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Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.01/A1

Topic: A.06. Developmental Disorders

Support: Brain and behavior research foundation young investigator award to Emmanuel Cruz Grant 29345

Title: Monocarboxylate transporter 2 and lactate dehydrogenase A and B protein expression in the brain and peripheral tissues in an Angelman syndrome mouse model

Authors: *M. RAMOS RIVERA[1], C. TORRES-ORTIZ[2], E. A. CRUZ TORRES[3]; [1]Pontifical Catholic Univ. of Puerto Rico, Ponce, Puerto Rico; [2]Pontifical Catholic Univ. of Puerto Rico, Ponce, PR; [3]Pharmacol., Ponce Sch. of Med. and Hlth. Sci., Ponce, PR

Abstract: Angelman syndrome (AS) is a neurodevelopmental disorder characterized by intellectual disability, muscle and movement defects, seizures, and a happy demeanor. Alterations in the maternal chromosomal region 15q11.2-q13.1 cause Angelman syndrome (AS) by deleting the maternal *UBE3A* gene, which encodes a ubiquitin-protein ligase E3 that plays a key role in protein degradation and nervous system development. In the Angelman syndrome mouse model, an altered metabolism has been observed, characterized by elevated levels of lactate, acetate, and succinate, as well as increased gene expression of lactate dehydrogenase A (*Ldha*) in mouse embryonic fibroblasts. We hypothesize that the loss of the maternal *Ube3a* gene expression affects the protein expression of monocarboxylate transporter 2 (MCT2), lactate dehydrogenase A (LDHA), and lactate dehydrogenase B (LDHB) in the AS mice model, which could contribute to the high lactate levels. Western Blot analysis measured the protein expression of MCT2, LDHA, and LDHB in the hippocampus, cerebellum, lung, heart, pancreas, and kidneys of 12-week-old *Ube3a* $^{m-/p+}$ AS and *Ube3a* $^{m+/p+}$ wild-type mice. The results reveal a significant difference in MCT2 protein expression in the pancreas, LDHA in the kidneys, and LDHB in the lungs, as well as in MCT2 and LDHB in the cerebellum, between genders and genotypes. Loss of Ube3a can increase the protein expression of LDHA, LDHB, and MCT2 in various brain and peripheral tissues, although not in all cases; this increase is also gender-specific.

Disclosures: M. Ramos Rivera: None. **C. Torres-Ortiz:** None. **E.A. Cruz Torres:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.02/A2

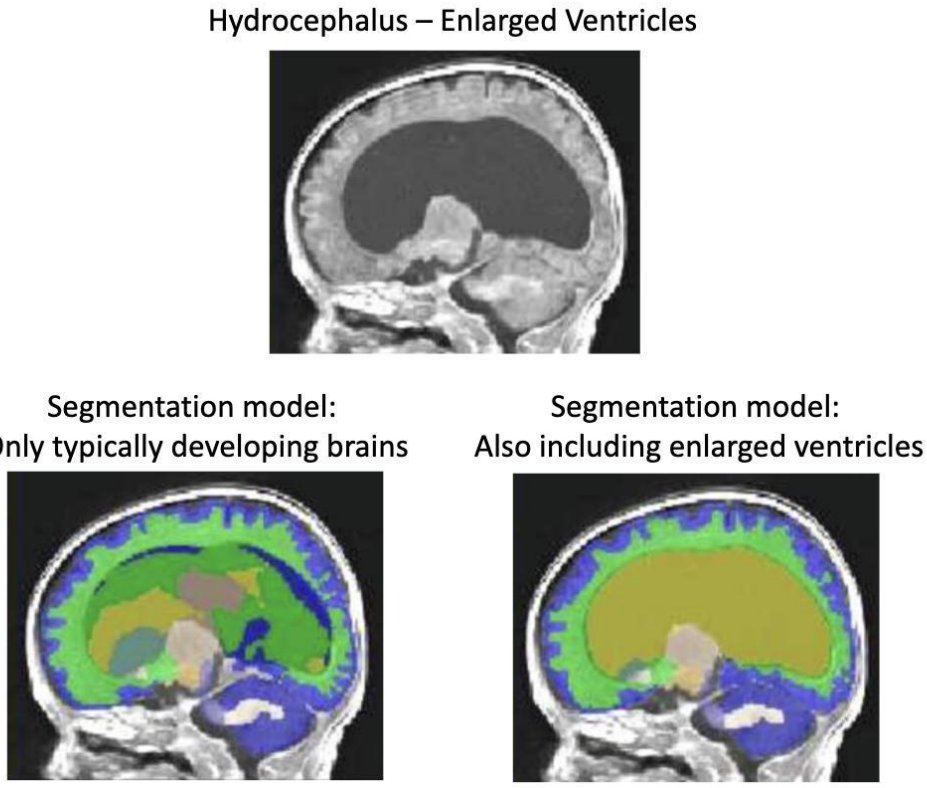
Topic: A.06. Developmental Disorders

Support: R01MH134966

Title: An automated segmentation model for pediatric brains with atypical neuroanatomy: Application for infants with ventriculomegaly and agenesis of the corpus callosum

Authors: ***S. STOYELL**[1], J. LUNDQUIST[1], J. KOWALSKI[2], E. FAIR[1], K. CARTER[1], A. BUNNELL[1], G. DANG[1], I. PEÑA PINO[1], L. A. MOORE[3], P. REINERS[1], J. ELISON[1], E. FECZKO[4], D. A. FAIR[3], K. B. WELDON[3], J. MOSER[3];
[2]Rehabil. Med., [3]Masonic Inst. for the Developing Brain, [1]Univ. of Minnesota, Minneapolis, MN; [4]Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Currently available automated processing pipelines for infant brains often result in inaccurate segmentations for infants with atypical neuroanatomy, representing a significant barrier to extending neuroimaging methods to pediatric clinical populations. To address this, a deep learning model is being trained to accurately segment infant brains across various neuroanatomical differences. Structural MRI data from N=7 infants with anomalous brain anatomy (N=2 ventriculomegaly, N=3 hydrocephalus, N=2 agenesis of the corpus callosum) was collected. Images were processed with BIBSNet, an existing segmentation pipeline for early life, and underwent extensive manual corrections. N=4 of these images were held out as a test set, while N=3 were added to supplement segmentations of typically developing brains (N=220) from the Baby Open Brains Repository. These images, along with synthetic images derived from them, were used to train a deep learning model. The new model demonstrated a higher average Dice similarity coefficient in the held out test set images (DSC=0.79) compared to the existing BIBSNet (DSC=0.74). The greatest improvements in model fit were in the lateral ventricles, where anatomical differences were most obvious (Figure 1). These improved segmentations can be used as inputs to existing functional processing pipelines for infants such as Nibabies and XCP-D to allow the accurate registration of functional data to structural images. This allows us to examine functional metrics in clinical populations, such as lateralization in functional connectivity in patients with agenesis of the corpus callosum, which has not yet been systematically explored in early development. More data is needed to improve model robustness and expand to other pediatric brain anomalies, but demonstrates the exciting potential of this new model to use automated advanced neuroimaging pipelines across clinical populations.



Disclosures: S. Stoyell: None. **J. Lundquist:** None. **J. Kowalski:** None. **E. Fair:** None. **K. Carter:** None. **A. Bunnell:** None. **G. Dang:** None. **I. Peña Pino:** None. **L.A. Moore:** None. **P. Reiners:** None. **J. Elison:** None. **E. Feczko:** None. **D.A. Fair:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); FIRMM software; Turing Medical Inc. **K.B. Weldon:** None. **J. Moser:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.03/A3

Topic: A.06. Developmental Disorders

Title: Omaveloxolone as a Disease-Modifying Therapy in Leigh Syndrome: Insights from Patient-Derived Neurons and an N-of-One Clinical Trial

Authors: L. WU, K. DYER, N. CARVAJAL, G. RIVERA DEL TORO, M. BLANCO, N. DOWNS, N. PERFITO, A. GUIN, *U. LEONE HADITSCH, C. MOXHAM;
Transcripta Bio, Palo Alto, CA

Abstract: Leigh Syndrome (LS) is a rare pediatric mitochondrial disorder that affects approximately 1 in 40,000 live births. It is characterized by impaired oxidative phosphorylation (OxPhos), energy deficiency, and progressive neurodegeneration. LS is caused by mutations in various mitochondrial and nuclear genes, including SURF1, which encodes a protein essential for the proper assembly and function of cytochrome c oxidase (complex IV) in the mitochondrial respiratory chain. In this study, we modeled key pathological features of LS using neurons derived from patients with SURF1 mutations to investigate the therapeutic potential of Omaveloxolone (Oma), an NRF2 activator known to enhance cellular antioxidant defenses and improve mitochondrial function. Treatment with Oma led to improved mitochondrial integrity, upregulation of pathways involved in autophagy and mitophagy, and normalization of gene expression profiles associated with apoptosis and ferroptosis. Additionally, in a preliminary clinical observation involving one patient, administration of Oma led to the upregulation of NRF2 target genes, OxPhos-related transcripts, and PGC1α expression in peripheral blood. These cellular and transcriptomic changes suggest that Oma may help restore mitochondrial function and provide therapeutic benefit by modifying disease progression in LS.

Disclosures: L. Wu: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options, Transcripta Bio. **K. Dyer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options, Transcripta Bio. **N. Carvajal:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock options, Transcripta Bio. **G. Rivera Del Toro:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options, Transcripta Bio. **M. Blanco:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock options, Transcripta Bio. **N. Downs:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock options, Transcripta Bio. **N. Perfito:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options, Transcripta Bio. **A. Guin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options, Transcripta Bio. **U. Leone Haditsch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options, Intellectual property rights. **C. Moxham:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options, intellectual property rights, Transcripta Bio.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.04/A4

Topic: A.06. Developmental Disorders

Support: NIH Grant 5128893

Title: A Novel Ube3a Reporter Mouse Enables Pogress Toward Small Molecule Therapeutics for Angelman Syndrome

Authors: *H. NOURIE;
Neurosci. Ctr., Univ. of North Carolina, Chapel Hill, Chapel Hill, NC

Abstract: Angelman syndrome is a rare neurodevelopmental disorder caused by mutations in or deletions of the maternally inherited copy of *UBE3A*. In neurons, the paternal copy of *UBE3A* is epigenetically silenced by a long antisense transcript, *UBE3A-ATS*. Disruption of *UBE3A-ATS* to restore UBE3A levels in neurons as a therapeutic strategy has shown mild clinical efficacy through ASO-mediated knockdown of the *UBE3A-ATS* transcript. While promising, ASOs have demonstrated side effects related to repeated intrathecal delivery under anesthesia, prompting our lab to search for alternative approaches that unsilence *UBE3A*. We have previously reported on the identification and characterization of a novel brain-penetrant small molecule paternal *UBE3A* unsilencer, (*S*)-PHA533533, through high content imaging utilizing the *Ube3a-YFP* mouse model. Here we present our efforts toward characterizing the structure-activity relationship of analogs of (*S*)-PHA533533 in the *Ube3a-I*RES-*N*anoLuciferase-*S*un1-sf*G*FP (*INSG*) mouse model, leading to the discovery of molecules with improved potency. The development and characterization of this next-generation *INSG* reporter mouse has rapidly accelerated small molecule screening efficiency with higher sensitivity. NanoLuciferase enables rapid, high-throughput, and reproducible quantification of paternal Ube3a activation after (*S*)-PHA533533 analog treatment in cultured primary neurons from mice with paternal inheritance of the *INSG* allele. The *INSG* model also harbors a nuclear tagged Sun1-sfGFP, facilitating rapid biodistribution assessments and fluorescence activated nuclear sorting for downstream single-nuclei analysis. Altogether, we highlight how this this novel *Ube3a-INSG* mouse model streamlines and advances our small molecule screening efforts and improves pharmacodynamic assessment of brain-penetrant molecules.

Disclosures: H. Nourie: None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.05/A5

Topic: A.06. Developmental Disorders

Title: Gene therapy for Creatine Transporter Deficiency: a new therapeutic horizon

Authors: *F. DI VETTA[1,2], L. IOVINO[1], L. DADÀ[3,4], R. D. HECTOR[5], J. SELFRIDGE[5], C. MONTANI[6], E. GHIRARDINI[1], F. CALUGI[1,4], G. SAGONA[1,7], P. ROSS[5], S. R. THOMSON[5],

T. PIZZORUSSO[1,4], A. GOZZI[8], S. COBB[5], L. BARONCELLI[1,7];
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Abstract: Creatine Transporter Deficiency (CTD) is a neurodevelopmental disorder linked to the X chromosome, caused by loss-of-function mutations in the SLC6A8 gene encoding for the creatine transporter (CrT). The hallmark of the pathology is the absence or reduction of cerebral creatine (Cr) levels, accompanied by intellectual disability, seizures, and autism-like behaviors. Currently, there are no effective treatments available for CTD. To explore gene therapy as a potential disease-modifying approach, we developed an adeno-associated virus serotype 9 (AAV9) vector carrying the human SLC6A8 gene under the control of a ubiquitous promoter. Intracerebroventricular injection of AAV9-hSLC6A8 into male newborn mice resulted in widespread brain expression of the transgene and significant increases in brain Cr content in knockout (KO) animals. This recovery of cerebral Cr was associated with the prevention of early neural hypoconnectivity, leading to improvements in stereotyped autistic-like behaviors and declarative memory in adult KO mice. However, the same treatment did not alleviate deficits in working memory. Furthermore, treated wild-type (WT) mice showed impaired memory performance, suggesting that overexpression of CrT may be detrimental by adversely affecting neural function. These findings highlight the therapeutic potential and possible challenges of gene therapy for CTD, emphasizing the need for precisely regulated transgene expression to ensure both efficacy and safety. To address this issue, we optimized the gene construct using two alternative strategies: (1) incorporating regulatory elements to mimic physiological CrT expression patterns, and (2) employing a synthetic regulatory system to limit CrT expression across all cell types. Preliminary data suggest that these new strategies yield more controlled and physiologically appropriate CrT expression, potentially enhancing both the safety and the therapeutic impact of the treatment.

Disclosures: F. Di Vetta: None. **L. Iovino:** None. **L. Dadà:** None. **R.D. Hector:** None. **J. Selfridge:** None. **C. Montani:** None. **E. Ghirardini:** None. **F. Calugi:** None. **G. Sagona:** None. **P. Ross:** None. **S.R. Thomson:** None. **T. pizzorusso:** None. **A. Gozzi:** None. **S. Cobb:** None. **L. Baroncelli:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.06/A6

Topic: A.06. Developmental Disorders

Support: NIH Grant R01HD110693

Title: Converging Mechanisms in Lissencephaly Spectrum Disorders

Authors: *I. Q. CHENG[1], C. ZHANG[2], A. LOUVI[3];
[1]Neurosurg., Yale Univ., New Haven, CT; [3]Neurosurg., [2]Yale Sch. of Med., New Haven, CT

Abstract: Human cortical development is an intricate and highly regulated process involving the coordination of numerous molecular pathways. Genetic mutations that disrupt these critical pathways can lead to malformations of cortical development (MCD). Lissencephaly spectrum disorder is a genetically heterogenous MCD commonly associated with epilepsy and intellectual disability. To date, there is no cure for lissencephaly—only supportive care is available for patients.In previous work, we employed two cerebral organoid models generated from patient-derived induced pluripotent stem (iPS) cells with a recessive mutation in P53-induced death domain protein 1 (*PIDD1*) or a heterozygous chromosome 17p13.3 microdeletion associated with Miller-Dieker lissencephaly syndrome (MDLS). We demonstrated that these organoids exhibit a thickened cortical plate, resembling clinical presentations of lissencephaly, and that both models show mTOR pathway hypoactivation and dysregulated translation. We have obtained and reprogrammed two additional patient-derived iPS cell lines with recessive mutations in WD Repeat Domain 62 (*WDR62*) or in CASP2 and RIPK1 domain containing adaptor with death domain (*CRADD*). Characterization of day 70 (D70) cerebral organoids from these additional lines revealed a converging molecular mechanism among all four genetically distinct lissencephaly subtypes. Specifically, the organoids exhibited mTOR hypoactivation and dysregulated translation, evidenced by significantly reduced levels of phosphorylated S6 (pS6)—a hallmark of mTORC1 activity—as well as decreased polysome abundance and increased monosome content, indicative of globally reduced translation.Our findings suggest that mTOR hypoactivation may represent a common converging pathway in the lissencephaly spectrum disorders. Ongoing projects in our lab aim to treat lissencephaly patient-derived cerebral organoids with mTORC1 activators in an effort to prevent and reverse pathological phenotypes. This work may be critical for elucidating the molecular mechanisms underlying lissencephaly and could provide valuable insights into potential therapeutic approaches.

Disclosures: I.Q. Cheng: None. **C. Zhang:** None. **A. Louvi:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.07/A7

Topic: A.06. Developmental Disorders

Title: Periodic and Aperiodic Electrophysiological Phenotypes of Angelman Syndrome in Humans and Mice

Authors: *D. P. MONTGOMERY, J. SHIDE, A. DIDOUCHEVSKI, M. S. SIDOROV;
Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington, DC

Abstract: Angelman syndrome (AS) is a rare neurodevelopmental disorder caused by loss of maternal UBE3A expression, leading to severe cognitive, motor, and speech impairments. Large delta (2-4 Hz) oscillations are a well-established feature of EEG recordings in children with AS and in rodent models of the disorder. Delta power has been shown to correlate with symptom severity in children and holds promise as an objective, quantifiable, and translatable biomarker for therapeutic development. However, traditional methods of quantifying delta power in AS conflate rhythmic (periodic) oscillations and broadband (aperiodic) shifts in the power spectrum, limiting accurate interpretation of the underlying neural dynamics. To better characterize these different components of the AS delta phenotype, we applied spectral parameterization (*specparam*) to EEG recordings from children with AS and local field potential (LFP) recordings from *Ube3a*$^{m-/p+}$ mice. This method allows for the separation of periodic delta oscillations from the 1/f-like aperiodic background of EEG/LFP power spectra. We found that in both species, increased delta power was driven by a combination of stronger periodic delta oscillations and an increase in the slope and offset of the aperiodic component. Periodic and aperiodic components exhibited distinct regional distributions and followed different developmental trajectories, indicating that they likely arise from separate neural mechanisms and may reflect distinct aspects of circuit dysfunction in AS. Importantly, periodic and aperiodic features were differentially associated with behavior. In children with AS, periodic delta power was most strongly associated with cognitive ability, whereas the aperiodic exponent (i.e., slope) was linked to fine motor deficits. In mice, aperiodic features (but not periodic delta power) were predictive of deficits in motor-based behavioral tasks. Together, these findings identify periodic and aperiodic spectral features as distinct, behaviorally relevant biomarkers of AS severity, with broad potential for evaluating therapeutic efficacy in both clinical and preclinical settings.

Disclosures: D.P. Montgomery: None. **J. Shide:** None. **A. Didouchevski:** None. **M.S. Sidorov:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.08/A8

Topic: A.06. Developmental Disorders

Support: NIH NICHD NCT 03518736

Title: Comparison of change in TIMP scores in response to SPEEDI intervention

Authors: *S. DUSING[1], C. BUTERA[2], C. BROWN[2], R. ATTAL[2];
[1]Univ. of Southern Carolina, Los Angeles, CA; [2]USC, Los Angeles, CA

Abstract: Cerebral palsy (CP) is the most common motor disability in childhood. Evidence-based early interventions like Supporting Play Exploration and Early Development Intervention (SPEEDI) during critical neuroplastic windows can improve neurodevelopmental outcomes for infants born preterm. However, it is unclear how this early intervention program impacts children who will go on to develop CP as an appropriate care transition prior to the time of an early diagnosis, and CP specific intervention is possible (3 - 6 months). The purpose of this case series is to begin to evaluate the efficacy of the SPEEDI intervention provided during the transition from the NICU to home in infants who go on to receive a CP diagnosis. SPEEDI is a parent training and motor based problem solving intervention for infants born preterm. Nine of 83 infants who were part of a clinical trial of SPEEDI were diagnosed with CP at 12 or 24 months of adjusted age. Three of the 9 infants included in this analysis were in the SPEEDI Early group who started intervention at visit 1 in the NICU at 35 to 42 weeks of gestation and when medically stable. The remaining 6 infants were in the control (no intervention) or SPEEDI Late group (started intervention at visit 2, 15 weeks post visit 1). The Test of Infant Motor Performance (TIMP) was completed pre and post intervention at visit 1 and again 15 weeks later at visit 2. We compared the SPEEDI Early group with the no intervention group (control and SPEEDI Late) on raw scores of TIMP between visit 1 and 2. Visual inspection of this small sample is used to describe differences in the individual data. The SPEEDI Early group improved by an average of 37.50 raw score points on the TIMP. Those who had not received intervention increased their raw score by an average of approximately 28.75 raw score points over the same period. Conclusion: While the result of this study provides some evidence for the SPEEDI intervention improving motor skills in 0-3-month-olds born preterm who go on to receive a CP diagnosis, all infants made progress during this period. As the early detection guidelines are beginning to be increasingly implemented to shift diagnosis of CP to 3 -6 months adjusted age, early interventions like SPEEDI may serve as a valuable treatment to help families transition from the NICU to CP specific intervention at the time of an early diagnosis.

Disclosures: S. Dusing: None. **C. Butera:** None. **C. Brown:** None. **R. Attal:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.09/A9

Topic: A.06. Developmental Disorders

Support: Center for Episelpy and NeuroDevelopmental Disorders (ENDD)

Title: Splice-switching antisense oligonucleotide therapy in a mouse model of SYNGAP1 haploinsufficiency

Authors: *A. BHATNAGAR[1,2], L. SICHLINGER[2], C. GROSS[1], R. L. HUGANIR[3], E. A. HELLER[1];
[1]Systems Pharmacol. and Translational Therapeut., [2]Ctr. for Epilepsy and Neurodevelopmental

Disorders (ENDD), Children's Hosp. of Philadelphia, Univ. of Pennsylvania, Philadelphia, PA; [3]Dept. Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: SYNGAP1-related intellectual disability (SRID) is a neurodevelopmental disorder characterized by developmental delay, intellectual disability, and epilepsy. Despite accounting for about 2% of all intellectual disability cases, SRID patients have no disease-modifying treatments currently available. SRID is typically caused by de novo variants affecting a single allele of the SYNGAP1 gene, resulting in haploinsufficiency of the SYNGAP1 protein, which is central to disease pathogenesis. Therefore, therapeutic strategies aimed at restoring SYNGAP1 protein levels are promising in directly treating the underlying cause of the disorder. In this study, we evaluate the potential of antisense oligonucleotide (ASO) therapy to rescue protein expression in a Syngap1$^{+/-}$ mouse model harboring a known causal variant in humans, c.3583-9G>A. This pathogenic variant introduces a cryptic splice acceptor site upstream of exon 17, leading to aberrant splicing, a frameshift, and a premature stop codon in the transcribed mRNA. We have designed steric-blocking ASOs specifically targeting the cryptic splice site to correct aberrant splicing and restore canonical SYNGAP1 mRNA and protein levels. Preliminary data from primary cortical neurons cultured from Syngap1$^{+/-}$ mice indicate that ASO treatment promotes canonical splicing and increases wild-type *Syngap1* mRNA levels *in vitro*. Future experiments include *in vivo* validation of restoration of SYNGAP1 protein levels and testing for behavioral phenotype rescue. In conclusion, our findings suggest that an ASO-mediated splice switching strategy has the potential to serve as a viable therapeutic strategy to treat SYNGAP1 haploinsufficiency and ameliorate SRID-associated symptoms.

