongoing in both general and neurologically impaired populations to fully evaluate VNS efficacy and biomarker relevance. We hope this exploratory project can transform VNS into a precision neuromodulation therapy.

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Poster

PSTR147: Stimulation Methods

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Program #/Poster #: PSTR147.22/SS1

Topic: J.08. Methods to Modulate Neural Activity

Support: ERC Consolidator Grant DiabetManager to Stanisa Raspopovic

Title: In vivo validated closed-loop optimization of vagus nerve stimulation paradigm for precise physiological modulation

Authors: *T. BROSSY[1], N. SECEROVIC[2], N. GOZZI[3], F. CIOTTI[4], S. ZANOS[5], S. RASPOPOVIC[6];
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Abstract: Vagus nerve stimulation (VNS) holds therapeutic promise for a wide range of conditions, including cardiovascular, inflammatory, metabolic, and neuropsychiatric disorders. However, its clinical feasibility remains limited by two key challenges: achieving selective stimulation that avoids off-target effects such as coughing, bradycardia, or airway constriction, and adapting stimulation paradigms to real-time physiological states. These difficulties arise from the anatomical and functional complexity of the vagus nerve, limitations of current neural interface technologies, and the high dimensionality of stimulation parameters that must be tuned. To address these challenges, we developed an AI-based framework capable of optimizing multiparametric stimulation parameters in a closed-loop manner. We first prototyped the optimization framework using VaStim, our highly realistic in silico model that estimates the responses of both myelinated and unmyelinated fibers on specific stimulating patterns, serving as a proxy for in vivo testing. Following refinement based on simulation outcomes, we validated the system in pig experiments. Stimulation was delivered to the cervical vagus nerve using a custom-developed electrode that integrates both intra- and extra-neural active sites. We monitored heart rate, respiratory frequency, laryngeal muscle activity, and continuous glucose levels in response to VNS. Based on these physiological outputs, the system autonomously adjusted stimulation parameters. The closed-loop framework demonstrated faster convergence and superior multi-objective optimization performance compared to expert-driven approaches, successfully identifying stimulation paradigms that achieved targeted physiological effects while minimizing off-target responses.
This work demonstrates that adaptive, physiology-driven optimization with computational prototyping enables efficient development of selective VNS paradigms. Our approach reduces reliance on exhaustive in vivo experimentation and supports the advancement of personalized, clinically viable neuromodulation therapies.

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Poster

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Program #/Poster #: PSTR147.23/SS2

Topic: J.08. Methods to Modulate Neural Activity

Title: Targeting cortical networks with electrical stimulation

Authors: *P. DZIALECKA, C. RAJA, A. MITRA;
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Abstract: Neuropsychiatric disorders impose an enormous global burden. Emerging evidence indicates these disorders arise from dysfunction in specific large-scale networks, not isolated brain regions. Current brain stimulation treatment approaches, such as deep brain stimulation or electroconvulsive therapy, focus either too narrowly on isolated regions or too broadly on the entire brain. We use widefield calcium imaging and optimized electrical stimulation approaches to show precise targeting of previously identified cortical networks in a variety of different ways. We also find that our method allows modulation of sensory evoked responses. Unlike other techniques, such as optogenetics, our solution is ready for rapid clinical translation and could quickly become a next-generation treatment with immense clinical potential.

Disclosures: P. Dzialecka: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stanford patent. **C. Raja:** None. **A. Mitra:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stanford patent.