Disclosures: A. Bhatnagar: None. **L. Sichlinger:** None. **C. Gross:** None. **R.L. Huganir:** None. **E.A. Heller:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.10/A10

Topic: A.06. Developmental Disorders

Support: NIH Grant R21NS137191

Title: Cortical excitatory neuronal Dyrk1a trisomy contributes to juvenile visual cortical plasticity impairment in Down syndrome model mice

Authors: M. RAMANI, R. YAN, X. PEI, ***C. M. WILLIAM**;
Pathology, New York Univ. Sch. of Med., New York, NY

Abstract: Disruption of activity-dependent plasticity during juvenile development may have long lasting effects on cognitive function in Down syndrome (DS). Ts65Dn and Ts1Rhr DS mouse models demonstrate defects in ocular dominance plasticity (ODP), a juvenile visual cortical response to monocular deprivation (MD) that results in strengthening and widening of

cortical responses to nondeprived eye stimulation. A likely candidate gene contributing to impairment, present in the Ts65Dn and Ts1Rhr models, is *dual-specificity tyrosine phosphorylation-regulated kinase 1A* (*Dyrk1a*).
To assess the role of *Dyrk1a* in ODP impairment in Ts1Rhr trisomic mice, Ts1Rhr trisomic mice and *Ts1Rhr;Dyrk1a*$^{+/-}$ mice (Ts1Rhr trisomic, *Dyrk1a* disomic mice) underwent 6-d MD beginning at P27-29. Cortical responses were measured by optical imaging of intrinsic signals in awake mice and the width of responsive visual cortex ipsilateral to the nondeprived eye was measured by post mortem *Arc in situ* hybridization. These assays were also performed in Ts1Rhr mice heterozygous for a floxed *Dyrk1a* allele (*Dyrk1a*^{fl}) and an allele of either a cortical excitatory (*Emx1-Cre*) or pan-inhibitory (*Gad2-Cre*) Cre-driver, and the results compared to Cre-negative littermate controls.
Dyrk1a disomy rescued ODP in Ts1Rhr mice (*Ts1Rhr* post-MD Ocular Dominance Index, ODI, 0.11±0.04; *Ts1Rhr;Dyrk1a*$^{+/-}$ post-MD ODI, -0.133±0.08; p=0.009, t-test; *Ts1Rhr* post-MD *Arc*$^{+}$ responsive domain width 977±88 microns; *Ts1Rhr;Dyrk1a*$^{+/-}$ post-MD domain width 1050±98 microns; p=0.002, t-test). Restoring *Dyrk1a* disomy in Ts1Rhr cortical excitatory neurons also rescued plasticity (*Ts1Rhr;Dyrk1a*$^{fl/+}$ post-MD ODI, 0.028±0.043; *Ts1Rhr;Emx1-Cre;Dyrk1a*$^{fl/+}$ post-MD ODI, -0.221±0.080; p=0.02, t-test, n=7-8 per group; *Ts1Rhr;Dyrk1a*$^{fl/+}$ post-MD response domain width, 826±68 microns; *Ts1Rhr;Emx1-Cre*;*Dyrk1a*$^{fl/+}$ post-MD domain width, 1082±69 microns; p<0.0001, t-test, n=8-9 per group), while restoration of disomy in inhibitory neurons (*Ts1Rhr;Gad2-cre;Dyrk1a*$^{fl/+}$ mice) did not. These data suggest that *Dyrk1a* trisomy in excitatory neurons impairs cortical plasticity in Ts1Rhr mice and contributes to juvenile plasticity impairment in DS. The identification of drug-targetable processes dysregulated by *Dyrk1a* trisomy may reveal therapeutic approaches to ameliorate impairment in the juvenile DS brain.

Disclosures: M. Ramani: None. **R. Yan:** None. **X. Pei:** None. **C.M. William:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.11/A11

Topic: A.06. Developmental Disorders

Support: NSF GRFP DGE-2146755
NICHD R01-HD095861

Title: Sulcal anatomy of ventral temporal cortex and reading development

Authors: *J. K. YAO[1], A. DAVISON[2], J. L. MITCHELL[3], M. YABLONSKI[3,4], J. D. YEATMAN[3,4,1];
[1]Psychology, [2]Symbolic Systems, [3]Grad. Sch. of Educ., [4]Stanford Sch. of Med., Stanford Univ., Stanford, CA

Abstract: Reading acquisition results from the interplay between biology and experience that unfolds across years of development. Prior work (Borst et al., 2016; Cachia et al., 2018; Bouhali et al. 2024) highlights how biology - having a gyral gap (i.e., interruption) in the left posterior occipitotemporal sulcus (lhpOTS) - predicts stronger reading abilities in typical readers, raising the possibility that the lhpOTS may be a biomarker for dyslexia. However, the extent to which this structure-behavior link generalizes to dyslexia or predicts responsiveness to reading intervention is unknown. We defined lhpOTS gaps in 95 dyslexic and 114 typically developing children (N=209; ages 5 - 13). In typical readers, we replicate prior findings: children with a lhpOTS gap exhibited significantly higher Test of Word Reading Efficiency (TOWRE) Index scores ($t = -2.13$, $p = .04$), and this was predictive above and beyond a model with age alone ($F = 5.3$, $p = .02$). In dyslexic children, the prevalence of lhpOTS gaps was comparable ($X^2 = 1.27$, $p = .26$), yet reading scores did not differ between children with continuous vs. interrupted lhpOTS ($t = .67$, $p = .5$). We also characterized the anterior lhOTS (lhaOTS). Interestingly, having a lhaOTS gap was associated with higher TOWRE scores in dyslexic children ($t = 2.31$, $p = .02$) but not typical readers, revealing a striking double dissociation: the posterior gap predicts reading in typical development, while the anterior gap predicts reading in dyslexia. Furthermore, having overall larger gyral gaps across both lhaOTS and lhpOTS predicted higher reading scores in both dyslexic and typical children ($F = 10.63$, $p = 1.5e-06$). While the lhpOTS gap did not predict reading scores at baseline for dyslexic children, prior work suggests it might predict longitudinal outcomes. In a subset of dyslexic children, who completed a reading intervention (N = 38), having a lhpOTS gap was not associated with reading growth rates or post-intervention scores (t's < 1.8, p's $> .09$). When combined with matched dyslexic controls (N = 19), a linear model shows that intervention experience ($t = 2.49$, $p = 0.01$), not lhpOTS morphology ($t = .23$, $p = .82$), significantly predicted reading improvement in dyslexic children (N = 57). In sum, though lhpOTS morphology reliably predicts reading skill in typical readers, it neither generalizes as a biomarker for dyslexia nor forecasts intervention response. Instead, intervention itself, and alternative anatomical measures, may better account for reading outcomes in dyslexia. Together, these results highlight distinct contributions of biology and experience across different pathways of reading development.

Disclosures: J.K. Yao: None. **A. Davison:** None. **J.L. Mitchell:** None. **M. Yablonski:** None. **J.D. Yeatman:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.12/A12

Topic: A.06. Developmental Disorders

Support: NIH

Title: Human Brain Laterality: BUD23 links reversed brain laterality in Williams syndrome with C. elegans

Authors: *J. R. KORENBERG;
Univ. of Utah, Salt Lake City, UT

Abstract: Brain lateralization has run amok in poorly understood neuropsychiatric disorders from dyslexia to schizophrenia and Williams syndrome (WS) where genetics is known but evolutionary models are few. Using ERPs (even related potentials) to directly measure brain activity and quantitative transcription in WS, we show that the evolutionarily conserved gene, BUD23 is related to reversed brain laterality for perception of direction of motion, the most ancient lateralized property. Combining data across evolution reveals striking conservation of BUD23 function in ribosome biogenesis and regulation of de novo methylation from C. elegans to man. Integrating these features with similarities of early embryogenesis in these distant species suggests a common component of central nervous system lateralization

Disclosures: J.R. Korenberg: A. Employment/Salary (full or part-time): University of Utah.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.13/A13

Topic: A.06. Developmental Disorders

Support: NIH Grant R21OD032463
NIH Grant R01MH133243
NIH Grant F31-HD105424

Title: Gene expression ceilings predict overexpression sensitivity

Authors: *J. T. PIERCE[1], S. SANCHEZ[2], S. IYER[2], A. FIORITO[2], B. SYED[2], E. BECKETT[2], N. MOURÃO[2], S. SMITH[2], K. M. PERKS[3];
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Abstract: Many genetic disorders are caused by gene duplication, but it is hard to know which genes are sensitive or tolerant to duplication. To identify factors that predict gene duplication sensitivity in the context of Down syndrome, we individually transformed 47 orthologs of 21st human chromosome genes into the nematode *Caenorhabditis elegans*. Half caused developmental, behavioral, or reproductive deficits as extra copies. Interestingly, most overexpression-sensitive genes displayed a ceiling in expression across wild *C. elegans*, as though individuals with higher levels are selected against in nature. This model extended to independent worm studies. Empirical testing of the model showed that controlled expression of genes above or below their ceiling thresholds largely predicted overexpression phenotypes in worm. The model also generalized to human. We found that duplication-sensitive genes that cause severe medical conditions (e.g. *APP*, *PCSK9*, *PMP22*, and *SNCA*) display a ceiling of expression in a healthy population. Likewise, about half of 1,048 genes contained within duplication-sensitive copy-number variant regions also display expression ceilings. Conversely,

the vast majority of 1,029 example duplication-tolerant genes do not display expression ceilings. Our model suggests that the presence and value of an expression ceiling observed in healthy members of a species predicts if, and at what level, a gene may be sensitive to cause an overexpression phenotype.

Disclosures: J.T. Pierce: None. **S. Sanchez:** None. **S. Iyer:** None. **A. Fiorito:** None. **B. Syed:** None. **E. Beckett:** None. **N. Mourão:** None. **S. Smith:** None. **K.M. Perks:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.14/A14

Topic: A.06. Developmental Disorders

Support: T21 Research Society (T21RS)

Title: Investigating Complement Proteins in Astrocyte-Derived Extracellular Vesicles from Individuals with Down Syndrome

Authors: N. E. OLIVEIRA[1], ***B. L. ZAMPIERI**[1,2];
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Abstract: Extracellular vesicles (EVs) are lipid bilayer-bound particles secreted by cells that play essential roles in intercellular communication, inflammation, and neuroplasticity. EVs released by brain cells can be detected in blood, serving as molecular mirrors of their cells of origin and providing insight into ongoing disease processes. Astrocytes, the most abundant glial cells in the central nervous system, are major sources and regulators of EV release. Astrocyte-derived EVs (ADEVs) influence key neurobiological functions, including synaptogenesis, neuronal survival, and plasticity. Under pathological conditions, they contribute to neuronal dysfunction and are implicated in the onset and propagation of neuropathology. Our current study explores their potential as non-invasive biomarkers for in vivo brain pathophysiology in Down syndrome (DS), a condition marked by early neurodegeneration and cognitive decline. Blood samples from individuals with DS and controls were collected (19-31yrs), and plasma was isolated and stored at -80 °C for subsequent EV isolation. Total EV (TEV) isolation from 1 mL of plasma was optimized using differential ultracentrifugation. Isolated TEVs were characterized by BCA assay, nanoparticle tracking analysis (NTA), transmission electron microscopy (TEM), and dot plot against tetraspanin antibodies to assess, respectively, total protein content, concentration, and size distribution, morphology, and immunophenotype. ADEVs, enriched through immunocapture targeting astrocyte-specific surface marker, will be further characterized as TEV, besides ELISA for complement proteins. Preliminary data confirm the successful isolation and characterization of TEVs. ADEV characterization is ongoing. If our hypothesis is supported, ADEVs from individuals with DS will show increased complement activation,

reflecting astrocyte-mediated inflammation. Investigating ADEVs and their role in complement system dysregulation will enhance our understanding of neuroinflammation in DS. To date, no published study has studied ADEVs in the plasma of individuals with DS, making this a novel approach to uncovering DS-associated neurological changes.

Disclosures: N.E. Oliveira: None. **B.L. Zampieri:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.15/A15

Topic: A.06. Developmental Disorders

Support: NIH R01NS137222
NIH R21HD116010

Title: Abelson tyrosine kinase signaling is enhanced in mouse and human models of Down syndrome

Authors: *T. HERGENREDER[1], L. KELLER[2], M. SBAROUNIS[1], G. SMITH[2], B. YE[3]; [2]Obstetrics/Gynecology, Physiology, and Urology, [3]Life Sci. Inst., [1]Univ. of Michigan, Ann Arbor, MI

Abstract: Down syndrome (DS) is characterized by a full or partial extra copy of human chromosome 21 (HSA21). The additional copy of the genes on this chromosome are associated with numerous health complications and symptoms associated with DS. One gene on this chromosome, *Down syndrome cell adhesion molecule (DSCAM)*, has been shown to be critically involved in neurodevelopment. In *Drosophila*, overexpression of DSCAM increases presynaptic terminal growth via activation of Abelson tyrosine kinase (Abl). Similarly, Ts65Dn mice, a model for DS that carry trisomy of two thirds of orthologous genes on HSA21, exhibit overgrowth of GABAergic axons and synapses in the neocortex. Genetic normalization of *Dscam* rescues this over inhibition, implicating *DSCAM* in inhibitory circuit dysfunction. While the Dscam-Abl pathway has been characterized in *Drosophila,* it remains unknown if this pathway is conserved in mammalian models. Here, we show that DSCAM, Abl, and phosphorylated (active) Abl protein levels are elevated in both the Ts65Dn mouse cortex and human GABAergic neurons derived from embryonic stem cells that are trisomic for HSA21. These findings suggest that the DSCAM-Abl mechanism is conserved in mammalian DS models and may contribute to inhibitory circuitry abnormalities, offering a potential therapeutic target for cognitive disability in DS.

Disclosures: T. Hergenreder: None. **L. Keller:** None. **M. Sbarounis:** None. **G. Smith:** None. **B. Ye:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.16/A16

Topic: A.06. Developmental Disorders

Support: NIH K23 HD112809-01
NIH KL2 TR002490-03S1
NIH R01 HD055741
NIH R01 HD055741-12S1

Title: Increased putamen size in children with Down syndrome is associated with fewer internalizing behaviors

Authors: *M. DENNEHEY[1], R. GRZADZINSKI[2], R. T. SCHULTZ[4], K. N. BOTTERON[5], N. MARRUS[5], M. A. STYNER[7], A. C. EVANS[8], S. KIM[3], R. C. MCKINSTRY[6], G. GERIG[9], J. PIVEN[10];
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Abstract: Despite global brain volume reductions in individuals with Down syndrome (DS), the putamen remains comparatively intact or relatively enlarged compared to controls. Limited research has explored the behavioral impacts that the putamen may have in children with DS. Smaller putamen volume has been linked to increased non-suicidal self-injurious behavior in depressed adolescents. In addition, children and adolescents with DS show increased maladaptive, depressive and anxious behaviors compared to typically developing controls. However, the relationship between putamen volume and internalizing behaviors in DS is unknown. To study this relationship, school-aged (7-11 years old) children with Down syndrome (n=35), autism spectrum disorder (ASD; n=29), or typical development (TD; n=80) underwent an MRI scan. Their caregiver completed a parent report of internalizing (anxious, depressed and somatic) and externalizing (aggressive and rule breaking) behaviors (the Child Behavior Checklist; CBCL; Achenbach, 2000). ANOVAs compared subcortical volumes, as well as CBCL scores, between groups. Correlations between CBCL scores and subcortical volumes were separately conducted for each group. Similar to previous reports, the putamen volume was preserved (relatively enlarged) in children with DS, while other subcortical regions were significantly smaller compared to TD and ASD. Children with ASD showed higher internalizing scores compared to DS and TD, and both DS and ASD showed elevated externalizing scores compared to TD. Increased left and right putamen volume was also significantly associated with fewer internalizing behaviors in children with DS, and not in children with ASD or TD, despite

no significant difference in putamen volume between groups. These findings suggest that the putamen in DS may play an important and unique role in regulating internalizing behaviors when compared to ASD and TD.

Disclosures: M. Dennehey: None. **R. Grzadzinski:** None. **R.T. Schultz:** None. **K.N. Botteron:** None. **N. Marrus:** None. **M.A. Styner:** None. **A.C. Evans:** None. **S. Kim:** None. **R.C. McKinstry:** None. **G. Gerig:** None. **J. Piven:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.17/A17

Topic: A.06. Developmental Disorders

Support: NIH INCLUDE R01 AR078663

Title: Adult cognitive and behavioral phenotypes in the TcMAC21 mouse model of Down syndrome

Authors: *E. OTTE[1], N. GORDON[1], A. FOLZ[1], C. R. GOODLETT[2], R. ROPER[1];
[1]Biol., [2]Psychology, Indiana Univ. Indianapolis, Indianapolis, IN

Abstract: Cognitive and behavioral phenotypes associated with Down syndrome (DS), including intellectual disability, balance dysfunction, and reduced cognitive flexibility, have been widely studied using the Ts65Dn DS mouse model. However, limitations of this model - including the triplication of several non-human chromosome 21 (Hsa21) orthologs - may limit the translatability of these studies from murine data to human application. The Tc(HSA21,CAG-EGFP)1Yakaz/J (TcMAC21) model was created by inserting a freely segregating long arm of Hsa21 as a mouse artificial chromosome (MAC). Understanding the behavioral and cognitive phenotypes associated with this newer model may provide valuable insights into the neuropathology of DS. We hypothesized that trisomic TcMAC21 mice would display sex-specific altered behavioral phenotypes and cognitive impairment when compared to euploid controls. We tested TcMAC21 mice beginning at postnatal day 45 (P45) on a battery of behavioral and cognitive tests, including locomotor activity, gait, balance beam, and Morris water maze (MWM). Results indicated similar activity levels in both male and female euploid and TcMAC21 animals, though trisomic animals of both sexes spent significantly more time in the center of the testing field when compared to euploid controls. Additionally, both male and female trisomic animals displayed trends of increased stride length when compared to euploid controls, despite reductions in weights of TcMAC21 animals. Male TcMAC21 animals showed significant deficits in spatial learning and memory when tested in both acquisition and reversal trials on the MWM. These data indicate that TcMAC21 mice recapitulate some, but not all, of the cognitive phenotypes observed in other mouse models of DS. The large deficits during MWM reversal learning in male TcMAC21 animals are consistent with impairments in cognitive

flexibility, and both male and female trisomic animals display behaviors associated with reduced anxiety. This study introduced novel experiments in the TcMAC21 model, including gait and balance beam analysis, while also modifying and repeating locomotor and MWM protocols previously conducted. These data support previous thigmotaxis and MWM acquisition trial data, while highlighting sex-specific differences not previously found in reversal trials. These findings support the importance of including both male and female animals in future studies using TcMAC21, and additional testing should be performed to better understand the applicability of this model in studies of DS.

Disclosures: E. Otte: None. **N. Gordon:** None. **A. Folz:** None. **C.R. Goodlett:** None. **R. Roper:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.18/A18

Topic: A.06. Developmental Disorders

Support: TWU Division of Biology
TWU Research Enhancement Program
Woodcock Institute for the Advancement of Neurocognitive Research and Applied Practice

Title: Trisomy 21 influence on Alzheimer's disease pathological markers: the role of mevalonate pathway products

Authors: *M. TABASSUM, D. L. HYNDS;
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Abstract: Trisomy 21 (Down syndrome) is the most prevalent, hereditary genetic neurodevelopment disorder resulting in intellectual disability and developmental delay. Children with Trisomy 21 develop early-onset Alzheimer's disease, characterized by extracellular amyloid-beta (Aβ) plaques and hyperphosphorylation of the microtubule-binding protein tau leading to formation of intracellular neurofibrillary tangles and progressive cognitive decline. Because the gene for amyloid precursor protein (APP) is on Chromosome 21, Trisomy 21 could increase the production of Aβ plaques through a gene dose effect. However, it is less clear how Trisomy 21 leads to tau hyperphosphorylation. Interestingly, it was recently determined that protein geranylgeranylation, particularly an increase in this post-translational modification on RhoA and Rab3, majorly contributes to Alzheimer's disease. We hypothesize that dysregulation of the mevalonate pathway in Trisomy 21 leads to increased tau phosphorylation and development of Alzheimer's disease pathology. We have determined that manipulating the levels of the mevalonate pathway products cholesterol (decreased with 20 μM lovastatin or maintained in serum-free medium with 10 μg/mL synthetic cholesterol) or geranylgeranyl pyrophosphate

(GGPP) with 10 μM geranylgeraniol in the presence of 20 μM lovastatin leads to decreased or increased RhoA activation associated with cellular membranes. Western blotting assays indicated that manipulating the mevalonate pathway affects tau phosphorylation, but not the processing of APP. These assays suggest that both cholesterol and protein geranylgeranylation are associated with tau phosphorylation. We are confirming that pharmacological manipulation of the mevalonate pathway promotes RhoA and Rab3 geranylgeranylation preferentially in Trisomy 21 mouse cortical neurons compared to wild-type neurons, and that this leads to increased tau dysregulation. Confocal microscopic analysis of cellular cholesterol content and protein colocalization (by filipin cholesterol staining) is being correlated with tau hyperphosphorylation results. Together, these results indicate that manipulating the mevalonate pathway in Trisomy 21 neurons disrupts cholesterol production and prenylation pathways to increase phosphorylated tau levels. To establish a molecular link, we are currently assessing whether these effects are dependent on sterol regulatory element binding protein 2 (SREBP2) activation. Should these mechanistic insights into mevalonate-targeted mechanisms hold, they may identify new treatment strategies for Alzheimer's disease prevention and intervention.

Disclosures: M. Tabassum: None. **D.L. Hynds:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.19/A19

Topic: A.06. Developmental Disorders

Support: NIH NIDCD R01DC019735

Title: Feeding and swallowing deficits in the adult Ts65Dn mouse model of Down syndrome: Videofluoroscopic swallow studies and automated home cage monitoring

Authors: G. SINGHAL[1], E. FISHER[1], A. DOUGLAS[2], Z. XING[2], Y. E. YU[2], N. P. CONNOR[3], *T. J. GLASS[1];
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Abstract: Introduction: Down syndrome (DS), typically caused by trisomy of chromosome 21, is associated with swallowing difficulties. Our previous work identified atypical swallowing in the DS mouse model Ts65Dn. However, it remains unclear whether atypical swallowing in Ts65Dn coincides with altered eating and drinking behavior in the home cage environment. To more comprehensively evaluate feeding and swallowing in this model, we assessed adult Ts65Dn mice through Videofluoroscopic Swallow Studies (VFSS) and continuous home cage monitoring with automated quantification of daily eating and drinking behaviors. This integrated approach allowed us to evaluate both oromotor and swallowing function, as well as typical

feeding behaviors. We hypothesized oromotor dysfunction would be manifested in Ts65Dn mice in VFSS and automated cage monitoring metrics. Methods: At 5 months of age, Ts65Dn and control mice were evaluated using VFSS (n=11 Ts65Dn [7M, 4F]; n=22 controls [13M, 9F]) and PhenoTyper analysis (n=20 per group, with 10M and 10F in each group). VFSS metrics included swallow rate (SR), jaw excursion rate (JER), interswallow interval (ISI), and jaw cycle swallow ratio (JSR). PhenoTyper metrics included food (g) and water (ml) intake, lick counts, beam break duration (feeding engagement, s), and distance traveled over light and dark cycles (a measure of activity level, cm). Data from males and females were pooled and analyzed using t-tests and ANOVAs, with significance set at $\alpha<0.05$. Results: The Ts65Dn group showed significantly higher ISI and JSR than the control group, suggesting reduced swallow efficiency and prolonged oral processing times. In PhenoTyper analysis, the Ts65Dn group spent significantly more time interacting with food, as indicated by longer beam break durations, despite similar food intake to the control group. This suggests behavioral deglutition phenotypes consistent with reduced feeding efficiency. Additionally, the Ts65Dn group traveled significantly greater distances over 24 hours, particularly during the dark phase. Conclusions: Findings from both VFSS and PhenoTyper analysis suggest that Ts65Dn mice exhibit altered swallowing function, atypical feeding behavior, and increased activity levels. The behavioral feeding phenotypes observed through automated cage monitoring may represent compensatory behavior for swallowing impairments detected through VFSS. This integrated assessment approach enhances our understanding of DS-associated oromotor dysfunction and underscores the utility of combining real-time functional and behavioral phenotyping in models of complex neurodevelopmental conditions.

Disclosures: G. Singhal: None. **E. Fisher:** None. **A. Douglas:** None. **Z. Xing:** None. **Y.E. Yu:** None. **N.P. Connor:** None. **T.J. Glass:** None.

Poster

PSTR424: Angelman and Down Syndrome and Other Neurodevelopmental Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR424.20/Web Only

Topic: F.04. Voluntary Movements

Title: Cognitive function improved following Assisted Cycling Therapy (ACT) in children with Down syndrome

Authors: *S. D. R. RINGENBACH;
Col. of Hlth. Solutions, Arizona State Univ., Phoenix, AZ

Abstract: Cognitive functioning is a hallmark deficit for people with Down syndrome (DS) affecting many aspects of daily living. Our previous research has shown improvements in cognitive function in adolescents and adults with Down syndrome following Assisted Cycling Therapy (ACT). Early intervention in children with DS, however, is crucial to improve their quality of life as early as possible and has not been investigated in part because there is not a

bicycle to fit young children. The present study modified an adult-sized bicycle to test the feasibility of ACT in young children with Down syndrome. Thus, the aim of this study is to explore if Assisted Cycling Therapy (ACT) would be feasible and have positive effects on cognitive functions in children with DS. All eleven children with Down syndrome (Male=9, Female=2) between the ages of 5 and 15 years old ($M_{\text{chronological age}}$ = 11.6 years, $M_{\text{mental age}}$ = 4.2 years.) completed 2x/week for 8 weeks of 30 minutes of Assisted Cycling Therapy (ACT), which is riding a stationary bicycle with mechanical motor assistance to maintain a cadence at least 35% greater than their voluntary cycling speed. This demonstrated the feasibility of ACT with younger children with Down syndrome of both sexes. In addition, information processing was measured using a simple reaction time test and problem solving was measured by the Tower of London test pre and post the eight week intervention. The results revealed significant improvements in information processing (Mpre=1650ms, Mpost=1143ms), $t(10)=2.4$, $p=.01$ and problem solving (Mprepeaktrialcompleted=4.8, Mpostpeaktrialcompleted=6.8), $t(9) = 2.1$, $p=.03$ following the eight week ACT intervention. The results of this study are discussed with respect to the upward regulation of neurotrophic factors following increased intrinsic feedback during ACT, resulting in improved cognitive functioning within the prefrontal cortex.

Disclosures: S.D.R. Ringenbach: None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.01/A20

Topic: A.06. Developmental Disorders

Support: Sao Paulo Research Foundation (FAPESP) grant #2022/12762-1
Sao Paulo Research Foundation (FAPESP) fellowship 2024/12825-9

Title: An autism spectrum disorder caused by haploinsufficiency of Transcription Factor 4 is characterized by impaired neuronal differentiation and increased expression of ID1 and ID3

Authors: *B. B. HERNANDES, F. PAPES;
Dept. Genetics, Evolution, Microbiology, and Immunology, Inst. of Biol., Univ. of Campinas (UNICAMP), Campinas, Brazil

Abstract: Autism spectrum disorders (ASD) are characterized by abnormal cognitive, motor, and communication phenotypes that seem to arise from impaired cortical development. However, much is still unknown about the molecular and cellular pathophysiology of ASDs. Our study focused on Pitt-Hopkins Syndrome (PTHS), an ASD caused by haploinsufficiency of the Transcription Factor 4 (*TCF4*) gene. We used patient-derived neural cells in 2D culture and organoids to show that PTHS cells display decreased progenitor proliferation and impaired neuronal differentiation. These analyses were conducted on cells and organoids derived from 5 PTHS male patients and respective fathers as controls, chosen based on the availability of

samples and statistical power analysis, indicating that the observed effect sizes are large and that a minimum sample size of 4 individuals is required. For measuring neural progenitor cell (NPC) proliferation, we treated NPCs with EdU, followed by examination on a flow cytometer. This experiment showed that PTHS neural progenitors display an approximate half-fold reduction in proliferation rate. Moreover, we seeded NPCs and differentiated them into neurons, followed by staining with SOX2 and MAP2 antibodies to calculate the ratio between the numbers of SOX2+ progenitors and MAP2+ neurons. This experiment revealed that PTHS neuronal cultures exhibit a significantly reduced number of progenitors relative to the content of differentiated neurons. Importantly, single-cell RNA-sequencing data from PTHS cortical organoids point to a reduction in the overall content of neurons. Curiously, these proliferation and differentiation defects in PTHS were accompanied by much higher expression of ID1 and ID3, partners of bHLH transcription factors devoid of DNA-binding domains which have been shown to inhibit differentiation when overexpressed in several cell types. Particularly, we observed that the expression of ID1 and ID3 is approximately 6 times higher in neural progenitors of PTHS organoids. Additionally, bulk RNA sequencing revealed 4- and 3-fold increases in the expression of ID1 and ID3 in PTHS neural progenitor cells in 2D culture, respectively. Finally, we have knocked down *TCF4* using antisense oligonucleotides (ASOs) on differentiating neuronal cultures, followed by qPCR determination that a lower *TCF4* expression leads to higher expression of ID1 and ID3. These results suggest that *TCF4* haploinsufficiency is causally linked with impaired neuronal differentiation via increased ID expression. Our study sheds light onto an autism spectrum disorder and may provide future targets for pharmacological therapy.

Disclosures: B.B. Hernandes: None. **F. Papes:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor in a patent application (WO2022072709A1) filed by UC San Diego, which contains some results regarding correction strategies for TCF4 expression in Pitt-Hopkins Syndrome..

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.02/A21

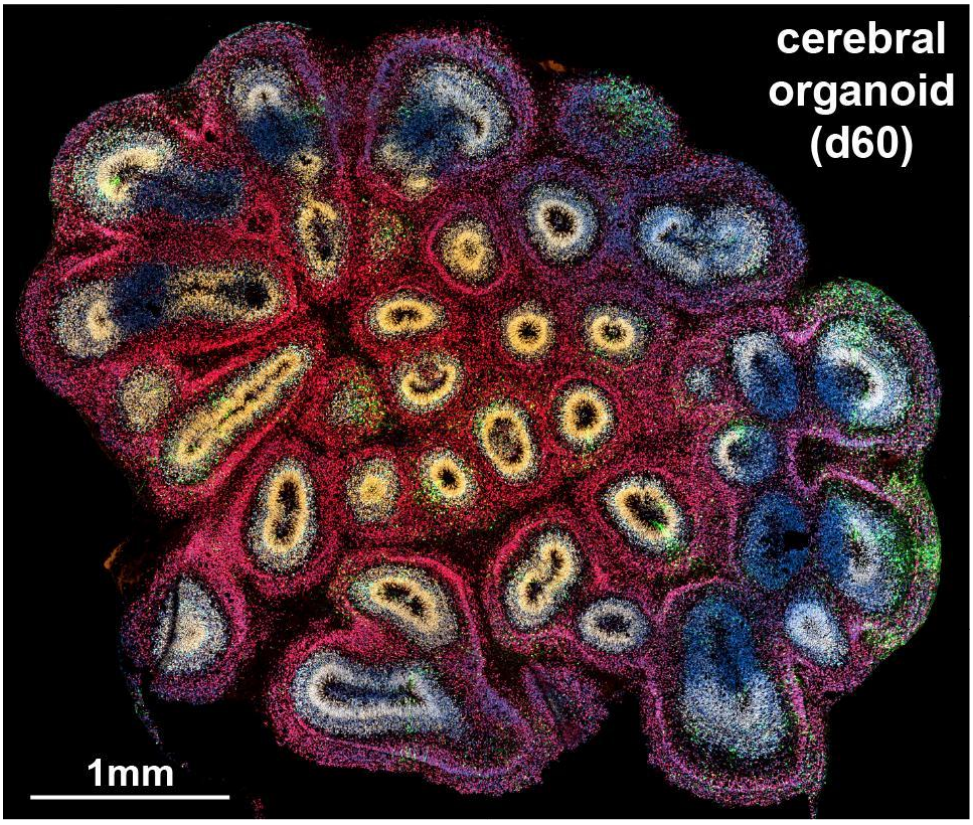
Topic: A.06. Developmental Disorders

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NEI K99 EY034603

Title: Parallel functional interrogations of autism risk genes reveal drivers of transcriptomic convergence and the female protective effect

Authors: *R. E. ANDERSEN[1], M. TALUKDAR[5], J. SONG[2], X. QIAN[3], D. EXPOSITO-ALONSO[4], R. DELGADO[5], C. A. WALSH[3];
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Abstract: The surprising number and functional diversity of genes implicated in autism spectrum disorder (ASD) has made it challenging to identify core pathophysiological mechanisms or envision interventions with broad therapeutic potential. Here, parallel CRISPR-Cas13-based knockdown of 28 ASD genes and neighboring long non-coding RNAs reveals striking convergence on shared transcriptomic effects and neurodevelopmental phenotypes in human neural progenitor cells and cerebral organoids. Perturbations of single ASD genes caused the widespread dysregulation of other ASD genes, and *de novo* reconstruction of gene regulatory networks uncovered the prominent risk gene *CHD8* as a critical driver of this convergence. The transcriptional activator *ZFX*, which escapes X chromosome inactivation in females, was also identified as a key regulator of ASD genes, revealing genetic underpinnings of the female protective effect. Thus, this study provides a crucial framework for uncovering how variants in diverse genes can cause convergent pathophysiological effects that ultimately result in a shared diagnosis.



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Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.03/A22

Topic: A.06. Developmental Disorders

Support: Congressionally Directed Medical Research Program W81XWH2110209

Title: Neuronal hyperactivity becomes mTORC1 independent due to epigenetic changes in Tuberous Sclerosis Complex

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Abstract: Tuberous Sclerosis Complex (TSC) is a neurodevelopmental disorder caused by pathogenic variants in *TSC1* or *TSC2*, resulting in chronic hyperactivation of mechanistic target of rapamycin complex 1 (mTORC1). Although mTORC1 is a well-established therapeutic target, the molecular mechanisms linking its dysregulation to long-term neuronal dysfunction remain poorly defined, limiting the effectiveness of current treatments. Here, we used human induced pluripotent stem cell (hiPSC)-derived excitatory neurons with biallelic *TSC2* loss to model the human neurodevelopmental trajectory of TSC. These neurons consistently exhibited reduced expression of the immediate early gene *EGR1* and impaired activity-dependent transcription. Integrated transcriptomic and epigenomic profiling revealed that these deficits stem from a failure in epigenetic maturation characterized by disrupted chromatin accessibility and histone modification dynamics during key developmental windows. By combining calcium imaging, optogenetics, and multielectrode array recordings, we further uncovered persistent network hyperexcitability in *TSC2*-deficient neurons. Strikingly, delayed mTORC1 inhibition with rapamycin mimicking postnatal treatment paradigms failed to reverse transcriptional deficits or normalize spontaneous activity. In contrast, early mTORC1 inhibition during neurodevelopment was significantly more effective in preserving transcriptional and functional integrity. This work identifies a previously unrecognized developmental window during which mTORC1 hyperactivity induces irreversible epigenetic and physiological changes in human neurons. These findings provide new mechanistic insight into how early mTORC1 dysregulation programs lasting neuronal dysfunction, even after mTORC1 signaling is restored. Our study establishes a direct link between developmental epigenetic remodeling and persistent hyperexcitability in a human model of TSC, revealing novel targets for durable therapeutic intervention. More broadly, this work demonstrates the power of stem cell-based disease models to uncover dynamic, developmentally timed mechanisms that are inaccessible in conventional systems, offering critical insights into the pathogenesis and treatment of TSC-associated neuropsychiatric disorders.

Disclosures: W. Afshar Saber: None. **J. Ruiz:** None. **N. Teaney:** None. **Z. Yang:** None. **I. Gisser:** None. **M. Sahin:** None. **K.D. Winden:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Program #/Poster #: PSTR425.04/A23

Topic: A.06. Developmental Disorders

Support: NSF Grant 2244127
AACPDM

Title: Dysregulation of transcription factor Nuclear factor I X (NFIX) in spastic cerebral palsy

Authors: B. ROMERO CARPIO[1], K. ROBINSON[2], S. K. YEAGER[3], V. PARASHAR[1], R. E. AKINS[4], M. SHRADER[5], ***M. BATISH**[1];
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Abstract: The Nuclear Factor I (NFI) family of transcription factors (NFIA, NFIB, NFIC, NFIX) orchestrates the expression of critical genes during embryonic development of muscle and the central nervous system. Among these, NFIX stands out as the sole NFI member involved in muscle development. Our recently published work revealed that a specific circular RNA derived from the *NFIX* gene (circNFIX) critically regulates the expression of MEF2C, a muscle-specific transcription factor, through its microRNA sponging activity of miR373-3p. We further showed that loss of circNFIX expression leads directly to diminished MEF2C levels in spastic cerebral palsy (CP), causing formation of aberrantly shortened and overstretched sarcomeres. Most critically, our preliminary investigations in CP muscle cells highlighted a significant, concomitant downregulation of not only circNFIX but also the linear NFIX transcript, suggesting a crucial, yet entirely unexplored, role for the linear NFIX protein in the pathophysiology of CP.Primary myoblasts (MBs) were isolated from muscle samples of CP patients (n=9) and non-CP controls (n=9) under an IRB-approved protocol. These MBs were then differentiated into myotubes (MTs). Cell cultures were validated by immunostaining for PAX7 and MYF5. We quantified NFIX mRNA levels in MBs, MTs, and skeletal muscle via qRT-PCR. NFIX protein expression and localization in MBs and MTs were assessed by immunofluorescence. To unravel NFIX's downstream consequences, the expression profiles of known NFIX transcriptional targets, crucial for muscle fiber formation, were evaluated by qRT-PCR. Complementary bioinformatic analyses were used to identify altered methylation patterns and putative binding sites for NFIX on the MEF2C promoter.We observed a reduction in NFIX mRNA as well as protein levels **in CP MBs, MTs, and skeletal muscle tissue.** Consequently, this led to a significant reduction in the expression of crucial downstream proteins indispensable for sarcomere structure and muscle contraction. Intriguingly, preliminary bioinformatic analysis

identified a plausible binding site for NFIX within the MEF2C promoter, strongly supporting a direct transcriptional regulatory role. Moreover, initial methylation analysis of the NFIX gene revealed an altered pattern in CP samples, suggesting epigenetic contributions to its reduced expression. These multifaceted findings robustly support our central hypothesis that NFIX downregulation represents a critical and previously unrecognized factor in the initiation and progression of the muscle pathology observed in spastic cerebral palsy, offering new avenues for therapeutic intervention.

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Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.05/A24

Topic: A.06. Developmental Disorders

Title: Regulation of CACNA1A expression by redirecting alternative splicing

Authors: *R. YANG[1], D. HUANG[2], K. HU[1], X. RUAN[1], C. HANSEL[2,3], X. ZHANG[1,3];
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Abstract: *CACNA1A* encodes the pore-forming subunit of the voltage-gated P/Q-type calcium channel, and hundreds of dominant *CACNA1A* mutations have been reported to cause a spectrum of neurological disorders, such as developmental delay, epilepsy, autism, ataxia, and hemiplegic migraine. However, the regulation of *CACNA1A* expression during development remains unclear, and there is limited treatment for *CACNA1A*-associated disorders. Here, we characterize an alternatively spliced exon in *CACNA1A* that induces nonsense-mediated mRNA decay (NMD) in mouse and human neural development. Genetic deletion of this NMD exon upregulated *Cacna1a* expression in the mouse brain, and alleviated long-term potentiation deficits and motor and learning abnormalities caused by a heterozygous knockout allele. We further developed splice-switching antisense oligonucleotides to bidirectionally regulate the NMD exon splicing and *CACNA1A* expression in human cells. Collectively, this study demonstrates the NMD exon as a bidirectional switch for *CACNA1A* expression, showing its potential as a therapeutic target for *CACNA1A*-associated disorders.

Disclosures: R. Yang: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PTC patent application. **D. Huang:** None. **K. Hu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PTC patent application. **X. Ruan:** None. **C. Hansel:** None. **X. Zhang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PTC patent application.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Program #/Poster #: PSTR425.06/A25

Topic: A.06. Developmental Disorders

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National Institute of Health and Medical Research (INSERM First-step)
European Union, WDR FEDER program

Title: Identification of novel genes and pathways essential for neural development

Authors: *A. AMELAN;
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Abstract: Neurodevelopmental disorders (NDDs) arise from disruptions in brain development, yet the underlying pathways remain incompletely understood. Here, we performed a genome-wide knockout screen and identified over 300 genes essential for neural differentiation. While enriched for known NDD genes, over 80% of the identified genes are novel. Dominant NDD genes were enriched for transcriptional regulators, whereas recessive NDD genes were predominantly involved in metabolic processes. Mouse models for eight genes (Eml1, Dusp26, Dynlrb2, Mta3, Peds1, Sgms1, Slitrk4 and Vamp3) revealed marked neuroanatomical abnormalities, including microcephaly in half of the cases. Focusing on PEDS1, a key enzyme in plasmalogen biosynthesis, we identified a bi-allelic variant in individuals with microcephaly, global developmental delay and congenital cataracts. In mice, Peds1 deficiency led to accelerated cell-cycle exit and impaired neuronal differentiation and migration. These findings uncover essential pathways for neural differentiation and provide a genetic framework for the discovery of novel genes associated with NDDs.

Disclosures: A. Amelan: None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Program #/Poster #: PSTR425.07/Web Only

Topic: A.06. Developmental Disorders

Support: NRF grant

Title: Spatio-temporal expression of bone morphogenetic proteins in the postnatal brain of a valproic acid-induced autism rat model

Authors: *P. M. MAMALI, B. C. MASEKO, I. MALUNGO;
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Abstract: Autism spectrum disorder (ASD) is a complex neurodevelopmental condition marked by deficits in social communication, repetitive behaviors, and sensory sensitivities. Despite advances in behavioral and genetic research, the molecular mechanisms driving atypical brain development in ASD remain unclear. Bone morphogenetic proteins (BMPs), members of the transforming growth factor-beta (TGF-β) superfamily, are critical regulators of neurogenesis, gliogenesis, dendritogenesis, and synaptic plasticity. While the role of BMPs during prenatal development is relatively established, their postnatal expression and function, particularly in the context of ASD, remain poorly understood. This study aims to investigate the spatio-temporal expression patterns of BMPs (2/4, 5/6/7, 12/13/14) and their receptors (BMPR1A, BMPR2) in the hippocampus and premotor cortex of valproic acid (VPA)-exposed and neurotypical Sprague-Dawley rats across postnatal development (days 0, 7, 14, 21, and 35). Using immunohistochemistry, stereology, and Golgi staining, we will quantify changes in BMP expression, neuronal complexity, and glial cell populations. Behavioural testing; spanning cognitive, motor, and anxiety domains will complement histological findings and allow for correlation between molecular expression and behavioral phenotype. We anticipate region- and age-specific alterations in BMP signaling in the VPA group, corresponding to disruptions in neuronal maturation and glial distribution. These findings will provide novel insights into the developmental trajectories of ASD-like phenotypes and may identify BMP-related pathways as potential therapeutic targets. By examining BMP dynamics during critical postnatal windows, this study seeks to bridge gaps in our understanding of neurodevelopmental plasticity in ASD.

Disclosures: P.M. Mamali: None. **B.C. Maseko:** None. **I. Malungo:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

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Program #/Poster #: PSTR425.08/A26

Topic: A.06. Developmental Disorders

Support: K01 MH119540
P50 HD103556
T32GM144636

Title: Investigating the behavioral and molecular effects of excess neonatal testosterone in wild-type mice

Authors: *P. QUINONES[1], E. HAGAN[2], T. ABEL[2], S. L. FERRI[3];
[2]Dept. of Neurosci. and Pharmacol., [3]Pediatrics, [1]Univ. of Iowa, Iowa City, IA

Abstract: Neurodevelopmental disorders (NDDs) are complex and highly heterogenous conditions that exhibit sex differences in onset, prevalence, and severity. One early developmental factor contributing to these disparities is the neonatal testosterone surge, which masculinizes the brain and establishes sex-specific circuits. Excess androgen exposure during this critical period is linked to increased NDD risk, yet the mechanisms remain unclear. We previously showed that a single neonatal testosterone propionate injection (100ug s.c. at P0) induces male-specific social behavior deficits in juveniles and contextual fear memory impairments in adulthood in C57BL/6J mice. In the current study, we tested whether these behavioral deficits could be pharmacologically rescued with D-cycloserine (DCS), a partial NMDA receptor agonist known to enhance receptor activity and modulate synaptic plasticity. DCS (32mg/kg, s.c) administered 30 minutes before behavioral testing rescued testosterone-induced behavioral deficits. The ability of DCS to restore behavior suggests impaired d-serine signaling, which is regulated by astrocytes and critical for NMDAR-mediated plasticity. To investigate the molecular mechanisms underlying both the testosterone-induced deficits and observed DCS rescue, we analyzed coronal brain sections containing the hippocampus and basolateral amygdala from juvenile males treated with either vehicle or testosterone at P0. These regions were selected due to their roles in social behavior and fear memory, as well as their known sexual dimorphism driven by sensitivity to perinatal gonadal hormones. Molecular analyses revealed increased PSD95 protein levels and decreased astrocytic markers in the hippocampus of testosterone-treated males. These findings suggest that early testosterone exposure may disrupt glia-neuron interactions, leading to long-term behavioral consequences. Ongoing studies using immunohistochemistry will assess NMDAR expression in both astrocytes and neurons to elucidate the cellular mechanisms contributing to the observed behavioral deficits. Identifying these molecular and cellular mechanisms is essential in identifying sex-sensitive therapeutic targets to support social and cognitive symptoms in NDDs.

Disclosures: P. Quinones: None. **E. Hagan:** None. **T. Abel:** None. **S.L. Ferri:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Program #/Poster #: PSTR425.09/A27

Topic: A.06. Developmental Disorders

Support: Massachusetts College of Pharmacy and Health Sciences Center for Research and Discovery Mini-Grant
UMass Boston internal project/start-up funds

Title: Long-term Behavioral Outcomes in Lactational Maternal Immune Activation Model

Authors: *P. EMADISAFAVI[1], C. HARTSGROVE[2], A. KENTNER[3], L. MAENG[4], S. DONALDSON[5];
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Abstract: Previous studies have underscored the importance of breastfeeding and parental care on offspring development and behavior. However, immune perturbations during lactation, a critical period for synaptic development and glial maturation, remain poorly understood, despite their potential long-term influence on neural circuits underlying behavior. This study evaluated the long-term behavioral effects of lactational maternal immune activation (MIA) in a mouse model. On postnatal day (PND) 8, lactating C57BL/6 dams received an intraperitoneal injection of lipopolysaccharide (LPS, 250 µg/kg) or saline. Offspring (n = 40; 10 males and 10 females per treatment group) were tested in adulthood (PND ~100) using a behavioral battery including the Open Field Test (OFT), Social Preference Test (SPT), and Novel Object Recognition (NOR). In the OFT, MIA-exposed offspring spent slightly less time in the center compared to controls, suggesting a potential increase in anxiety-like behavior. In the SPT, MIA animals showed a slightly increased preference for the novel conspecific relative to controls, particularly in males, suggesting a potential enhancement in social interest; however, these differences were not statistically significant. Social discrimination scores followed a similar trend. NOR performance was variable but showed no consistent memory impairments. Following behavioral testing, animals underwent a restraint stress protocol, after which brains were collected to evaluate microglial activation and c-Fos expression; these data will be presented at the meeting. Effects are modest and heterogeneous under the current experimental parameters. These results underscore the importance of developmental timing in shaping behavioral vulnerability to early-life immune events.

Disclosures: P. EmadiSafavi: None. **C. Hartsgrove:** None. **A. Kentner:** None. **L. Maeng:** None. **S. Donaldson:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Program #/Poster #: PSTR425.10/A28

Topic: A.06. Developmental Disorders

Support: Pilot Grant from Endeavor Health GRT03388
NIH 5R01NS119251-04

Title: Comparative Analysis of Neonatal Hypomyelination Models Using Spatial Transcriptomics

Authors: *R. B. FABRES[1], S. ZHANG[2], I. GOUSSAKOV[3], J. DUAN[4], A. DROBYSHEVSKY[5];
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Abstract: White matter injury (WMI) is a major cause of morbidity in premature infants, contributing to 5%-10% of cerebral palsy cases and up to 50% of cognitive and behavioral deficits in the United States. Two commonly used preclinical models, intermittent hypoxia (IH) and hypoxia-ischemia (HI) are widely employed to investigate the effects of WMI. The internal capsule (IC) and corpus callosum (CC) are major white matter tracts undergoing active myelination during the neonatal period, making them particularly vulnerable to hypoxic insults. This study aims to compare the effects of IH and HI models on myelination as well as the involvement of inflammatory cells in the IC and CC. We evaluated five oligodendrocyte (OL) subtypes, along with astrocytes, microglia, and activated microglia in IC and CC at postnatal day 12 (P12) and day 20 (P20) using spatial transcriptomics (CosMx, Novogene). For the HI model, C57BL/6 mice at P10 underwent permanent ligation of the left carotid artery followed by 45 minutes of hypoxia (8% O_2 / 92% N_2). For the IH model, P3 mice were exposed to 5% O_2 / 95% N_2, twice daily for five consecutive days. Animals were euthanized at P12 and P20, perfused transcardially, and brains were post-fixed in 4% paraformaldehyde, dehydrated in an ethanol series, embedded in paraffin, and coronally sectioned at 7 μm. Slides were submitted for CosMx spatial transcriptomic analysis (NanoString Technologies), and data analysis was performed using the Seurat package in RStudio. Our results demonstrate that IH and HI models affect OL populations differently, and these effects vary by brain region. In the IC, the IH model caused earlier and more pronounced changes in OL differentiation-related gene expression compared to HI. In contrast, the CC was more affected by HI. Moreover, in the HI group, mature OL s in both regions showed reduced expression of myelination-associated genes. This was accompanied by greater activation of inflammatory cells and increased intercellular communication between these cells and mature OLs, potentially contributing to the observed hypomyelination. Overall, our study provides critical insights into how each model of neonatal hypoxia differentially impacts white matter development. This knowledge can help refine preclinical strategies and guide therapeutic research tailored to the underlying pathology of each model.

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Poster

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Program #/Poster #: PSTR425.11/A29

Topic: A.06. Developmental Disorders

Support: Foundation For Prader-Willi Syndrome Research Grant 22-0321
Foundation for Prader-Willi Syndrome Research Grant 23-0447
Texas Tech University start-up grant
Cancer Prevention and Research Institute of Texas Scholar Award
RR200059

Title: Loss of the Prader-Willi Syndrome Gene Magel2 rewires the mouse hypothalamus transcriptome in fed and fasted states revealed by single-nucleus RNA sequencing

Authors: *D. STEPIHAR[1], C. BUSTAMANTE[2], M. HOYOS SANCHEZ[1], T. BAYAT[1], F. POPY[1], I. CASTRO-PIEDRAS[3], J. DIAZ-RIAÑO[5], I. PONOMAREV[4], S. MYERS[1], K. FON TACER[1];
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Abstract: *MAGEL2*, a member of the MAGE gene family, is a paternally expressed imprinted gene located on Chromosome 15, within the Prader-Willi Syndrome (PWS) critical region. Pathogenic loss-of-function mutations in *MAGEL2* cause Schaaf-Yang Syndrome (SYS), while the deletion of the whole gene contributes to the complex phenotype of PWS, both rare neurodevelopmental disorders characterized by neonatal hypotonia, endocrine dysfunction, hyperphagia, and severe disruptions in satiety and energy homeostasis. Despite *MAGEL2*'s established enrichment in the hypothalamus and known roles in endosomal protein trafficking and neuroendocrine signaling, its specific function in the hypothalamic response to metabolic challenges such as fasting remains undefined. To address this gap, we implemented a controlled 24-hour fasting paradigm to induce nutritional stress in adult male wild-type (WT) and *Magel2*$^{pA/m+}$ knockout (KO) mice (n=4 per group). Following fasting, hypothalami were rapidly dissected, snap frozen, and stored at -80C until single-nucleus RNA sequencing (snRNA-seq) was performed. We have pooled nuclei from two animals per group and used 10x Genomics Chromium technology for single nucleus RNA sequencing. Computational data processing and analysis was done by CellRanger (v7.2.0) and Seurat (v5.0.3), through which we identified and annotated 23 distinct hypothalamic cell populations using validated marker genes. Quantitative analysis revealed no significant shifts in cell type proportions across experimental groups, indicating cell composition stability. However, differential gene expression analysis uncovered extensive transcriptional reprogramming, predominantly within non-neuronal cell populations, including microglia, tanycytes, endothelial cells, and oligodendrocyte precursor cells, suggesting these cell types are highly responsive to both genotype and metabolic state. Collectively, these findings demonstrate that MAGEL2 modulates hypothalamic cellular and molecular adaptations to fasting-induced stress and provide novel insights into the pathophysiological mechanisms underlying feeding dysregulation in MAGEL2-related neurodevelopmental syndromes. This work lays a foundation for future functional studies aimed at targeting hypothalamic pathways to ameliorate metabolic symptoms in PWS and SYS.

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Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Program #/Poster #: PSTR425.12/A30

Topic: A.06. Developmental Disorders

Support: NIMH KO1MH119540
P50 HD103556

Title: Investigating the effects of neonatal testosterone dysregulation on development and behavior in wild-type mice

Authors: *E. HAGAN[1], D. PREUSCHL[2], A. P. LANGE[2], N. POLEKSIC[3], M. WEIS[4], B. POWERS[4], C. TESAR[1], P. QUINONES[4], S. L. FERRI[2];
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Abstract: Neurodevelopmental disorders (NDDs) are complex conditions which are characterized by an individual's ability to reach certain motor, developmental, cognitive and social milestones as these disorders affect how the brain develops and functions. NDDs are highly prevalent, affecting 1 in 6 individuals. Research has consistently demonstrated a male sex bias in NDDs; for example, Autism Spectrum Disorder affects 3 to 4 times as many males as females. The mechanism of this robust sex bias is not well understood. Here, we have utilized a novel experimental system of neonatal treatment with testosterone, to disrupt sex-specific developmental pathways in mice to determine their effects on development and behaviors relevant to NDDs. We have previously demonstrated that a single injection of testosterone administered to wild-type mice on the day of birth, during a critical period of brain masculinization akin to mid-gestation in humans, induces male-specific deficits in social approach and fear memory. The present experiments investigate the effects of excess neonatal testosterone on physical and neuromuscular reflex developmental milestones in mouse pups, including pinna unfolding, eye opening, surface righting, cliff avoidance and bar suspension. Preliminary data have revealed several developmental delays in mice treated on the day of birth with testosterone compared to control mice. We have also found decreased ultrasonic vocalizations, which are one of the earliest communicative behaviors between mother and offspring, in males treated with testosterone and changes in their vocal repertoire at postnatal day 5. To determine the brain circuity involved in this male susceptibility, we have used the brain wide activity mapping using the iDisco clearing method and lightsheet microscopy to quantify cFos immediate early gene expression throughout the brain. Our preliminary data indicates that excess testosterone during neonatal development causes differential activation in response to social approach in several brain regions, including the basolateral amygdala (BLA), hippocampus, and striatum. Our results suggest that brief periods of hormonal dysregulation during specific critical developmental periods can induce proximate and long-lasting neurodevelopmental disruptions. Currently we are investigating the mechanisms of these sex

specific vulnerabilities to developmental and behavioral deficits. These findings will aid in advancing the current understanding of how the brain is susceptible to neurodevelopmental impairments to improve risk assessment and help identify novel treatment targets.

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Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.13/A31

Topic: A.06. Developmental Disorders

Title: Fibrinogen Accumulation, Oxidative Stress, and Apoptosis in the Fetal Brain Induced by Maternal Influenza A Virus Infection

Authors: *R. J. GONZALEZ-RICON[1], A. M. OTERO[2], A. M. ANTONSON[4], I. CHALEN[3]; [1]Univ. of Illinois Urbana-Champaign, Champaign, IL; [2]Animal Sci., Univ. of Illinois Urbana-Champaign, Urbana, IL; [3]Dept. of Animal Sci., Univ. of Illinois Urbana-Champaign, Champaign, IL; [4]Animal Sci., Univ. of Illinois, Urbana-Champaign, Urbana, IL

Abstract: Maternal influenza A virus (IAV) infection during pregnancy is a risk factor for neurodevelopmental disorders (NDDs) in offspring. Oxidative stress, triggered by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, is a key mechanism in NDD pathogenesis. Fibrinogen, a plasma protein known for its role in coagulation, has also been associated with neurodegenerative inflammation and oxidative responses after breaching the blood-brain barrier. However, its presence and potential contribution to oxidative stress and apoptosis in the fetal brain following IAV-induced maternal immune activation (MIA) is unknown. We hypothesize that compromised vascular integrity following maternal IAV infection contributes to microglial response and subsequent neuronal loss in the developing fetal brain. Pregnant C57BL/6NTac mice were intranasally inoculated with IAV (10^4 $TCID_{50}$) or saline at gestational day (GD) 9.5. Fetal brains were collected at GD16.5 to assess apoptosis in $Sox2^+$ and $NeuN^+$ cells via cleaved caspase-3 and DNA fragmentation (ApopTag Red). To examine microglial ROS production and potential stimulation by fibrinogen, phosphorylated $p47^{phox}$—a cytosolic subunit of NADPH oxidase—will be measured in $P2RY12^+$ microglia alongside fibrinogen labeling. Our findings show increased fibrinogen accumulation in neurogenic regions of fetal brains exposed to maternal IAV, which positively correlates with Iba1 immunofluorescence. Preliminary data indicate region-specific apoptosis in subventricular zones and elevated ROS production in the meninges and cortex. Ongoing experiments will determine whether this region specificity contributes to long term disruptions in neuronal differentiation and circuit wiring. These results suggest that maternal IAV infection increases fetal blood-brain barrier permeability, as evidenced by fibrinogen accumulation in neurogenic regions. This extravasation of fibrinogen may stimulate microglial/macrophage oxidative

responses and contribute to apoptotic cell death, highlighting a potential mechanistic link between MIA, blood-brain barrier dysfunction, and disrupted fetal brain development.

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Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.14/A32

Topic: A.06. Developmental Disorders

Support: NIH Grant 5R01NS134128-23

Title: The impact of clinically relevant Syt1 variants on synaptic transmission and plasticity

Authors: *E. D. BAGATELAS[1,2], Q. ZHOU[3], E. T. KAVALALI[2];
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Abstract: Baker Gordon Syndrome (BAGOS), or Synaptotagmin-1 associated neurodevelopmental disorder, is a rare condition characterized by global developmental delay, hypotonia, facial dysmorphisms, ophthalmic abnormalities, hyperkinetic movements, and absent speech. Fewer than 40 cases have been identified since its classification in 2015, all associated with *de novo* mutations in the *SYT1* gene encoding synaptotagmin-1 (syt1), a calcium-sensing protein essential for neurotransmitter release. Despite established clinical phenotypes, the mechanistic impact of these mutations on synaptic transmission and plasticity remains poorly understood. This study focuses on 11 disease-associated *syt1* variants, localized to the conserved C2A and C2B domains, and elucidates their effects on neurotransmitter release and synaptic plasticity. Using electrophysiology and pharmacology in primary neuronal cultures, this work investigates how specific point mutations in syt1 alter its synaptic function, disrupt intramolecular interactions, and impair mechanisms of plasticity. Understanding these mechanisms is essential for uncovering BAGOS pathophysiology and informing future therapeutic development.

Disclosures: E.D. Bagatelas: None. **Q. Zhou:** None. **E.T. Kavalali:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.15/A33

Topic: A.06. Developmental Disorders

Support: FRIA - FNRS

Title: Understanding the molecular mechanisms causing the Van Maldergem syndrome

Authors: *K. STAM, J. ANGÉLIQUE, Y. JOSSIN;
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Abstract: The organization of the six-layered cerebral cortex is dependent on a tight coordination and regulation of the proliferation, differentiation of the neural stem cells and migration of the neurons. Disruptions in these processes can lead to malformations of the cortex. In the Van Maldergem syndrome, mutations in *Dchs1* or *Fat4* genes result in intellectual disabilities and neuronal heterotopia. While the defect was described as partially resulting from a dysfunctional cortical progenitor proliferation, the mechanism leading to this heterotopia is still unclear. Indeed, Fat4 and Dchs1 are also expressed in the cortical migration zone. But their functions in postmitotic neurons and migration in the cerebral cortex are not known and they could be one of the main causes of neuronal heterotopias found in the Van Maldergem syndrome. Using *in vivo* gain- and loss-of-function mouse models, combined with molecular and cellular approaches, we dissected the molecular and cellular mechanism by which Fat4 and Dchs1 control excitatory neuronal migration in the developing neocortex.

Disclosures: K. Stam: None. **J. Angélique:** None. **Y. Jossin:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.16/A34

Topic: A.06. Developmental Disorders

Title: Developmental abnormalities of cerebellar granule neurons correlate with autistic traits in male Npc1 mice

Authors: *G. MASSA[1], S. CAMUSO[2], L. BABICOLA[3], R. STEFANELLI[1], M. RIVA[4], J. MORENO-BRAVO[4], M. FIORENZA[1,3], S. CANTERINI[1,3];
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Abstract: Despite being conventionally classified as a lysosomal neurodegenerative disorder, Niemann-Pick type C1 (NPC1) disease is shown to disrupt neurodevelopment, according to mounting data. In particular, behavioral abnormalities result from altered neural cell differentiation and functional maturation. Among these, we have previously demonstrated that

cerebellar granule cells (GCs), one of the most prevalent excitatory neuronal populations in the cerebellum, exhibit an imbalance between proliferation and differentiation in *Npc1* animals. Using Golgi staining, we observed morphological abnormalities in GCs of *Npc1* mice, including excessive dendritic branching, increased spine density, and delayed spine maturation throughout postnatal cerebellar development and adulthood (P11, P30, P60). These anomalies were evident in both sexes but followed distinct temporal trajectories: female mutants displayed earlier dysregulation of spine morphology, whereas male mutants showed more pronounced abnormalities in adulthood. These structural defects were accompanied by significant downregulation of key synaptic genes and proteins, such as Snap25, Shank3, and Nlgn3, suggesting impaired synaptic stability and function.
To ascertain whether these cellular phenotypes translated into region-specific anatomical changes, we employed iDISCO+ tissue clearing combined with 3D volumetric imaging of the cerebellar cortex and the dentate gyrus of the hippocampus, two brain regions characterized by high GC density, involved in cognitive and social functions. We detected significant volumetric abnormalities in both structures of *Npc1* mutants at P15, prior to the onset of overt neurodegeneration, supporting the hypothesis of GC-driven regional vulnerability.
Changes in ultrasonic vocalization amplitude at P8 indicated early social communication disturbances in both sexes. By P30, however, only male mutants exhibited reduced sociability in the Three-Chamber Test, suggesting a sex-specific susceptibility to a typical autism-relevant behavioral phenotype.
In summary, our results show that only male *Npc1* mutants exhibit changes in social behavior linked to slightly distinct patterns of aberrant CG differentiation in male and female *Npc1* mice. This model offers a valuable tool for investigating the developmental mechanisms underlying neurodevelopmental disorders, including autism spectrum conditions.

Disclosures: G. Massa: None. **S. Camuso:** None. **L. Babicola:** None. **R. Stefanelli:** None. **M. Riva:** None. **J. Moreno-Bravo:** None. **M. Fiorenza:** None. **S. Canterini:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

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Topic: A.06. Developmental Disorders

Support: the National Natural Science Foundation of China (32071040 to BL, 82071241 and 81871048 to LH)
Guangdong Basic and Applied Basic Research Foundation (2023B1515040019 to BL)
Guangdong Project (2017GC010590 to BL)

Title: Early life stress (ELS)leads to abnormal cerebellar development in mice

Authors: *M. YAN[1], X. ZHANG[2], L. HUANG[3], B. LI[4];
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Abstract: Early-life stress(ELS) is a significant risk factor for neurodevelopmental disorders(NDD) in adults. Although the cerebellum has been demonstrated to be involved in regulating higher-order functions such as cognition, social behavior, and emotion, and its developmental process is crucial for the formation of various behaviors, moreover, cerebellar development exhibits heightened susceptibility to environmental perturbations. However, the impact of early-life stress on cerebellar development remains unclear. In this study, using an early maternal separation (MS) model, we found that adult MS mice exhibit abnormal cerebellar development. Although the thickness of individual cortical layers in the cerebellum showed no significant changes, Localized regions of the cerebellar cortex exhibited disrupted lamination, with the Purkinje cell layer invading the internal granular layer. Further investigation revealed a marked reduction in the density of Purkinje cells—the sole output neurons of the cerebellar cortex. Morphological analysis of the surviving Purkinje cells demonstrated decreased dendritic branching and reduced maximal radial extent in MS mice compared to WT mice, indicating morphological simplification. Electrophysiological recordings further confirmed diminished intrinsic excitability of Purkinje cells in MS mice. These results collectively indicate that early-life stress induces cerebellar developmental abnormalities, primarily characterized by reduced Purkinje cell density and morphological simplification.

Disclosures: M. yan: None. **X. Zhang:** None. **L. Huang:** None. **B. Li:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Topic: A.06. Developmental Disorders

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NIH Grant P50 HD103556
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Simons Foundation Autism Research Initiative (SFARI) Grant 345034
Roy J. Carver Chair in Neuroscience

Title: Ino80e overexpression rescues male-specific DNA damage in direct pathway striatal neurons of 16p11.2 hemideletion mice

Authors: *B. KELVINGTON[1], J. KIM[2], R. FAIR[1], J. KASUYA[1], T. ABEL[3];
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Abstract: 16p11.2 hemideletion (16p DEL) confers a high risk for neurodevelopmental disorders (NDDs) with males more likely to have an NDD diagnosis and report greater impairments than females, which is consistent with an overall sex-bias in NDDs. Male, but not female, mice modeling 16p DEL exhibit deficits in reward learning. However, the cellular and molecular basis for this sex-specific behavior is unknown. We found that dopamine receptor D1-expressing medium spiny neurons (D1+ MSNs), participants in the direct striatal pathway, play a crucial role in reward learning deficits resulting from 16p DEL, as conditional deletion in this population recapitulates this male-biased behavior. These neurons in the nucleus accumbens also exhibit decreased *in vivo* activation in response to a rewarding stimulus. Accumbal D1+ MSNs of 16p DEL males exhibit increased DNA damage, as assessed by γH2AX puncta, and decreased expression of the repair protein 53BP1, suggesting that disrupted DNA repair may underpin D1+ MSN dysfunction. Interestingly, overexpression of *Ino80e*, a gene located within the 16p11.2 region and a component of the Ino80 chromatin remodeling complex, ameliorates DNA damage in male D1+ MSNs. The Ino80 is known to facilitate DNA repair through chromatin remodeling at sites of DNA damage. These data implicate male-biased disruptions in DNA repair as a contributor to sex-specific vulnerability in NDDs and suggest that targeting DNA repair pathways may offer new therapeutic opportunities to ameliorate the most challenging aspects of NDDs.

Disclosures: B. Kelvington: None. **J. Kim:** None. **R. Fair:** None. **J. Kasuya:** None. **T. Abel:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Topic: A.06. Developmental Disorders

Support: NIH 1K08NS112598
CDMRP W81XWH2110209
NIH R01NS113591

Title: Non-cell autonomous effects of second hit variants in organoids and cortical tubers in Tuberous Sclerosis Complex

Authors: *K. D. WINDEN[1], I. GISSER[1], T. T. PHAM[1], J. RUIZ[1], K. HARBAUGH[1], T. KASAI[2], S. CHELVANAMBI[2], S. SINGH[2], M. SAHIN[1];
[1]Boston Children's Hosp., Boston, MA; [2]Brigham and Women's Hosp., Boston, MA

Abstract: Structural abnormalities are common causes of refractory epilepsy, and while progress has been made in understanding the genetic changes associated with these malformations, the pathogenic mechanisms often remain unclear. Dysregulation of the mechanistic target of rapamycin (mTOR) pathway contributes to a subset of focal cortical dysplasia types, including malformations observed in patients with Tuberous Sclerosis Complex (TSC). Heterozygous inactivating variants in TSC1 or TSC2 are sufficient to cause this disease, but second hit variants in these genes have been identified in several pathological lesions associated with TSC. However, most cortical malformations in TSC do not have second hit variants, and therefore, a critical question is whether these genetic changes are necessary for their development. We used organoids generated from heterozygous patient-derived induced pluripotent stem cells and isogenic stem cells with second hit variants, and we found that the presence of TSC2-null cells impaired excitatory cortical neuron differentiation of surrounding cells. Furthermore, we demonstrated that this is accomplished by factors secreted in extracellular vesicles from TSC2-null cells and that this is associated with inhibition of the transcriptional coactivator, YAP1. Knockdown of one specific factor, AMOT, in TSC2-null cells rescued YAP1 expression and neuronal differentiation. Finally, we analyzed cell type specific gene expression in malformations in patients with TSC and observed similar patterns of dysregulation to those identified in organoids. These data define a novel pathogenic mechanism underlying the development of focal brain malformations in TSC and related mTORopathies, which will aid in understanding the epileptogenicity of these lesions.

Disclosures: K.D. Winden: None. **I. Gisser:** None. **T.T. Pham:** None. **J. Ruiz:** None. **K. Harbaugh:** None. **T. Kasai:** None. **S. Chelvanambi:** None. **S. Singh:** None. **M. Sahin:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Topic: A.06. Developmental Disorders

Support: research grant to F.P. (#2022/12762-1)
research fellowships to P.K.K.F. (#2024/18734-5), G.D.V. (#2024/20077-2), B.B.H. (#2024/12825-9), and J.G.R.B. (#2025/09026-0).

Title: Brain organoids reveal impaired Netrin-1 signaling in Pitt-Hopkins Syndrome, a monogenic autism spectrum disorder

Authors: *F. PAPES, G. D. VERÇOSA, N. GASPARINE FIGUEIREDO, P. K. K. FORTI, B. B. HERNANDES, L. LEE DEPIERI, J. G. R. BUENO;
Dept. Genetics, Evolution, Microbiology, and Immunology, Inst. of Biol., Univ. of Campinas (UNICAMP), Campinas, Brazil

Abstract: Autism spectrum disorders (ASD) are characterized by clinical manifestations across a range of phenotypic domains; however, much is unknown about their molecular pathophysiology. In this project, we have chosen to investigate Pitt-Hopkins Syndrome (PTHS), a monogenic type of autism caused by haploinsufficiency of the *TCF4* gene, which codes for the Transcription Factor 4 protein. This condition displays a combination of profound cognitive and motor disabilities, absence of speech, *corpus callosum* dysgenesis, as well as peculiar facial features. We have used brain organoids derived from PTHS patients to probe their molecular alterations, via a combination of single-cell and bulk transcriptomics, immunostaining, and functional assays in vitro. Single-cell RNA sequencing indicated that the mutations in *TCF4* cause a deficit in the contents of several neuronal subtypes during neural development, including deep-layer (CTIP2+) and superficial-layer (SATB2+) cortical neurons. Our results further show that there is a 50% decrease in the ratio between MAP2+ neurons and SOX2+ neural progenitor cells, as revealed by immunostaining of patient-derived neuronal cultures and of a post-mortem sample. Together, these results suggest a lower differentiation rate in the developing PTHS cortical tissue. Strikingly, in these samples, we also identified a significant alteration in the expression of several receptors for the chemotactic signaling molecule Netrin-1, including UNC5C and DCC. The expression of UNC5C exhibits an approximately 2-fold reduction in PTHS neurons in 2D culture and in glutamatergic neurons of PTHS organoids, as verified by bulk, single-cell RNA sequencing, and immunostaining experiments. Importantly, these effects could be reversed in neurons and organoids in which the *TCF4* mutations were rescued back to the normal genotype, suggesting that Netrin-1 signaling depends on and acts downstream of TCF4 transcriptional regulation. Considering that Netrin-1 signaling is important for cortical neurogenesis and for the formation of long-range neuronal connections to and from the cortex, we hypothesized that the PTHS neuronal differentiation defects involve deficits in Netrin-1 signaling. In keeping with this hypothesis, Netrin-1 administration to PTHS neurons was able to rescue the aberrant differentiation phenotype, as well as the formation of neuronal projections. Our results may contribute to the identification of specific molecular targets for pharmacological therapy in a devastating childhood autism spectrum disorder.

Disclosures: F. Papes: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor in a patent application (WO2022072709A1) filed by UC San Diego, which contains some results regarding correction strategies for TCF4 expression in Pitt-Hopkins Syndrome.. **G.D. Verçosa:** None. **N. Gasparine Figueiredo:** None. **P.K.K. Forti:** None. **B.B. Hernandes:** None. **L. Lee Depieri:** None. **J.G.R. Bueno:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Program #/Poster #: PSTR425.21/A39

Topic: A.06. Developmental Disorders

Support: Sao Paulo Research Foundation (FAPESP) grant #2022/12762-1
Sao Paulo Research Foundation (FAPESP) fellowship 2024/18734-5

Title: Organoids and neurons in 2D culture reveal that autism-related haploinsufficiency of Transcription Factor 4 is accompanied by defects in neuronal migration and impaired expression of chemotactic guidance molecules during development

Authors: *P. K. K. FORTI[1], N. GASPARINE FIGUEIREDO[2], F. PAPES[2];
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Abstract: Autism spectrum disorders (ASD) are characterized by impaired cognitive, motor, and communication abilities, but much is still unknown about their molecular and cellular mechanisms. Understanding these characteristics is fundamental to developing effective therapeutic strategies. In this study, we chose to investigate Pitt-Hopkins Syndrome (PTHS), an ASD monogenically caused by mutations in the Transcription Factor 4 gene, which allows us to correlate the disease's molecular features and clinical manifestations. Our analysis of patient-derived neurons and organoids showed that the neural tissue displays neuronal migration defects, as judged by live-cell imaging, as well as evaluation of the expression of migration markers via immunostaining, RT-qPCR, and bulk and single-cell transcriptomics. These analyses were conducted on cells and organoids derived from 5 PTHS male patients and respective fathers as controls, chosen based on the availability of samples and statistical power analysis, indicating that the observed effect sizes are large and that a minimum sample size of 4 individuals is required. For live-cell-imaging, a gap was created by removing a streak of cells from the plate floor in neuronal cultures differentiated from neural progenitor cells, followed by imaging every 12 hours for 10 days. Image scoring was performed using specialized software, revealing that some PTHS neuronal cell lines show a reduction in neuronal migration, as determined by the number of cells occupying the gap, the area filled by neuronal processes, as well as migration speed. Moreover, the expression of neuronal migration marker CRMP1 exhibits an approximately 10-fold reduction in PTHS neurons and a 2-fold reduction in PTHS organoids, as verified by bulk and single-cell RNA sequencing experiments, respectively. We also detected much lower cytological expression of CRMP1 in PTHS neurons in 2D culture and in organoids. Importantly, these migration defects were accompanied by dysregulated expression of several chemotactic guidance molecules, including Ephrins and their receptors. Particularly, the expression of receptors EPHA5 and EPHA6 was severely reduced in brain organoids, including a diminishment of 94% and 80% in excitatory pyramidal neurons, respectively. Additionally, bulk RNA sequencing revealed a reduction in the expression of EPHA5 and EPHA6 in PTHS neurons in 2D culture. We raise the hypothesis that the migration defects observed in patient-derived cells are due to changes in chemotactic signaling. Our results shed light on the pathophysiology of PTHS and may contribute to the development of specific therapies for autism spectrum disorders.

Disclosures: P.K.K. Forti: None. **N. Gasparine Figueiredo:** None. **F. Papes:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor in a patent application (WO2022072709A1) filed by UC San Diego, which contains some results regarding correction strategies for TCF4 expression in Pitt-Hopkins Syndrome..

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.22/A40

Topic: A.06. Developmental Disorders

Support: NIH Grant GR127112

Title: Cell fate shift in basal ganglia organoids modeling tourette syndrome.

Authors: *R. RAUTHAN[1], G. GRYGLEWSKI[2], N. FARAH[3], F. M. VACCARINO[4];
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Abstract: Tourette syndrome (TS) is a childhood onset neuropsychiatric disorder characterized by repetitive involuntary movements or vocalizations known as tics that are caused by deficits in sensorimotor gating. Brain postmortem immunohistochemical and RNA-sequencing studies from severe TS cases show ~50% decrease in Parvalbumin fast-spiking (PV+), Somatostatin/NOS and cholinergic (ChAT+) interneurons in the dorsal striatum (caudate and putamen) of the basal ganglia (BG) but the time of origin and developmental mechanisms of this interneuron (IN) deficit in TS remains unclear. Inadequate treatments available for TS necessitate better understanding of its pathophysiology. We have previously recapitulated interneuron deficit in organoids derived from induced pluripotent stem cell (iPSC) lines of 5 patients with persistent TS, patterned to a ventral forebrain fate and observed significant downregulation of early regulators of interneuron identity (NKX2.1, DLX1-6, MEF2C, LHX8, SOX6 and SIX3), increase in GLI2/GLI3 (which are repressor proteins of the SHH pathway) and ventral telencephalic mis-patterning during organoid differentiation in TS. In the current study, we investigate the reasons for this altered fate of the basal ganglia progenitors by generating BG organoids comprising the three ganglionic eminences (GE) and adjacent regions of the diencephalon/mesencephalon derived from iPSC lines of 13 subjects with clinical diagnosis of persistent or remitted TS and 13 neurotypical control participants. From a preliminary scRNA sequencing analysis of BG organoids at terminal neural differentiation day 30 (TD30), we confirm the depletion of INs in the TS as compared to controls (8 out of 11 persistent TS lines show less than 10 percent composition of ganglionic eminence IN cell types as opposed to 4/13 in controls). We also observe a concomitant increase in TH+ cells of the midbrain region in TS compared to controls, suggesting a cell fate shift from the ventral forebrain identity. We are following up with a multiome analysis to fine map the cell-type specific transcriptomes and active chromatin states at two time points in organoids, post neural induction and TD30. Our findings will dissect out the gene regulatory network associated with GE interneuron loss and this developmental cell fate shift in TS.

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Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Program #/Poster #: PSTR425.23/A41

Topic: A.06. Developmental Disorders

Support: NIH Grant 1R44ES036385

Title: Human iPSC-derived CNS and blood-brain-barrier platform for assessing toxicity of environmental and industrial compounds on neuronal activity, glial morphology, and BBB properties.

Authors: *K. L. GORDON[1], C. G. RINES[2], S. GILMORE-HALL[2], L. HARRISON[4], V. A. MARTINEZ[5], A. SMITH[4], B. TEKWANI[3], J. PRICE[3], I. M. PEDERSEN[5], P. MCDONOUGH[3]; [1]Biol., Vala Sci. Inc., San Diego, CA; [2]Biol., [3]Vala Sciences, Inc., San Diego, CA; [4]Biol., Vala Sciences, Inc, San Diego, CA; [5]The Scintillon Inst., San Diego, CA

Abstract: Neurodevelopmental disorders (NDs) affect nearly 15% of children in the US. Certain environmental toxicants and industrial chemicals have been linked to NDs, with the developing CNS being vulnerable to chemical exposure. We are developing in vitro human-relevant platforms for screening toxic effects of chemicals on neurodevelopment in advance of their linkage to adverse human effects. Five representative compounds of various classes were chosen from the NIEHS Developmental Neurotoxicity Screening Assay Chemical Lists and tested in 2D tri-culture and 3D blood-brain-barrier (BBB) models to assess toxicity. 2D hiPSC-derived tri-cultures of neurons, astrocytes and microglia were established in 384-well dishes. Cultures were matured, then treated with test compounds for 48 or 96 hours. For live functional assays, cultures were loaded with calcium dye, TMRM, and Hoechst and imaged on the IC200-Kinetic Image Cytometer with videos for calcium transients acquired at 4 Hz. Cultures were immunostained for neurons (Map2), astrocytes (GFAP), and microglia (IBA1). Functional and morphological changes were assessed using CyteSeer analysis software. For the BBB models, 3D cultures of primary human brain microvascular endothelial cells (BMEC) alone, or co-cultures of BMEC, iPSC-derived pericytes and astrocytes (3-cell type BBB) are established using the 64-chip Mimetas platform with Col 1/Col IV ECM and flow to create sheer stress. Continuous 3D TEER and dual barrier integrity (BI) assays performed every 2-3 days are used to assess intact tubule formation and barrier integrity, including prior to and 72 hours after compound exposure. 3D chip cultures are fixed and stained for ZO-1 to detect changes in BBB structure and function. BMEC tubule coverage by astrocytes and pericytes are assessed by dual-IF analysis of astrocytes (GFAP/S100β/AQP4), pericytes (NG2), and BMEC (ZO-1). Azoxystrobin (AZOX) had the strongest effects on CNS tri-cultures, causing neuron and microglial death, mitochondrial depolarization, decrease in active cells and spikes per cell, and altered microglia morphology. Dolutegravir, chlorpyrifos (CPS), and bisphenol-A (BPA) reduced astrocyte branching. In the BMEC BBB model, CPS, BPA, PFOA, and AZOX all led to increased tracer permeability, loss of TEER, and changes to TJP expression/structure, demonstrating loss of barrier integrity after 6

days of culture. When employing the full 3-cell type 3D BBB model, we determined significant BBB toxicity only by BPA (and rotenone). Our 3D BBB and 2D CNS models are an innovative platform for evaluating toxicity of environmental and industrial chemicals to both the BBB and CNS.

Disclosures: K.L. Gordon: None. **C.G. Rines:** None. **S. Gilmore-Hall:** None. **L. Harrison:** None. **V.A. Martinez:** None. **A. Smith:** None. **B. Tekwani:** None. **J. Price:** None. **I.M. Pedersen:** None. **P. McDonough:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

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Program #/Poster #: PSTR425.24/A42

Topic: A.06. Developmental Disorders

Title: Developing an optical electrophysiology assay for functional analysis of patient-specific SCN2A variants in human NGN2-derived neurons

Authors: S. M. LARDELL[1], ***C. NODIN**[1], J. PIHL[1], P. KARILA[1], A. ELTOKHI[2], S. K. ADNEY[3], K. S. HO[4], S. M EGAN[4], J. R. COTTRELL[4];
[1]Cellectricon AB, Mölndal, Sweden; [2]Dept. of Biomed. Sci., Mercer Univ. Sch. of Med., Columbus, GA; [3]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [4]FamilieSCN2A Fndn., Gettysburg, PA

Abstract: Pathogenic variants in the *SCN2A* gene, which encodes the voltage-gated sodium channel $Na_V1.2$, are causative of a broad range of neurodevelopmental disorders, including epilepsy, autism spectrum disorder, and intellectual disability. Despite the growing interest in *SCN2A*-related disorders, the field lacks scalable, standardized functional screening assays to interpret the effects of variants on neuronal excitability and to test new therapeutic candidates in a human neuron context. To address this need, we are developing an optical electrophysiology assay using stem cell-derived human neurons with engineered disease-associated *SCN2A* variants. Using the CellAxess platform from Cellectricon, the assay will integrate Ca^{2+}-dye fluorescence imaging with electrical field stimulation of NGN2-derived excitatory neurons grown in 384-well plates. In parallel, using CRISPR/Cas9, we are introducing patient-specific *SCN2A* variants, including gain-of-function, loss-of-function, and mixed function variants, into an isogenic human pluripotent stem cell line. This assay system will support preclinical testing of multiple therapeutic modalities, such as small molecules, antisense oligonucleotides, and gene editing, tailored to specific variant effects and designed to restore normal neuronal excitability. While initially focused on *SCN2A*, the assay framework is adaptable to other channelopathies, such as those involving *SCN1A*, *SCN3A*, and *SCN8A*, which share overlapping pathophysiology. This broader applicability positions the platform as a tool for advancing therapeutic development across a spectrum of ion channel-related disorders.
Here, we discuss the progress made, through the concerted efforts of the non-profit organization

the FamilieSCN2A Foundation and the biotech Cellectricon, in understanding and developing new treatments for *SCN2A*-related disorders.

Disclosures: S.M. Lardell: A. Employment/Salary (full or part-time): Cellectricon AB. **C. Nodin:** A. Employment/Salary (full or part-time): Cellectricon AB. **J. Pihl:** A. Employment/Salary (full or part-time): Cellectricon AB. **P. Karila:** A. Employment/Salary (full or part-time): Cellectricon AB. **A. Eltokhi:** None. **S.K. Adney:** None. **K.S. Ho:** None. **S. M Egan:** None. **J.R. Cottrell:** None.

Poster

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Topic: A.06. Developmental Disorders

Support: NYS OPWDD

Title: Lead Exposure During Neurodevelopment Alters Brain Volume in Dugesia dorotocephalata

Authors: I. MASSARO[1], M. SCOTTO[2], *S. GUARIGLIA[1];
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Abstract: Early brain overgrowth is a hallmark of certain neurodevelopmental disorders, including autism spectrum disorder (ASD), and may be shaped by environmental exposures. To examine the impact of developmental lead (Pb^{2+}) exposure on brain morphology, we used *Dugesia dorotocephalata*, a planarian species capable of complete brain regeneration within seven days post-decapitation. Animals were continuously exposed to spring water (control) or Pb^{2+} at concentrations of 0.1 ppm, 0.25 ppm, or 0.5 ppm throughout the regenerative period. Brains were immunostained for synapsin (Developmental Studies Hybridoma Bank, Iowa) before iDISCO tissue clearing, imaged using a Fluoview 3000 confocal microscope (Evident Biosciences), and analyzed using FIJI. Three-dimensional segmentation was performed to define the brain as the region of interest (ROI) and calculate total brain volume. Pb^{2+} exposure significantly affected brain volume (one-way ANOVA, $F(3,36) = 8.941$, $p = 0.0001$). Post hoc Tukey's tests revealed that both the 0.1 ppm ($p = 0.0099$) and 0.5 ppm ($p = 0.0257$) groups had significantly reduced brain volumes compared to the control group. Interestingly, the 0.25 ppm group did not differ significantly from the control ($p = 0.8160$), suggesting a non-monotonic dose-response curve. This may reflect a narrow concentration window in which compensatory mechanisms transiently buffer against neuroanatomical disruption. Together, these findings demonstrate that developmental lead exposure alters brain volume in a dose-dependent, yet nonlinear manner. This work establishes a high-resolution volumetric analysis pipeline that combines synapsin labeling, optical clearing, confocal imaging, and 3D segmentation for quantifying neurodevelopmental outcomes in planarians. The model offers a manipulable and

sensitive platform for investigating how environmental toxicants impact brain structure during regeneration.

Disclosures: M. Scotto: None. **S. Guariglia:** None.

Poster

PSTR425: Molecular Mechanisms Underlying Developmental Disorders III

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR425.26/A44

Topic: A.06. Developmental Disorders

Support: Special Research Fund for Central Universities, Peking Union Medical College (2023-RC310-02)
National Natural Science Foundation of China (32170550)
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National Natural Science Foundation of China (32471041)
Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2024-I2M-ZD-012)

Title: Oncogenic fusions converge on shared mechanisms in intiating astroblastoma

Authors: *Y. SHI[1,2];
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Abstract: Chromosomal rearrangements and gene fusions are the initial events in the development of many cancers. Astroblastoma (ABM), a brain cancer of unknown cellular origin and challenging to treat, is associated with diverse in-frame gene fusions, including MN1-BEND2 and MN1-CXXC5 . However, it remains unclear whether these gene fusions contribute to tumorigenesis. Here we show in mice that these two ABM-associated fusions converge on similar molecular activities and initiate malignancy specifically in ventral telencephalon neural progenitors. BEND2 and CXXC5 recognize similar DNA motifs, which indicates a convergence on downstream gene regulation. Expression of MN1-BEND2 in ventral telencephalon neural progenitors results in aberrant cell proliferation, impaired differentiation, a perivascular occupancy pattern of cells reminiscent of ABM and acquisition of an ABM-associated transcriptional signature. By contrast, MN1-BEND2 expression in dorsal telencephalon neural progenitors leads to extensive cell death. This cell-type-specific malignancy depends on OLIG2 expression. Mechanistically, both ABM-associated fusion proteins (MN1-BEND2 and MN1-CXXC5) induce overlapping transcriptional responses, including the activation of a therapeutically targetable PDGFRα pathway. Collectively, our data suggest that distinct ABM-

associated fusions upregulate shared transcriptional networks to disrupt the normal development of ventral telencephalon neural progenitors, which leads to oncogenic transformation. These findings uncover new avenues for targeted ABM treatment.

Disclosures: Y. shi: None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.01/A45

Topic: A.07. Development of Neural Systems

Title: Advancing AAV Capsid Engineering for Targeted Gene Therapy Using PackGene's π-Icosa Platform

Authors: *I. SONG;
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Abstract: Adeno-associated virus (AAV) is a widely used gene delivery vector, but its clinical utility is constrained by limitations in tissue specificity, immune evasion, and transduction efficiency. To address these challenges, we developed the π-Icosa Capsid Engineering System, a platform combining rational design, directed evolution, and AI-driven prediction models to engineer AAV capsids with enhanced targeting, manufacturability, and reduced off-target effects. The platform integrates an AI-based targeting prediction model, built on a transformer architecture and pre-trained using protein language models, which achieved an AUC of 0.83 on directed evolution datasets for accurate tissue-specific tropism prediction. Building on these advancements, the π-Icosa platform employs a proprietary algorithm to design and screen diverse capsid libraries, followed by iterative in vivo testing to identify optimized variants. This approach has yielded novel AAV capsids with improved tissue tropism. Muscle-targeting variants PG016, PG017, and PG018 demonstrated superior transduction compared to AAV9 and MyoAAV 4A. CNS-targeting variant PG008 in mice, along with additional ongoing library screening, has resulted in many candidates that achieved 10^3-10^6-fold higher reporter gene expression in NHPs. Retinal-targeting variants PG021 and PG022 efficiently transduced retinal ganglion cells (RGCs), Müller glial cells, and inner nuclear layer (INL) cells. For ex vivo T-cell therapy, variants PG009, PG010, PG012, and PG013 exhibited 10x higher infectivity in primary human T cells compared to wildtype AAV6. Furthermore, to complement the engineering of these advanced AAV capsids, a manufacturability prediction model was developed to generate AAV mutants with high packaging efficiency (up to 97%), 2-3 times higher yields than wildtype AAV, and enhanced sequence diversity, enabling the discovery of novel capsids with improved properties. These results demonstrate the potential of integrating AI-driven approaches with rational design and directed evolution to overcome key gene therapy challenges. The π-Icosa

platform enables the development of highly specific, efficient, and manufacturable AAV variants, advancing the field toward safer and more effective therapeutic applications.

Disclosures: I. Song: None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

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Topic: A.07. Development of Neural Systems

Support: NIH Grant F30HD117619
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Title: All-optical in vivo circuit interrogation to test predictions from computational modeling unveils a role of parvalbumin interneurons in developmental cortical network desynchronization.

Authors: *M. WU[1], M. MARIANI[1], T. JAIN[4], A. KOTHARI[1], M. DIPOPPA[2], C. PORTERA-CAILLIAU[3];
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Abstract: Understanding how cortical circuits mature is critical as proper wiring of these circuits enables complex abilities such as sensory processing to develop. Initially, spontaneous neuronal activity in the developing neocortex is characterized by intermittent, brief bursts of synchronous network events that interrupt much longer periods of silence. Network activity then undergoes a crucial transition (during the second postnatal week in mice) from these large events to an asynchronous, sparse neuronal firing that is energetically and computationally more efficient. However, 1) the evolution of excitatory and inhibitory population dynamics during desynchronization and 2) the mechanisms driving desynchronization, have not been fully elucidated. Thus, we used in vivo longitudinal 2-photon calcium imaging in mice from postnatal days (P) 9 to 14 to characterize the evolution of network dynamics. We expressed GCaMP8s in Nkx2.1-Cre;Ai14 mice to simultaneously record from excitatory (Exc) neurons and inhibitory (Inh) neurons derived from the medial ganglionic eminence in layer 2/3 of the primary somatosensory cortex (S1). We found that the trajectories of Exc and Inh activity patterns diverge, such that correlations between Exc-Exc neuron pairs decrease and plateau by P13 while the correlation between Inh-Inh neuron pairs only slightly decreases. To gain mechanistic insight, we generated a computational model that incorporates different classes of Inh interneurons and imposed values of their density and synaptic strength across development based on published literature. This model reproduced the pairwise correlations observed experimentally. We then applied *in silico* perturbations to predict how manipulating the activity

of different interneuron subtypes would influence desynchronization. One model solution predicts that activation of the parvalbumin (PV) population will decrease network synchrony while activation of the somatostatin (SST) population will increase network synchrony during the second postnatal week. We tested this hypothesis using in vivo 2-photon optogenetics to acutely activate the PV or SST populations at P10, 12, and 14. To selectively activate PV interneurons, we used an intersectional genetic strategy in which we expressed Con/Foff-ChRmine, a red-shifted opsin, in conjunction with syn-GCaMP8s in Nkx2.1-Cre;SST-flp mice. This allows for simultaneous recording of network activity and activation of the opsin-expressing population. We show that activation of PV interneurons at P10 significantly decreases network synchrony. We also use Coff/Fon-ChRmine in SST-flp mice to selectively activate SST interneurons.

Disclosures: M. Wu: None. **M. Mariani:** None. **T. Jain:** None. **A. Kothari:** None. **M. Dipoppa:** None. **C. Portera-Cailliau:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.03/A47

Topic: A.07. Development of Neural Systems

Support: VIEP-BUAP
SECIHTI No. 1273741

Title: Adenosine enhances spontaneous vestibular afferent discharge via A_{2A}receptors in early chicken development

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Abstract: Purinergic compounds act as neurotransmitters and neuromodulators from the early stages of neuronal development. While P1 receptor activation modifies the activity of auditory afferents in the chicken embryo, its effect on vestibular fibers remains poorly understood. This study evaluated adenosine's effect on spontaneous vestibular afferent discharge in chicken (*Gallus domesticus*) during embryonic (E15, E18, E21) and early postnatal (P5) development using multi-unit extracellular recordings from the posterior ampulla nerve. Our results showed that adenosine perfusion [10 μM] significantly increased vestibular afferent discharge at all ages (E15 and E18: $p<0.01$; P5: $p<0.05$), with maximum effect at E21 (75.4 ± 28.1%, t-paired test: $t= -4.769$, $p<0.05$). Co-application with caffeine [100 μM] (non-selective antagonist) significantly inhibited this response (E15 and P5: $p<0.05$; E21: $p<0.01$), peaking at E18 (-70.48 ± 6.8%; t-paired test, $t = 5.402$, $p<0.001$), while theophylline [100 μM] (non-selective antagonist) reduced

adenosine response at E21 (-52.9 ± 5.2%; t-paired test: t= 7.213, p<0.001). Caffeine alone significantly decreased basal afferent discharge in an age-dependent manner (one-way ANOVA: $F_{(3,15)}$= 4.288, p<0.05; followed by Tukey's *post-hoc*: q= 4.183, p<0.05), with maximum reduction at E21 (-44.2 ± 8.8%; t-paired test, t =3.419; p<0.05). The A_{2A} receptor-specific agonist PSB-0777 [3 μM] increased afferent discharge at E21 (38.7 ± 8.8%; t-paired test: t= -3.494, p<0.01), an effect blocked by caffeine (-45.9 ± 8.3%; t-paired test: t=4.025, p<0.01). These results indicate that adenosine positively modulates spontaneous vestibular discharge through A_{2A} receptors. However, the differential magnitude of inhibition between endogenous adenosine effects and basal discharge reduction suggests the involvement of compensatory mechanisms or alternative pathways that require further exploration.

Disclosures: F. Cepeda Salazar: None. **A. Flores:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.04/A48

Topic: A.07. Development of Neural Systems

Title: Changes in the thalamus and visually mediated behavior after cortical deletion of Emx2

Authors: E. KINFE[1], M. ABERLE[1], A. CHOVUCHOVU[1], C. TAPSON[1], O. OLOWONIYI[1], E. ADUMAH[1], P. HULM[1], C. SCHAFFER[1], S. AKHIDENOR[1], A. B. ZEMBRZYCKI[2], *A. M. STOCKER[1];
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Abstract: Functional areas in the neocortex develop under the influence of key transcription factors, including Pax6, Sp8, COUP-TFI, and Emx2. Emx2 plays an important role in regulating the posterior neocortex and visual areas. Previous studies have shown that Emx2 knockout reduces primary visual area (V1) size, but other potential subcortical changes remain unclear. Previous research has demonstrated cortex-specific deletion of a key patterning transcription factor resulted in changes to the thalamus. We investigated whether the cortex-specific deletion of Emx2 (cKO) that results in a reduced V1 also caused changes to the thalamus and visually mediated behavior. Our results revealed that the dorsal lateral geniculate nucleus of the thalamus was not impacted by the change in V1 size. Yet we did observe a change in a different thalamic nucleus following Emx2 deletion from the cortex. The thalamic reticular nucleus (TRN) was significantly reduced in size after the critical period, measured at post-natal day 38 in mice. However this reduction was not apparent in TRN prior to the critical period, measured at post-natal day 18 in mice. These data suggest that experience-dependent modifications are necessary for this change. We also investigated whether the changes to the visual system neural anatomy have an impact on behavior. We utilized the visual cliff test, and found that prior to the onset of

the critical period that Emx2 cKOs explored the cliff more than controls. After the critical period however, both Emx2 cKOs and controls avoided the cliff. We also utilized a looming visual stimulus, and found prior to the onset of the critical period that all animals, irrespective of genotype, were unresponsive to the test. After the critical period, both Emx2 cKOs and controls exhibited normal behavioral responses to the looming stimulus. These results suggest that the changes observed in the TRN help correct visually mediated behavior that is aberrant in young Emx2 cKOs.

Disclosures: E. Kinfe: None. **M. Aberle:** None. **A. Chovuchovu:** None. **C. Tapson:** None. **O. Olowoniyi:** None. **E. Adumah:** None. **P. Hulm:** None. **C. Schaffer:** None. **S. Akhidenor:** None. **A.B. Zembrzycki:** None. **A.M. Stocker:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

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Topic: A.07. Development of Neural Systems

Support: National Research Foundation of Korea (NRF) grant by MSIT 2022R1C12003395
National Research Foundation of Korea (NRF) grant by MSIT 2020R1C1C1011074

Title: Axon-dependent myelination and nerve injury responses: Investigating the role of amphiregulin

Authors: *Y. SHIN[1], J. SHIN[2];
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Abstract: During peripheral nerve development, Schwann cells enwrap axons, and myelin sheaths are established through the close alignment of the Schwann cell membrane and the expression of myelin proteins. When the nerve is injured, Schwann cells engage in demyelination, accompanied by axon degeneration, followed by subsequent nerve regeneration. To facilitate the study of myelination and demyelination processes that naturally occur *in vivo* and to explore potential therapeutic interventions toward myelin-related diseases, we have devised a research methodology utilizing an *in vitro* co-culture system of rodent Schwann cells and dorsal root ganglion (DRG) neurons. Immunofluorescence staining for periaxin and MBP differentially labels the progression of myelin formation and demyelination after axotomy. Using this system, we investigated a novel axon-dependent myelination mechanism. Amphiregulin (Areg), recognized as an epidermal growth factor receptor (EGFR) ligand, holds an unknown

role in myelination. By knocking down *Areg* in cultured DRG neurons and co-culturing them with Schwann cells, we observed a significant impairment in *in vitro* myelination by Schwann cells. Furthermore, inhibiting EGFR function with two distinct EGFR inhibitors also led to a reduction in the myelination levels. Additionally, recombinant amphiregulin treatment significantly enhanced Schwann cell migration from mouse nerve explant cultures, similar to the effects of NRG1 treatment, thereby supporting the pivotal role of Areg signaling in Schwann cells during nerve repair. In summary, our findings strongly suggest that Areg plays a crucial role in peripheral myelination and nerve injury responses.

Disclosures: Y. Shin: None. **J. Shin:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

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Program #/Poster #: PSTR426.06/A50

Topic: A.07. Development of Neural Systems

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National Research Foundation of Korea (NRF), Ministry of Science and ICT RS-2021-NR058920
KBRI basic research programs 25-BR-05-04

Title: Effects of visual experience on proliferation of oligodendrocyte progenitor cells in primary visual cortex of mice

Authors: *H. SHIN[1], N. HASHIMOTO[2], S.-J. JEONG[1], H. D. KAWAI[2];
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Abstract: Sensory experience modulates the proliferation and differentiation of oligodendrocyte progenitor cells (OPCs). We previously found that binocular enucleation increases the undifferentiated state of OPCs in the primary visual cortex (V1) of mice during postnatal days (P) 22-25. In this study, we examined whether monocular deprivation (MD) similarly promotes OPC proliferation during this period. We compared the effects of monocular enucleation (ME) and lid suturing (LS), which does and does not sever optic nerves, respectively. We found that OPC proliferation, as detected by bromodeoxyuridine (BrdU), increased in both the contralateral binocular and monocular regions of V1 following ME (P22-25), compared to the ipsilateral V1.

In LS mice, proliferating and cell-cycling OPCs increased specifically in the contralateral monocular region of V1, but not in the binocular region. Reactive gliosis as detected by glial fibrillary acidic protein (GFAP) expression and macrophage accumulation as measured by CD68 were elevated in the contralateral side of the dorsal lateral geniculate nucleus (dLGN) after ME, but not on the ipsilateral side nor in either side of dLGN in LS mice. Meanwhile, c-Fos-expressing parvalbumin (PV)-immunopositive neurons apparently decreased in the contralateral side of V1 in LS mice. Our previous research suggested that visual enucleation mediates OPC undifferentiation through the Sonic hedgehog (Shh) signaling pathway. We found that Gli1, a key Shh pathway factor, is expressed within V1. Overall, these findings suggest that both LS and ME regulate OPC undifferentiation in the contralateral monocular region of V1 in a neuronal activity-dependent manner, independent of thalamic gliosis.

Disclosures: H. Shin: None. **N. Hashimoto:** None. **S. Jeong:** None. **H.D. Kawai:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.07/A51

Topic: A.07. Development of Neural Systems

Support: GT START UP

Title: Spatiotemporally dynamic control of beat-IIa expression by a steroid hormone pathway is critical for proper circuit formation in the fly visual system

Authors: *J. DEORA[1], M. TREESE[3], M. OZEL[4], S. JAIN[2];
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Abstract: Highly dynamic and neuron-type specific patterns of gene expression are a conserved feature of developing nervous systems during circuit formation, and are expected to be critical for proper wiring. Several mechanisms that control the neuron-type specificity of gene expression have been described. However, how timing is controlled and how temporal specificity of gene expression contributes to wiring specificity, remain unknown. We recently showed that a steroid hormone, Ecdysone, regulates wiring globally in the fruit fly visual system by controlling the timing of a neuron-type specific set of target genes (Jain *et al.* 2022). To understand how this pathway controls target genes in a neuron-type specific manner, we focus on *beat-IIa*, an immunoglobulin-superfamily cell recognition protein-coding gene with previously described roles in circuit formation. We find that *beat-IIa* is expressed with different dynamics in two related neuron-types (L3 and L5), while being regulated by the Ecdysone-pathway in both. Knock-down of *beat-IIa* in a cell-type specific manner leads to a loss of dendritic arbors in L5 neurons, and a defect in the ability of L3 neurons to control axonal targeting of another neuron-

type, R8. Importantly, peak expression of *beat-IIa* in L3 and L5 neurons coincides with the developmental timing of R8 axonal growth and L5 dendritic arbor formation respectively. This suggests that the proper cell-type specific timing of *beat-IIa* is critical for its roles in circuit formation. We are now using nuanced genetics tools to modify the temporal expression of *beat-IIa* in a cell-type specific manner to test this hypothesis. Lastly, analysis of gene regulatory networks assembled using single-nucleus multiome (RNA-Seq + ATAC-Seq) data across fly pupal development, revealed several transcription factors (TFs) that may mediate cell-type specific temporal expression of *beat-IIa*. Roles for these TFs in the regulation of *beat-IIa* are currently being tested, and will be key for understanding how the Ecdysone-pathway controls the timing of target genes differently in different neuron-types. Taken together, this work provides mechanistic insight into the temporal regulation of gene expression in developing neurons, and how timing influences wiring specificity. Given that dynamic spatiotemporal gene expression is ubiquitous across species during circuit formation, we expect the principles identified here to be broadly applicable.

Disclosures: J. Deora: None. **M. Treese:** None. **M. Ozel:** None. **S. Jain:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

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Program #/Poster #: PSTR426.08/A52

Topic: A.07. Development of Neural Systems

Support: NIH Brain Initiative Grant RF1MH132591
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Title: Development of Presynaptic Networks to Distinct Cortico-Cortical Projection Neuron Populations in Primary Visual Cortex

Authors: *J. M. RATLIFF[1], N. BLAHA[2], J. PI[3], Y. KIM[4], E. J. KIM[1];
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Abstract: The functional properties of different neuronal cell types are determined by their intrinsic molecular and physiological properties, as well as the synaptic connections they make. In the mammalian cerebral cortex, extensive work has been done to elucidate the connectivity rules of different neuronal cell types, showing that connections are both highly stereotyped and reflective of functional roles within the circuits they reside. However, little work has been done to examine how cell-type specific connectivity profiles are sculpted over development, as well as

what roles experience versus genetic programming play in this process. Here, we are addressing this question using a modified protocol involving the use of G-deleted rabies virus as a monosynaptic retrograde tracing tool, allowing the capture of brief developmental snapshots of presynaptic networks to genetically defined populations. Using this protocol in combination with tissue clearing and lightsheet imaging-assisted 3D mapping, we are tracking how the local and long range inputs to two populations of cortico-cortical projection neurons in layers 2/3 and 5 of the mouse primary visual cortex change over postnatal development, as well as what role retinal activity plays in this process. Our preliminary findings indicate that the presynaptic networks to both of these populations undergo substantial refinement, exhibiting an overall reduction in both local and long range inputs. This work establishes a powerful new experimental approach for mapping the development of cell-type specific connectivity, and provides the groundwork for mechanistic insights into the developmental origins of psychiatric disorders associated with aberrant cortical connectivity.

Disclosures: J.M. Ratliff: None. **N. Blaha:** None. **J. Pi:** None. **Y. Kim:** None. **E.J. Kim:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

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Topic: A.07. Development of Neural Systems

Support: 5U24DA055330-02

Title: Age associations with neonatal cortical thickness in the HBCD Study

Authors: *A. RIGBY[1], D. PECHEVA[2], P. PAREKH[2], D. J. HAGLER, Jr.[3], J. LINKERSDOERFER[2], C. MAKOWSKI[4], T. L. JERNIGAN[5], A. M. DALE[2];
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Abstract: Postnatal cortical development involves a cascade of cellular events as infants age, including synaptogenesis, glial proliferation and migration, myelination, and programmed cell death. These microstructural changes likely contribute to macroscopic alterations in cortical morphometry detectable via structural MRI. Among morphometric measures, apparent cortical thickness undergoes rapid changes during early infancy. Advances in infant neuroimaging now enable in vivo investigation of these changes with increasing anatomical precision. To accurately capture regional cortical thickness variation in the first month of life, large-scale datasets with dense sampling during this dynamic developmental period are necessary. The Healthy Brain and Cognitive Development (HBCD) Study is a multisite initiative that will follow over 7,000 infants from birth through early childhood. Using data from the inaugural HBCD 1.0 data release, we

examined associations between postmenstrual age at scan and cortical thickness during the neonatal period in a sample of 276 infants (124 females) aged 0-1 months. Cortical segmentation of T2-weighted MRI scans was performed using BIBSNet, a convolutional neural network trained for infant brain anatomy, followed by quantification of regional apparent cortical thickness using the Glasser parcellation. We used the Fast and Efficient Mixed Effects Algorithm to model the effect of postmenstrual age on regional apparent cortical thickness, with sociodemographic factors, genetic principal components, and scanner/software version as covariates, followed by multiple comparisons correction using Matrix Spectral Decomposition. We found two bilateral regions showing significant increases in cortical thickness associated with postmenstrual age at scan: left V1 ($\beta = 0.022$, 95% CI [0.015, 0.031], $p < 0.001$); right V1 ($\beta = 0.02$, 95% CI [0.012, 0.027], $p < 0.001$), left primary sensory cortex ($\beta = 0.019$, 95% CI [0.012, 0.027], $p < 0.001$), and right primary sensory cortex ($\beta = 0.015$, 95% CI [0.008, 0.022], $p < 0.001$). The significant age-related increases observed in primary sensory cortices are consistent with early maturation of these areas. As more longitudinal data is collected, clearer brain developmental trajectories in this dynamic time period could be mapped. These results offer a first glimpse of the developing brain in a large sample of infants and highlight the promise of a large-scale population neuroscience approach to characterizing neonatal brain development and identifying reliable biomarkers.

Disclosures: A. Rigby: None. **D. Pecheva:** None. **P. Parekh:** None. **D.J. Hagler:** None. **J. Linkersdoerfer:** None. **C. Makowski:** None. **T.L. Jernigan:** None. **A.M. Dale:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CorTechs Labs.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

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Program #/Poster #: PSTR426.10/A54

Topic: A.07. Development of Neural Systems

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Title: Developmental Principles that Instruct Long-range Cortico-cortical Connectivity in the Mouse Visual Cortex

Authors: *M. W. JACOBS[1], J. RATLIFF[2], A. SORONOW[2], H. JAMES[2], J. EDDY[2], J. A. NICHOLS[3], E. KIM[2];

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Abstract: Cortico-cortical projection neurons (CCPNs) link distant cortical areas to enable sensory integration, distributed computation, and complex behavior. In the adult mouse primary visual cortex (V1), CCPNs send long-range, target-specific projections to higher visual areas (HVAs), often forming reciprocal motifs. However, the developmental logic governing these circuits remains unresolved. Competing models suggest either early exuberant connectivity followed by pruning, or direct genetically instructed targeting.

To evaluate these models, we mapped the postnatal development of V1→HVA axonal projections using dual retrograde labeling with cholera toxin subunit B, sequential viral tracing using AAVs, and G-deleted Vesicular stomatitis virus(VSV)-based bulk anterograde analysis. We find that V1CCPNs overwhelmingly favor single-target outputs throughout development, with limited evidence of early dual projections or exuberance. Even at pruning-relevant stages, co-labeling rates are low, arguing against widespread initial promiscuity across multiple HVAs. AAV-mediated sequential retrograde labeling revealed that neurons projecting to medial HVAs (PM, AM, RSP) extend axons earlier than those targeting lateral HVAs (AL, LM, POR), despite similar physical distances. This suggests a spatially biased temporal program for target engagement. Anterograde tracing confirms early medial specificity and reveals transient lateral exuberance, largely resolved by postnatal day 24.

To distinguish pruning from cell loss, we compared short vs. long-incubation lateral retrograde labeling, revealing no reduced cell body labeling consistent with axon retraction rather than apoptosis. Additionally, correlation of antero and retrograde labeling reveals reciprocal HVA→V1 connectivity emerges later and independently, showing significant like-to-like correlation only in adulthood.

These data support a model of early target specificity, spatially staggered maturation, and selective motif refinement, challenging classical exuberance-based frameworks of cortical circuit development.

Disclosures: M.W. Jacobs: None. **J. Ratliff:** None. **A. Soronow:** None. **H. James:** None. **J. Eddy:** None. **J.A. Nichols:** None. **E. Kim:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.11/A55

Topic: A.07. Development of Neural Systems

Support: NIH R01EY033835

Title: Assessing Visual Category Representations in Infant Visual Cortex using fMRI

Authors: *C. G. TYAGI, V. S. NATU, D. ORTIZ, K. PEREZ, J. HORENZIAK, K. GRILL-SPECTOR;
Psychology, Stanford Univ., Stanford, CA

Abstract: *How do visual category representations emerge in infancy?* There is a debate in the field regarding the emergence of early visual representation and whether multiple category representations develop simultaneously or sequentially. Prior research suggests that face, body, and place representations are all present in young infants,[1,2] whereas other research has found that face representations appear first, between 4 and 6 months of age, followed by body and place representations after 6 months.[3] As these studies employed different methods (EEG/fMRI) and formats (grayscale stills vs. colored videos), this raises the question if measurement modality or visual features like motion contribute to differences across prior studies. Regardless, the precise anatomical locations of visual category representations in infancy are yet to be defined. To address these gaps in knowledge, we collected fMRI data using a dedicated infant coil from nine infants aged 4 to 6 months while they viewed colorful videos[1] and grayscale images[3] across four visual categories: faces, limbs, objects, and places. Blank baseline presentations were interspersed between stimuli presentations. Four infants were excluded from the analysis due to excessive motion (> 2 voxels). For four of the five infants with usable fMRI data, we reconstructed their cortical surfaces from their whole brain T1w and T2w scans.
We find that in all of the 4- to 6-month-old infants with usable data, viewing faces, places, limbs and objects produces robust visual activation relative to baseline in early visual cortex in the posterior occipital lobe and calcarine sulcus. We observe higher responses to faces compared to other stimuli in the fusiform gyrus near the mid-fusiform sulcus in three infants and for limbs in lateral occipital sulcus in two infants. However, we do not find higher responses to places compared to other stimuli in the collateral sulcus in any of the 4-6 months-olds. Our findings provide evidence that different visual category representations emerge at different timepoints in infancy, with face and limb representations emerging before place representations.
References: 1. Kosakowski, H. L., et.al. Selective responses to faces, scenes, and bodies in the ventral visual pathway of infants. Curr. Biol. 32, 265-274.e5 (2022). 2. Xie, S., et.al. Visual category representations in the infant brain. Curr. Biol. 32, 5422-5432 (2022). 3. Yan, X., et.al. When do visual category representations emerge in infants' brains? eLife 13, RP100260 (2024).

Disclosures: C.G. Tyagi: None. **V.S. Natu:** None. **D. Ortiz:** None. **K. Perez:** None. **J. Horenziak:** None. **K. Grill-Spector:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.12/Web Only

Topic: A.07. Development of Neural Systems

Support: Pratiksha Trust

Title: Neuroanatomical organization of the human fetal pretectum in the second trimester.

Authors: S. ARUNESH[1], M. BOTA[1], S. VENKATESH[1], N. GANESAN[1], H. KUMAR[2], M. SIVAPRAKASAM[1], *R. VERMA[3,1];
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Abstract: The neuroanatomical organization of the human pretectum (PRT) is poorly understood, because of few studies, as compared to other species. PRT is commonly described as a group of nuclei involved in key oculomotor functions, such as the pupillary light reflex and optokinetic nystagmus. In this study, we investigate the developmental progression of the human PRT and the neighbouring midbrain during the second trimester. We provide the first systematic account of its topographical, cytoarchitectural, and chemoarchitectural organization, to our knowledge. We examined five fetal brain specimens, ranging from 14 to 25 gestational weeks (GW). These brains were serially cryosectioned at 20 μm thickness in the coronal plane and processed for histological staining: Nissl, and immunohistochemistry: parvalbumin (PV), calbindin (CB) and calretinin (CR). As early as 14 GW, we identified eight nuclei in the PRT and in the neighbouring midbrain: the nucleus of the optic tract (NOT), the anterior pretectal nucleus (APN), the posterior pretectal nucleus (PPN), the olivary pretectal nucleus (OPN), the medial pretectal nucleus (MPN), the central tegmental area (CTA), the magnocellular nucleus of the posterior commissure (MCPC), and the precommissural nucleus (PRC). We also identified the dorsal and the lateral terminal nuclei of the AOS. Rostrally, the APN is located below the thalamic posterior limitans. It is cell-sparse in Nissl stain, it develops two subdivisions by 23 GW, and with no CR immunoreactivity. Caudally, the CTA is a densely packed region in Nissl-stained sections at all stages, and with strong PV-positive processes by 25 GW. Dorsal to the CTA, the PPN was identified as an elongated and cell-sparse region bordered medially by the MPN, and laterally by the OPN. At 25 GW, the PPN, MPN, and OPN have only PV immunoreactivity. The OPN was consistently round across ages, with cells arranged in a characteristic whirlpool-like pattern. The NOT, located between the MPN and OPN, becomes a distinct nucleus by 17 GW, and it can be further subdivided by 25 GW. The MCPC, identified lateral to the periaqueductal gray, is characterized by a cell-sparse matrix interspersed with large cells. The PRC was noted as a cell-sparse area situated ventral to the habenula. This study provides insights into the development of the pretectum in humans.

Disclosures: S. Arunesh: None. **M. Bota:** None. **S. Venkatesh:** None. **N. Ganesan:** None. **H. Kumar:** None. **M. Sivaprakasam:** None. **R. Verma:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.13/A56

Topic: A.07. Development of Neural Systems

Title: Investigation of the transcriptomic landscape of the primate fovea across developmental time using state of the art spatial transcriptomics approach

Authors: *M. KRUEGER, A. LA TORRE;
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Abstract: The *fovea centralis* (fovea) is a specialized region of the primate retina that plays crucial roles in high-resolution visual acuity and color perception. It consists of a small pitted invagination located a few millimeters temporal to the optic nerve disc. The fovea is characterized by a high density of cones and an absence of rod photoreceptors. Other unique anatomical properties also contribute to the fovea remarkable visual capabilities, including a peripheral displacement of the inner neurons and absence of retinal vessels in the foveal center to facilitate the direct illumination of the photoreceptors. The development of the fovea has been the subject of study for over a century, yet the molecular, cellular, and mechanical factors that contribute to its development are not well understood. To elucidate transcriptional differences across the retina, we have employed Slide-seq, a cutting-edge spatial transcriptomics technology that enables high-resolution, genome-wide gene expression profiling while preserving tissue architecture. This approach allows precise comparison of the fovea with its surrounding retinal, retinal pigment epithelium (RPE), and choroidal tissues. I have generated preliminary datasets from early fetal rhesus macaque samples (40-, 50-, and 78-days gestational age), which revealed spatial transcriptional signatures and demonstrated the feasibility of this approach. These data will provide a comprehensive atlas of region- and age-specific gene expression, enabling the identification of molecular pathways involved in foveal development thereby addressing critical gaps in our understanding of central vision development.

Disclosures: M. Krueger: None. **A. La Torre:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.14/A57

Topic: A.07. Development of Neural Systems

Support: Brain Canada Foundation and Azrieli Foundation

Title: Functional Near-Infrared Spectroscopy (fNIRS) based functional connectivity as a biomarker of delirium in critically ill children

Authors: *B. KRIVORUK[1], K. WONG[2], M. ASSAF[3], H. RAVI[2], H. SUN[2], T. NYLAND[2], S. SRINIVASAN[3], D. CARVALHO[3], K. STUBBS[2], M. KENT[4], H. VAHIDI[6], E. G. DUERDEN[5], S. LALGUDI GANESAN[7];
[1]Neurosci., [2]Univ. of Western Ontario, London, ON, Canada; [3]LHSC, London, ON, Canada; [5]Applied Psychology, [4]Western Univ., London, ON, Canada; [6]Sch. of Med., Stanford Univ.,

Stanford, CA; [7]Paediatrics & Clin. Neurolog. Sci., Schulich Sch. of Med. & Dentistry, Western University, London (ON), London, ON, Canada

Abstract: Delirium is common in hospitalized and critically ill children and is associated with long-term morbidity and mortality. Although tools like the Cornell Assessment of Pediatric Delirium (CAPD) are widely used for delirium detection, they rely purely on observable behaviour and are imperfect. Functional near-infrared spectroscopy (fNIRS) offers a non-invasive bedside approach to objectively assess brain health and disease. This exploratory study examined whether fNIRS-derived functional connectivity (FC) could identify neurophysiological signatures of delirium. Resting-state data were collected from 28 participants (1 month to 18 years) across 31 bedside 20-minute fNIRS sessions (11 delirious, 20 non-delirious), with delirium identified based on a combination of CAPD scores and clinician assessments. The CAPD scores were higher during delirium (M = 13.3, SD = 4.3) than during non-delirium (M = 3.9, SD = 3.4). A generalized estimating equation model showed that increased FC between right temporal and left temporoparietal brain regions was independently associated with the presence of delirium (B = 5.08, $p < .05$, FDR-corrected). Sedative-opioid use also showed an independent association with delirium status (B = 2.55, p = .018). A second model found that higher delirium severity, as measured by CAPD scores, was associated with sedative-opioid use (B = 4.68, $p < .001$), developmental delay (B = 3.99, p = .045), and younger age (B = -0.23, p = .005). These findings suggest that fNIRS-based functional connectivity could serve as a biomarker for delirium and complement the current behavioural screening for ICU delirium in critically ill children.

Disclosures: B. Krivoruk: None. **K. Wong:** None. **M. Assaf:** None. **H. Ravi:** None. **H. Sun:** None. **T. Nyland:** None. **S. Srinivasan:** None. **D. Carvalho:** None. **K. Stubbs:** None. **M. Kent:** None. **H. Vahidi:** None. **E.G. Duerden:** None. **S. Lalgudi Ganesan:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.15/A58

Topic: A.07. Development of Neural Systems

Support: NICHD grant HD109454
NCATS 1U01TR002764-01A

Title: Replicable functional connectivity patterns associated with sensory over-responsivity in children.

Authors: *H. LUO[1], C. M. SYLVESTER[2], M. CAMACHO[3], D. M. BARCH[4], R. SCHWARZLOSE[5];
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Univ. Sch. of Med., St Louis, MO; [3]Washington Univ. Sch. of Med., SAINT LOUIS, MO; [4]Dept Psychol & Psychiatry, Washington Univ., Saint Louis, MO; [5]Washington Univ. in St Louis, Saint Louis, MO

Abstract: Sensory over-responsivity (SOR) affects 15-20% of children and is a common feature of autism spectrum disorder and other psychiatric conditions. SOR severity exists on a continuum, with mild SOR constituting approximately two-thirds of SOR cases in community samples. While prior work identified reduced connectivity between sensorimotor/salience networks and subcortical regions in severe SOR, these findings have not been replicated across independent samples nor in children with mild SOR. We aimed to identify whether there are a specific, replicable functional connectivity (FC) patterns associated with mild SOR to better understand the underlying neurobiology of SOR.We analyzed resting-state fMRI data from 9,197 children (ages 9-10) in the community-based ABCD study. Participants with mild or no SOR were randomly divided into two matched exploratory (n=4,193) and replication (n=4,188) groups. We tested brain-wide FC patterns using hierarchical mixed-effects models controlling for demographics, motion, and clinical symptoms. FC pairs showing significance ($p<0.01$) in sequential MLMs (demographics; demographics + symptoms) were advanced for replication testing. We further tested extension to severe SOR (n=457) and an independent clinical dataset (Healthy Brain Network, n=356).Whole-brain FC pattern analyses revealed significant correlations between exploratory and replication samples ($\rho=0.31$, $p<0.001$) and with severe SOR patterns ($\rho=0.55$, $p<0.001$). Of 9 significant candidate FC pairs identified in exploratory analyses, 2 demonstrated robust replication: reduced cingulo-opercular network to left ventral diencephalon connectivity ($\beta=-0.04$, $p<0.01$) and reduced sensorimotor hand network to left hippocampus connectivity ($\beta=-0.03$, $p<0.01$. Effects in 5 of 9 FC pairs replicated to severe SOR, including reduced hippocampal-sensorimotor FC, which was also identified in our prior analysis of severe SOR. Although neither cingulo-opercular-left ventral diencephalon nor somatomotor hand-left hippocampus FC were significantly associated with SOR in the smaller HBN sample, the direction of cingulo-opercular-left ventral diencephalon FC-SOR effects were consistent.This study provides the first evidence of replicable FC alterations in mild SOR, demonstrating reduced cortico-subcortical connectivity involving cingulo-opercular networks, sensorimotor regions, hippocampus, and ventral diencephalon. Pattern consistency across mild and severe SOR suggests shared neural bases like differences in hippocampal circuits that may impair adaptive sensory prediction and modulation processes.

Disclosures: H. Luo: None. **C.M. Sylvester:** None. **M. Camacho:** None. **D.M. Barch:** None. **R. Schwarzlose:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.16/A59

Topic: A.07. Development of Neural Systems

Support: NIH Grant NS106244
NIH Grant EY022730

Title: A cortico-reticular-thalamic inhibitory feedback loop generates spindle-burst oscillations in dLGN to refine thalamocortical connections during development.

Authors: M. C. FOX[1], R. G. HERRERA-MOLINA[1], *M. T. COLONNESE[2];
[1]Pharmacol. & Physiol., The George Washington Univ., Washington DC, DC; [2]The George Washington Univ., Washington, DC

Abstract: During brain circuit formation, powerful oscillations synchronize activity throughout the cortex and thalamus. In the visual system, these oscillations are called 'spindle-bursts,' and they are initiated by spontaneous retinal waves, which are critical for the normal development of visual circuitry. The oscillatory component of spindle-bursts arises in the lateral geniculate nucleus (dLGN), and these oscillations synchronize firing in the visual cortex (VC) and dLGN. Here, we test the hypothesis that inhibitory feedback from the thalamic reticular nucleus (TRN) mediates the generation of spindle-burst oscillations in response to retinal waves and, thereby, is essential for the refinement of thalamocortical circuitry mediated by retinal waves. We used unilateral, virally-mediated, conditional expression of tetrodotoxin to reduce synaptic release from parvalbumin or GAD-expressing neurons of the thalamic reticular nucleus (TRN), which provide the large majority of inhibitory innervation to dLGN during the period of retinal waves. Tetrodotoxin expression eliminated VC spindle-burst oscillations specifically on the injected side in 6-8 day-old mice, but did not reduce firing rates or otherwise dramatically change the pattern of cortical activity. Thalamocortical refinement was measured by microinjection of fluorescent microspheres bilaterally in VC at P12. The spread of retrogradely transported beads in the dLGN was 48% ($p<0.0001$) greater on the infected side in animals showing viral expression in vTRN, compared to only 3% ($p=0.78$) in injected animals with no vTRN expression. Thus, spindle-burst oscillations mediated by vTRN are required for the typical refinement of thalamocortical connectivity. Acute reduction of TRN firing using conditional DREADD (PSAM) expression also reduced spindle-burst oscillations at similar ages. Combined recording in dLGN and vTRN using 8-shank polytrodes revealed strong activation of vTRN during retinal waves and fast-synchronization of vTRN-vTRN and vTRN-dLGN neuron pairs during spindle-bursts. Combined with prior work showing that corticothalamic feedback neurons are required for spindle-bursts and in vivo recordings that show a late development of functional dLGN to vTRN synapses, suggests that spindle-bursts are generated by vTRN feedback inhibition to dLGN routed through the thalamocortical loop. We propose that the synchronization provided by these oscillations is required for the thalamocortical connections to make use of the information conveyed in retinal waves to refine their connectivity.

Disclosures: M.C. Fox: None. **R.G. Herrera-Molina:** None. **M.T. Colonnese:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.17/A60

Topic: A.07. Development of Neural Systems

Support: NICHD Grant HD109454

Title: Examining associations between brain volume and sensory over-responsivity in infancy

Authors: *S. R. OVERSCHMIDT[1], H. LUO[2], C. M. SYLVESTER[3], J. L. LUBY[4], R. SCHWARZLOSE[5];
[1]Psychiatry, Washington Univ. in St. Louis Sch. of Med., St. Louis, MO; [2]Psychiatry, Washington Univ. Sch. of Med., St. Louis, MO; [3]Psychiatry, Washington Univ. Sch. of Med., St Louis, MO; [4]Psychiatry, Washington Univ. Sch. of Med., Saint Louis, MO; [5]Psychiatry, Washington Univ. in St Louis, Saint Louis, MO

Abstract: Prior work has shown that accelerated brain growth is associated with autism in early childhood. In our recent study of brain volume in preadolescents from the Adolescent Brain Cognitive Development (ABCD) Study, we found opposing, small effect-size associations of total brain volume with sensory over-responsivity (SOR) and other autistic traits. Specifically, brain volume was positively associated with SOR and negatively associated with other autistic traits in multivariate models, suggesting heterogeneity in volumetry associations with autistic traits at this age. To investigate the developmental origins of these effects, we analyzed data from the Early Life Adversity, Biological Embedding, and Risk for Developmental Precursors of Mental Disorders (eLABE) Study - a longitudinal, infant sample enriched for social disadvantage (45% female). We analyzed total brain volume (TBV) derived from structural MRI at neonatal and 2-year (Y2) timepoints in relation to a measure of emerging SOR (i.e., Sensory Sensitivity subscale) and a composite measure representing reduced or delayed social development (an average of reversed, z-scored Empathy, Imitation, and Social Relatedness subscales) from the Infant Toddler Social Emotional Assessment (ITSEA) at Y2. We first probed associations between Y2 delayed social development, Y2 SOR, and a latent factor measure of social disadvantage using Spearman's correlations. We found a modest positive association between delayed social development and Y2 SOR ($p = 0.006$, $\rho = 0.168$, $n = 268$), and social disadvantage was moderately positively correlated with both Y2 delayed social development and Y2 SOR ($p < 0.001$, $\rho = 0.324$, $n = 271$; $p < 0.001$, $\rho = 0.304$, $n = 268$). To investigate the relationships between the behavioral variables and TBV, we used multivariate linear regression models with age at scan, child sex, social disadvantage, Y2 SOR, and Y2 delayed social development as covariates and Y0 and Y2 TBV as outcome variables. We found no significant effects between either Y2 delayed social development or Y2 SOR and Y0 TBV ($p = 0.238$, $B = -0.069$, $n = 242$; $p = 0.892$, $B = -0.008$, $n = 242$). Similarly, we found no significant effects between either Y2 delayed social development or Y2 SOR and Y2 TBV ($p = 0.941$, $B = -0.006$, $n = 107$; $p = 0.400$, $B = 0.071$, $n = 107$); however, despite these null results, the directions of beta weights for Y2 SOR and Y2 delayed social development in the model predicting Y2 TBV are consistent with those from the prior study in older children. Given the small effect sizes observed in older children, the current study may be underpowered to detect these effects. Future work with larger samples is needed.

Disclosures: S.R. Overschmidt: None. **H. Luo:** None. **C.M. Sylvester:** None. **J.L. Luby:** None. **R. Schwarzlose:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.18/A61

Topic: A.07. Development of Neural Systems

Support: NIH Grant 5R01MH126481-05
NIH Grant 1F30DC022213-01

Title: Foxp2 in the Inferior Colliculus

Authors: *M. JANKOVIC[1], A. J. HOLLEY[2], J. R. GIBSON[3], G. KONOPKA[2];
[2]Neurosci., [1]UT Southwestern Med. Ctr., Dallas, TX; [3]Dept. of Neurosci., UT Southwestern, Dallas, TX

Abstract: Sensory processing abnormalities in neurodevelopmental disorders (NDDs), including autism spectrum disorder, affect quality of life and can cause maladaptive sensory behaviors. The transcription factor Foxp2, linked to NDDs and speech disorders, has a notable specific expression pattern in several auditory processing regions of the brain including corticothalamic projection neurons, the medial geniculate nucleus of the thalamus, and cells in the inferior colliculi (IC), a nearly obligatory station of the ascending auditory pathway in the midbrain that performs crucial auditory processing functions. To investigate the understudied role of Foxp2 in the IC, we created a developmental conditional knockout of Foxp2 in the excitatory neurons of the IC. Our data indicate significant changes in the proportion of specific neuronal populations in the IC and altered cortical responses to sound in IC-Foxp2-deficient mice, underscoring a pivotal role of Foxp2 in auditory processing. Ongoing research aims to understand the cellular and circuit changes caused by the loss of Foxp2 expression in IC. We are carrying out single nuclei transcriptomic and chromatin accessibility experiments to identify unique and overlapping genes and regulatory regions downstream of Foxp2 in the development of the IC and how it affects auditory processing and cellular projections. Preliminary data suggest alterations in expression of crucial patterning protein receptors and ligands, such as Epha4, that could affect input and output targeting and internal connectivity. We also find that specific populations are under metabolic stress post-hearing age. Using ex vivo electrophysiological recordings, we aim to identify changes in cell and circuit function of single and paired cells to determine synapse dysregulation and/or cellular excitability alterations caused by the loss of Foxp2. By detailing the transcriptomic and electrophysiological landscape of the IC and its development and function shaped by Foxp2, our data advance our understanding of sensory processing deficits in NDDs.

Disclosures: M. Jankovic: None. **A.J. Holley:** None. **J.R. Gibson:** None. **G. Konopka:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.19/A62

Topic: A.07. Development of Neural Systems

Support: Rita Allen Foundation
O'Donnell Brain Institute Sprouts Grant

Title: Prdm12 Regulates Cell Type Specific Programs in the DRG

Authors: *S. S. JOBBINS[1], H. C. LAI[2];
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Abstract: The peripheral nervous system contains numerous cell types, each responsible for detecting unique sensations such as noxious stimuli, temperature, touch, itch, and proprioception. Coordinating the development and maintenance of these cell identities is crucial for proper function, yet the mechanisms governing their specification and preservation remain unclear. Identification of these cell identity programs will provide important insights into the basic biology and mechanisms required for sensory neuron diversification. The transcription factor PRDM12 is known to be required during development for the initial cell fate acquisition of pain sensing neurons (nociceptors) and its expression is maintained into adulthood. However, the molecular programs governed by PRDM12 during embryogenesis and adulthood are unknown. This project investigates how the role of PRDM12 changes throughout developmental time and tests the hypothesis that transcription factor development and maintenance programs are distinct processes. We used two previously established mouse models in which *Prdm12* is knocked out in peripheral sensory neurons: one starting in embryogenesis, and the other in which knockout occurs conditionally during adulthood. We found that knockout of PRDM12 in the adult dorsal root ganglia (DRG) produces cell-type specific changes in gene expression, indicating that PRDM12 regulates unique cell type-specific transcriptional programs in sensory neuron subtypes. Ongoing experiments are testing how the cell type-specific transcriptional programs regulated by PRDM12 in the adult differ from those controlled during embryogenesis. Overall, this project will advance our understanding of how somatosensory neuron identity is initiated and maintained, providing important fundamental knowledge of nociceptor biology.

Disclosures: S.S. Jobbins: None. **H.C. Lai:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.20/B1

Topic: A.07. Development of Neural Systems

Support: NIH/NIDCD Grant DC007695
NIH/NIDCD Grant DC007695-S1

Title: Spontaneous Activity is Necessary for the Synchronous Growth of the Calyx of Held and Intrinsic Matching of Postsynaptic Excitability in the Medial Nucleus of the Trapezoid Body

Authors: *N. BENITES[1], D. T. HELLER[2], E. AMICK[3], A. A. DAGOSTIN[4], S. M. YOUNG, Jr.[5], H. P. VON GERSDORFF[6], G. A. SPIROU[2];
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Abstract: During neural circuit formation, nascent synaptic contacts are exuberant in nature, ensuring proper neural connectivity, and undergo a period of pruning of superfluous inputs, followed by maturation and strengthening of the remaining contacts. In sensory systems, patterned spontaneous activity (SA) originates in the peripheral sense organ. It propagates through the central nervous system, prior to the onset of external stimulation, playing a crucial role in shaping the synaptic architecture. The calyx of Held (CH) is the primary terminus of globular bushy cells (GBCs), whose cell bodies are located in the ventral cochlear nucleus (VCN) and innervate principal neurons (PNs) in the medial nucleus of the trapezoid body (MNTB). Previous manipulations to eliminate SA at the developing CH have involved genetic strategies that also affect cochlear function and may induce homeostatic compensatory mechanisms in GBCs. To overcome this confounding factor, direct manipulation of synaptic transmission through viral vector-mediated, rapid-onset expression of tetanus neurotoxin (TeNT) targeting GBCs was employed to silence activity at the CH:MNTB synaptic connection. The effects of *in vivo* synaptic silencing at the CH:MNTB connection delay the maturation of the MNTB PNs intrinsic physiological properties. Following TeNT expression, PNs remain in an immature hyperexcitable state, with a tonic firing pattern, high input resistance, and depolarized resting membrane potential. We employed non-biased techniques to classify PNs following TeNT expression, including principal component analysis and K-means clustering. These statistical analyses are robust, and we are the first ones to apply them in this biological system. To identify potential mechanisms underlying these changes, we employed a single-compartment Hodgkin-Huxley model of the PN. Simulations comparing the effects of TeNT show differential expression of voltage-gated potassium channels (K_V). Additionally, the model demonstrated that not just one conductance could account for the persistent tonic firing properties in PN following TeNT expression, but rather a variety of them, set up in different proportions. Morphological analysis of transduced calyxes shows impaired growth with reduced volume and increased thickness. This study highlights the vital role of SA in triggering the rapid growth of the CH and the synchronous maturation of the MNTB PN's physiological properties.

Disclosures: N. Benites: None. **D.T. Heller:** None. **E. Amick:** None. **A.A. Dagostin:** None. **S.M. Young:** None. **H.P. von Gersdorff:** None. **G.A. Spirou:** Other; Dr. Spirou is SCEO in SyGlass company..

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.21/B2

Topic: A.07. Development of Neural Systems

Support: NIH Grant EY034617-01

Title: The Role of Long-range Inhibitory Neurons in Postnatal Neocortical Development

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Abstract: The regulation of cortical circuit development by spontaneous neuronal activity during the first postnatal weeks in mice is a critical time for cortical circuit assembly. This time period in humans (corresponding to the last trimester of pregnancy) is a highly sensitive period for neurodevelopmental disorders. These spontaneous network events have also been associated with patterns of synchronous neocortical activity observed during sleep states. These recurring network events initially stem from self-generated stimuli originating from peripheral organs, such as retinal waves in the retina. During development, cortical activity patterns shift from external reception to internal generation. This developmental transition occurs during the second postnatal week (P10-P14), termed the "critical period of internalization." Despite its relevance, we still do not have a clear picture of how spontaneous activity shapes the maturation and function of neocortical networks. Understanding this step, especially in the early postnatal weeks in mice, would allow us to understand how abnormal development of these networks could lead to neuropsychiatric illnesses, such as epilepsy, autism spectrum disorder (ASD), and schizophrenia. Evidence shows the contribution of early forming, highly connected GABAergic neurons leads to spontaneous synchronization of networks in the developing mouse brain. We hypothesize that the function of neocortical long-range interneurons that co-express somatostatin and neuronal nitric oxide synthase is critical for the emergence of spontaneous patterns of postnatal synchronous activity and the maturation of sleep patterns. This study can help elucidate the role of long-range SST/nNOS inhibitory cells in postnatal development of neocortical networks in mice, which will allow us to further understand and investigate how their dysfunction can lead to neuropsychiatric illnesses.

Disclosures: J. Barnett: None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.22/B3

Topic: A.07. Development of Neural Systems

Support: NIH R00EY030909
NIH 5T32GM137793-04

Title: Nicotine exposure alters spontaneous retinal activity during visual system development

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Abstract: The development of the visual system depends on spontaneous activity, known as retinal waves, which spread across the retina and visual neural axis. In mice, one of the key circuit components critical to the prevalence of retinal waves is the nicotinic acetylcholine receptor. Nicotine use, the primary psychoactive chemical in tobacco and vape cigarettes, is a pervasive public health issue affecting 1.3 billion people worldwide by firsthand and secondhand smoke exposure. To this day, despite known visual deficits reported from nicotine exposure during development, whether nicotine exposure affects retinal waves is not known. To begin to address this knowledge gap, I first utilized high-density multielectrode array (HD-MEA) recordings of ex vivo neonatal mouse retinas to study the impact of acute nicotine exposure on retinal waves. Preliminary results from these experiments reveal a concentration-dependent effect of nicotine on spontaneous activity in the retina. At concentrations similar to fetal firsthand smoke exposure, nicotine abolishes retinal waves, whereas at concentrations equivalent to high and low fetal secondhand smoke exposure, nicotine alters the spatiotemporal properties of retinal waves. These data suggest nicotine exposure, even in small amounts, can alter the properties of visual system development known to rely on retinal waves. I address this hypothesis by examining the effect of chronic nicotine exposure on eye-specific segregation in the thalamus, retinotopic mapping in the superior colliculus, and vascularization in the retina. The results of my studies provide a mechanistic understanding of why nicotine exposure via tobacco or vape smoke affects the development of the visual system.

Disclosures: E.A. Gauthier: None. **A. Tiriac:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.23/B4

Topic: A.07. Development of Neural Systems

Support: NIH R00EY030909
R25 GM134979

Title: A toolbox for analyzing the spatiotemporal properties of retinal waves

Authors: *K. M. YEAGER, R. GUPTA, A. TIRIAC;
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Abstract: The precise development of the visual system is driven by retinal waves, which are bursts of spontaneous activity that propagate across retinal neurons in a wave-like fashion. In mice, retinal waves begin embryonically and continue until eye opening at the end of the second postnatal week. Since the retinal circuitry is actively developing throughout the first two postnatal weeks, the mechanisms for generating and propagating retinal waves are changing. Due to the active development of the retina, retinal waves exhibit highly dynamic spatiotemporal properties during this period. These spatiotemporal properties have been shown to instruct to the development of the visual system, including eye-specific segregation, retinotopic mapping, direction selectivity and potentially retinal vascularization. Currently, there is no method for the automatic detection and high-throughput analysis of the spatiotemporal properties of retinal waves. To overcome this barrier, we have created a practical open-source toolbox to automatically detect retinal waves and analyze their spatiotemporal properties from data collected using multielectrode arrays or calcium imaging. We apply this toolbox to enrich our understanding of retinal waves. First, we uncover novel dynamic spatiotemporal properties of retinal waves in the first two postnatal weeks. Second, we apply this toolbox on ultra long physiological recordings to demonstrate that the spatiotemporal properties of waves change throughout the day. Third, we demonstrate that this toolbox can detect waves in the presence of pharmacological agents that increase the baseline firing of neurons, potentially enabling the discovery of novel factors that perturb retinal waves and visual development. Finally, we demonstrate that this toolbox can be used to analyze other types of wave-like data. Our toolbox is an intuitive interface that provides a systemized method to segregate and analyze retinal waves and other wave-like data.

Disclosures: K.M. Yeager: None. **R. Gupta:** None. **A. Tiriac:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.24/B5

Topic: A.07. Development of Neural Systems

Support: NINDS (R01 NS128286)
NINDS (R56 NS110951)

Title: Transcriptional and translational profiles of learning across developmental age in males and females

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Abstract: Developmental learning can have lifelong effects on neural function and behavior. The ability to learn is not uniform across development, with critical periods that reflect distinct neural states that are especially receptive to experience. While adult learning mechanisms are well characterized, the factors that limit or promote learning across developmental phases remain less understood. To investigate fundamental questions about how maturation and sex influence learning processes, we characterized the molecular responses to song experience across development using a system with a known critical period for learning: the zebra finch songbird. In this species, juvenile males and females perform sensory song learning that determines adult behaviors. Males have a defined critical period for this learning, but it is unclear if females do, though the ages at which they learn overlap. As adults, both sexes perform song recognition learning. The auditory forebrain is a locus for all of this learning, though evidence so far is that juvenile sensory song learning has distinct mechanisms in males and females, with no major sex differences in adults. To advance understanding of how age, sex, and experience influence auditory forebrain properties that may promote and limit the ability to learn, we performed immunoprecipitation-based riboTRAP. We processed auditory forebrain samples from males and females across the developmental learning phase (posthatch days 23, 30, 60, 67) and adults, who had either been left in silence (baseline) or exposed to playback of novel songs, which triggers genomic responses previously confirmed to support learning. Analysis revealed not just the expected induction of immediate early genes such as FOS, but also reveals novel genes that are differentially transcribed and translated, depending on the age and sex of the individual. For example, HTR genes for receptor subtypes 1 and 2 are differentially translated after song playback experience, indicating as-yet unstudied roles for serotonin signaling at synapses, BDNF regulation may be especially robust early in auditory forebrain development, prior evidence that mTOR signaling is essential for juvenile male sensory song learning is supported by the differential translation of LAMTOR proteins with song playbacks. Hub and functional analysis highlighted core cellular processes such as those dependent on mitochondrial function in the organization and plasticity of the developing auditory forebrain. Together, our findings highlight temporally dynamic, sex-specific molecular responses that may support distinct learning strategies across development.

Disclosures: A. Batistuzzo: None. **S.E. London:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.25/B6

Topic: A.07. Development of Neural Systems

Support: R21 HD110855

Title: Landscape of critical period learning: a single-cell atlas of the juvenile zebra finch auditory forebrain

Authors: *P. PARISHAR[1], Z. JIANG[2], K. V MAHESHWAR[1], Y. PENG[2], S. POTT[2], S. E. LONDON[1];
[1]Dept. of Psychology, [2]Dept. of Med., Univ. of Chicago, Chicago, IL

Abstract: Adult behaviors often reflect the long-term effects of developmental experience. In some cases, specific experiences only have profound effects on the brain and behavior during restricted critical periods in development. These defined periods provide the opportunity to identify neural properties that support and limit the ability to learn. The male zebra finch songbird has a well-defined developmental critical period for sensory song learning, essential for them to produce socially meaningful songs as adult. Juvenile females also learn from song experiences; they cannot sing but reveal biases in song preference as adults. Males effectively perform sensory song learning at posthatch day (P) 30, though it is less clear that females have such a distinct onset to their learning phase. To understand how specific cell types in the developing brain encode sensory information for learning, we performed single-nucleus (sn) RNA-seq and snATAC-seq multiomics on a brain area required for sensory song learning, the auditory forebrain. We constructed a comprehensive cellular atlas from males and females at P23 and P30 following a controlled silence or novel song playbacks experience. We obtained 157,365 nuclei (1741 to 12617 cells per sample) from 24 birds (3 for each combination of sex, age, song exposure). Using the snRNA-seq data, we identified a broad spectrum of excitatory and inhibitory neuronal populations and non-neuronal cell types. Paired chromatin accessibility measurements facilitated the identification of cis-regulatory elements for each of these cell types. Cluster-specific differential gene expression analysis identified select cell subtypes that are particularly sensitive to the song playback experience, characterized through induction of immediate early genes, including FOSL2, EGR3, NR4A3, and HOMER1. Comparing cell-type composition across conditions confirmed several small excitatory and inhibitory neuron populations responding to song. In addition, we confirmed shifts in maturation associated cellular subtypes between P23 and P30. Our study presents the first comprehensive single-cell atlas of the developing zebra finch auditory forebrain, demonstrating how song, age, and sex dynamically modulate the transcriptional and epigenetic landscape across its diverse cell population and further deepens our understanding of critical periods and sensory learning across vertebrates.

Disclosures: P. Parishar: None. **Z. Jiang:** None. **K. V Maheshwar:** None. **Y. Peng:** None. **S. Pott:** None. **S.E. London:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.26/B7

Topic: A.07. Development of Neural Systems

Support: NINDS (R56 NS110951)
NINDS (R01 NS128286)

Title: In vivo functional testing of molecular mechanisms for female developmental learning

Authors: *K. V MAHESHWAR[1,2], S. CHARI[1,3], S. E. LONDON[1,2,3];
[1]Inst. for Mind and Biol., [2]Dept. of Psychology, Neurosci. Inst., Univ. of Chicago, Chicago, IL;
[3]The Col. at The Univ. of Chicago, Chicago, IL

Abstract: Early developmental experiences can have lasting effects on brain function and behavior. Zebra finches provide a powerful model for investigating how development learning shapes behavior in adulthood. Juvenile sensory song learning in zebra finches has life-long consequences for both males and females. In males, it guides adult song structure and in females, it generates biases in song preferences. Given that developmental timelines for learning and brain regions involved in auditory processing overlap between sexes, a key question is whether males and females share molecular mechanisms underlying sensory song learning. In males, activity-dependent gene expression in the auditory forebrain — including induction of immediate early genes like ZENK, regulated by the ERK (extracellular signal-regulated kinase) signaling pathway — is crucial for forming tutor song memories. Disrupting ERK signaling during the critical period in males impairs adult song copying, indicating its essential role in sensory song learning. But whether ERK signaling is similarly required in females remains unknown. Here, we tested whether ERK pathway activity is necessary for sensory song learning in juvenile female zebra finches. We infused U0126 — an inhibitor of MEK1/2 that then prevents ERK activation — into the auditory forebrain, followed by tutor exposure. Tutor sessions were video-recorded to quantify the juveniles' engagement with the adult as a measure of social interest. To assess the effects of the manipulation on song preference in adulthood, we used an operant conditioning perch-trigger assay, where each perch played either the tutor song or a novel song when the bird landed on it. Preference for the tutor song served as a behavioral index of successful memory formation. If ERK signaling is required, we predicted that ERK-suppressed females would show reduced tutor song preference compared to controls. Initial bootstrapping analyses revealed no significant difference in tutor song preference between the experimental and control females. Importantly, the results suggest while ERK signaling is critical for tutor memory formation in males, females may rely on alternative pathways, highlighting potential sex-specific molecular mechanisms for sensory learning in zebra finches . This underscores the importance of studying female learning directly, rather than extrapolating from male models.

Disclosures: K. V Maheshwar: None. **S. Chari:** None. **S.E. London:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.27/B8

Topic: A.06. Developmental Disorders

Support: R01NS104038

Title: Loss of Lgl1 causes periventricular heterotopia due to disruptions in overall cellular polarity

Authors: *O. PERICAK[1], S. KIM[2];
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Abstract: Development of the cerebral cortex is a highly organized process which begins after closure of the neural tube. Neural progenitor cells that line the ventricles are oriented in an apicobasal polarity manner to guide the differentiation and migration of cells. This cellular polarity plays a critical role in controlling the division and cell fate of progenitors. The main progenitors of the cortex, apical radial glial cells (aRGCs), anchor to the ventricular surface through adherens junctions and interact with neighboring cells through apical and basal polarity complexes, composed of Crb/Pals1/Patj (apical domain), Pard3/Par6/aPKC (apical domain) and Scrib/Lgl/Dlg (basal domain) proteins, which function to link and regulate cell-cell signaling pathways. The interplay between basal and apical polarity complexes is essential for appropriate lineage progression and subsequent neuron production. Disruption to polarity processes or mutations in polarity genes contribute to a variety of human conditions. Periventricular heterotopia (PH) is one such abnormality that is characterized by accumulation of gray matter along the ventricular lining. PH is associated with mutations in various genes, some of which are involved in maintaining apicobasal polarity. Lethal giant larvae 1 (Lgl1) is a basal polarity protein that aids in regulating cell division and the polarity of progenitor cells. The loss of Lgl1 is known to cause PH in mouse models, yet the mechanism underlying this is still unknown. We hypothesize that the loss of Lgl1 causes PH by disrupting other apicobasal polarity complexes and altering cell signaling that promotes cell proliferation and cell junction defects. Immunofluorescence staining on mouse embryonic dorsal cortices revealed that the apical domain marked by apical polarity complex protein Pals1 is expanded with the loss of Lgl1. Rather than being retained to the apical surface, the localization of Pals1 is basally shifted. Closer analysis of the ventricular surface with phalloidin staining also revealed widened apical endfeet, or the where the aRGCs attach to the apical surface. Given the disruption to the apical domain, we generated a conditional double KO of Crb1/Crb2 and Lgl1, which resulted in a partial rescue of the heterotopia seen in the Lgl cKO alone. The size of the apical endfeet was also comparable to WT in the double cKO. Together, these results suggest that PH arises due to an imbalance in both apical and basal polarity. Future directions for this work include single cell RNA sequencing to more closely examine the molecular profile of individual cells and to clarify the underlying mechanism involved in PH.

Disclosures: O. Pericak: None. **S. Kim:** None.

Poster

PSTR426: From Molecules to Circuits: Insights Into Brain Development and Sensory Processing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR426.28/B9

Topic: A.07. Development of Neural Systems

Title: Task switching impairs associative memory in childhood

Authors: *A. DECKER[1], J. D. GABRIELI[2], N. OFEN[3], X. J. CHAI[4];
[2]Dept Brain/Cognit Sci., [1]MIT, Cambridge, MA; [3]Inst. of Gerontology, Wayne State Univ., Detroit, MI; [4]McGill Univ., Montreal, QC, Canada

Abstract: Frequent task switching is a hallmark of our modern lives. The volume of digital content and notifications leads to routine, externally triggered shifts in attention, which increase cognitive load, mental fatigue and impair learning and memory. But while the costs of task switching are well-documented in adults, less is known about their effects during *childhood* - a period when learning and memory abilities are developing. Here, we examine how task switching affects late developing associative memories, which depend heavily on attention[4]. We also investigate how fMRI BOLD responses that coincide with task switching differs across development. Children, adolescents, and adults (n=81; ages 7-25) performed a memory encoding task in the scanner, followed by a memory test outside the scanner. During encoding, participants viewed unique words and made either animacy judgments (living/nonliving) or size judgments (bigger/smaller than a shoebox), with task and font combinations randomly intermixed across 180 trials. Trials were labeled as "stay" if the same judgment task was repeated, or "switch" if the task changed from the previous trial. After scanning, participants completed a memory test assessing recall of words and associative details (font and judgment task). **We found that participants** were less likely to form associative memories after switch than stay trials ($p = .002$). This effect was strongest in younger participants (age × trial type: $p = .009$). Indeed, task switching reduced memory for details in children ($p = .001$), but not in adolescents or adults ($ps > .32$). Whole-brain fMRI contrasts revealed greater activation for switch than stay trials in posterior regions, including the superior parietal lobe and precuneus. The relationship between age and switch-related activation was strongest in younger participants (bilateral superior parietal: $p = .02$; bilateral precuneus: $p = .09$), with follow-up analyses confirming higher activation in children and adolescents than adults ($ps < .03$). Together, these findings show that task switching disrupts complex associative memories more in children than adults and coincides with stronger brain responses to task switches. The impairing effects of task switching on memory therefore may be one factor contributing to why children's memories are often less detailed and rich than adults.

Disclosures: A. Decker: None. **J.D. Gabrieli:** None. **N. Ofen:** None. **X.J. Chai:** None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.01/B10

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Profile of a new muscarinic M4 receptor (M4R) positive allosteric modulator (PAM) with antipsychotic-like efficacy

Authors: *C. MOMBEREAU, J.-L. PAPARIN, D. S. DUPUIS, A. JAVAULT, E. DOUETTE, C. FERRY, D. W. SCHELSHORN, M. SCHNEIDER, M. KALINICHEV, J.-P. ROCHER, R. LUTJENS;
Neurosterix Pharma sarl, Geneva, Switzerland

Abstract: For over 60 years, schizophrenia treatments have relied on similar mechanisms of action, by blocking dopamine receptors, showing limited efficacy on positive (psychosis) symptoms but barely addressing negative (impaired social functioning) and cognitive (learning and memory) symptoms[1]. In addition, a third of patients does not respond to these approaches, and severe side-effects leading to treatment change or discontinuation are frequent. In 2024, approval of KarXT/Cobenfy™ marked a breakthrough with muscarinic M_4 receptor activation, offering a new validated avenue for efficacious treatments of schizophrenia[2]. KarXT is a combination between xanomeline, an M_1/M_4 receptor orthosteric agonist, and trospium chloride, a peripherally restricted pan-muscarinic acetylcholine receptor antagonist[3]. Despite this progress, residual side effects, limited efficacy for negative and cognitive symptoms, and dosing challenges highlight the need for improved M_4-targeted treatments. Using a positive allosteric modulator (PAM) approach offers several advantages compared to an orthosteric agonist, including greater selectivity, physiological and context-dependent effects, lower risk of overstimulation, and therefore the potential for tailored therapeutic effects with fewer adverse effects[4]. Here we describe the profile of compound NTX-A, a novel muscarinic M_4 positive allosteric modulator (PAM) identified using Neurosterix' unique allosteric modulation drug discovery platform. NTX-A is a potent and highly selective M_4 PAM, metabolically stable, bioavailable and brain penetrant. NTX-A demonstrated potent and long-lasting in vivo efficacy in rodent models.

Disclosures: C. Mombereau: A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **J. Paparin:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **D.S. Dupuis:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **A. Javault:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **E. Douette:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **C. Ferry:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **D.W. Schelshorn:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **M. Schneider:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des

Mines 9, 1202 Geneva, Switzerland. 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.; Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **M. Kalinichev:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **J. Rocher:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland. **R. Lutjens:** A. Employment/Salary (full or part-time): Neurosterix Pharma sarl, Chemin Des Mines 9, 1202 Geneva, Switzerland.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.02/B11

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Preclinical characterization of M_4 muscarinic receptor positive allosteric modulator NS-136

Authors: D. CHEN, L. ZHAO, H. JIA, C. ZHANG, *D. XU, Y. QU, **J. H. SHEN**; NeuShen Therapeut., Shanghai, China

Abstract: The M_4 muscarinic acetylcholine receptor plays a key role in cognition, memory, emotion, and motor control, and represents a promising therapeutic target for the treatment of schizophrenia—offering a novel approach that does not rely on postsynaptic dopamine D_2 receptor antagonism. NS-136 is a novel positive allosteric modulator (PAM) of the M_4 receptor currently in a Phase 1 clinical trial in healthy volunteers. Preclinical studies have shown that NS-136 exhibits robust antipsychotic activity and a favorable pharmacokinetic profile.
In [^{3}H] N-methylscopolamine ([^{3}H] NMS) binding assays, NS-136 enhanced the potency of acetylcholine, consistent with its mechanism as a positive allosteric modulator. In the conditioned avoidance response (CAR) test—a validated animal model for assessing antipsychotic efficacy—NS-136 dose-dependently reduced conditioned avoidance behavior (CAR%) by increasing voluntary escape responses, without prolonging escape latency. Additionally, in the Sprague-Dawley rat catalepsy model, NS-136 did not induce extrapyramidal symptoms, indicating a low risk of motor side effects.
NS-136 also demonstrated strong brain penetration, as evidenced by high Kp, uu and brain-to-plasma (B/P) ratios across multiple species. These findings suggest efficient central nervous system (CNS) exposure, which may contribute to enhanced therapeutic efficacy in CNS disorders.
In summary, NS-136 is a potent and selective M_4 PAM with a promising preclinical safety and pharmacokinetic profile, supporting its potential as a next-generation antipsychotic therapy.

Disclosures: **D. Chen:** A. Employment/Salary (full or part-time): NeuShen Therapeutics. **L. Zhao:** A. Employment/Salary (full or part-time): NeuShen Therapeutics. **H. jia:** A. Employment/Salary (full or part-time): NeuShen Therapeutics. **C. Zhang:** A. Employment/Salary (full or part-time): NeuShen Therapeutics. **D. Xu:** A. Employment/Salary (full or part-time): NeuShen Therapeutics. **Y. Qu:** A. Employment/Salary (full or part-time): NeuShen Therapeutics. **J.H. Shen:** A. Employment/Salary (full or part-time): NeuShen Therapeutics.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.03/B12

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: Grant-in-Aid for JSPS Fellows 24KJ2106

Title: Altered causality judgment in a ketamine mouse model of schizophrenia

Authors: *R. SUZUKI, Y. KOSAKI;
Psychology, Waseda Univ., Tokyo, Japan

Abstract: An abnormal sense of agency, a subjective sensation that one's action produces a specific outcome, is one of the core symptoms of schizophrenia. Specifically, patients with predominantly positive symptoms are more likely to overestimate their influence on external events compared with healthy individuals (e.g., Daprati et al., 1997; Haggard et al., 2003; Maeda et al., 2013). However, the neural mechanisms underlying such abnormalities have not been well understood, partly due to a lack of studies using animal models of schizophrenia. In this study, we examined whether causal attribution of an external event is altered in mice treated with ketamine, a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist commonly used to model key aspects of positive symptoms (e.g., Schmack et al., 2021). We initially trained C57BL/6J mice on a discrimination task in which either animal's voluntary response or a pseudo-response generated by a computer led to a stimulus change in the experimental chamber (the insertion of two levers, the illumination of two lights positioned above the levers, and the extinction of the magazine light). The animals were then required to press one lever (a contingent lever) if the stimulus change was caused by their own action, and the other lever (a noncontingent lever) if the change occurred independently of their behavior. After acquiring this discrimination, half of the animals were given an intraperitoneal injection of 16 mg/kg ketamine prior to each test session, while the remaining animals received 0.9% saline as a control. The results showed that ketamine-treated mice made more false alarms (i.e., pressing a contingent lever when the stimulus change occurred independently of their responses) compared to control subjects when the response-independent stimulus change followed the voluntary response with some delay. This suggests that they are more likely to associate their actions with subsequent external events over a temporal gap, indicating that an extended temporal window for the

formation of associations between actions and events may underlie the impaired causality attribution. Overall, the current finding has a direct relevance to human studies in patients with positive symptoms of schizophrenia and provides a valuable animal model approach for elucidating the mechanisms underlying the altered sense of agency in this disorder.

Disclosures: R. Suzuki: None. **Y. Kosaki:** None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.04/B13

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Stanley Center for Psychiatric Research

Title: Disrupted Sleep-Dependent Neural Oscillations and Transcriptomic Changes in the Cacna1g Loss-of-Function Mouse Model Implicated in Schizophrenia

Authors: *A. ASAN[1], R. LIN[2], N. GOBLE[3], T. YAU[1], S. SIMMONS[1], S. CHOI[2], E. YU[4], J. Q. PAN[5];
[2]Stanley Ctr. for Psychiatric Res., [1]Broad Inst. of MIT and Harvard, Cambridge, MA; [3]Broad Inst. of MIT and Harvard, Boston, MA; [4]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [5]Stanley Ctr. for Psychiatric Res., Broad Inst., Acton, MA

Abstract: Sleep is critical for optimal brain function, regulating gene expression and brain network oscillations that shape behaviors like emotion and cognition. Disruptions in sleep microarchitecture are a well-established feature of schizophrenia (SCZ). Rare loss-of-function (LoF) variants in CACNA1G, encoding the T-type calcium channel CaV3.1, increase SCZ risk, but the mechanisms remain elusive. Using Cacna1g LoF mice, we reveal profound disruptions in sleep-related oscillatory patterns, including impaired spindles, slow oscillations, and cortical connectivity during sleep, which comprehensively recapitulates impaired sleep neurophysiology in people with SCZ. Notably, we observed a complete absence of the typical 24-hour variation in theta frequency oscillations in Cacna1g KO mice, highlighting CaV3.1 as a critical upstream regulator for imposing circadian patterns onto brain rhythmicity during the sleep-wake cycle. At the molecular level, Cacna1g LoF induces widespread transcriptomic changes across multiple brain regions, with greater impact during the light phase. These diurnal gene expression changes notably affect genes regulated by sleep-wake homeostasis, particularly within intratelencephalic excitatory neurons. These findings establish the Cacna1g LoF as a model for phenocopying major neurophysiological deficits in SCZ, underscore the critical role of CACNA1G/Cav3.1 in coordinating molecular signaling and network dynamics during sleep, and provide mechanistic insights into the pathophysiology of sleep disturbance in disease.

Disclosures: A. Asan: None. **R. Lin:** None. **N. Goble:** None. **T. Yau:** None. **S. Simmons:** None. **S. Choi:** None. **E. Yu:** None. **J.Q. Pan:** None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.05/B14

Topic: H.05. Mood Disorders

Title: Evaluating the effects of insulin on dopamine signaling in 3q29-associated schizophrenia mouse model

Authors: *M. K. BARTOLE, S. SRIRAMOJI, M. E. BOCARSLY;
Pharmacology, Physiol. and Neurosci., Rutgers NJMS, Newark, NJ

Abstract: Schizophrenia is a chronic mental disorder that affects behavior, emotion, and cognitive functioning characterized by dysregulated dopamine in the brain. The human 3q29 deletion genotype is associated with an increased risk of schizophrenia, and mice with this deletion display behaviors and phenotypes consistent with models of schizophrenia. Metabolic differences associated with the 3q29 deletion have been observed in humans, but little is known about the physiological mechanisms underlying these metabolic effects and their connection to dysregulated dopamine signaling in the dorsal striatum. Utilizing the 3q29 deletion mouse model, we will evaluate the role of insulin on dopamine signaling and 3q29 metabolic differences. Fast scan cyclic voltammetry studies in the striatum have revealed differences in dopamine signaling between 3q29 deletion mice and control littermates, with 3q29 deletion mice showing increased levels of striatal dopamine release and decreased clearance of dopamine, indicating dysfunction of the dopamine transporter (DAT), in the dorsal striatum compared to littermate controls. Interactions between insulin signaling and DAT have been previously described, with phosphorylation and function of the DAT dependent on insulin signaling, indicating a potential role of insulin as a mediator of the dysfunctional dopamine dynamics observed in the 3q29 deletion mice. This study aims to evaluate the role of insulin on dopamine signaling as it relates to the 3q29 deletion model of schizophrenia. Utilizing fast scan cyclic voltammetry, we will explore the effects of insulin administration on striatal dopamine release and clearance in 3q29 deletion mice. We will also evaluate levels of brain insulin receptors and the associated signaling proteins involved in insulin signaling pathways and mediating dopamine dynamics. Together, this data will allow us to characterize the role of insulin within the dorsal striatum as a potential mediator of differences in metabolism and striatal dopamine dynamics in 3q29 deletion mice compared to littermate controls.

Disclosures: M.K. Bartole: None. **S. Sriramoji:** None. **M.E. Bocarsly:** None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.06/B15

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Stanley Family Foundation

Title: Functional connectome meta-analysis across SCHEMA schizophrenia models using functional ultrasound imaging

Authors: *Z. FU;
Broad Inst. of MIT and Harvard, Cambridge, MA

Abstract: Neural circuits form the functional units of brain computation, whose deficits have been shown mechanistically to cause cognitive and behavioral abnormalities in humans and animal models. To overcome the low throughput and inaccessibility in human patients of circuit-based investigations such as in vivo or ex vivo experimentations, advances in "functional connectome" using non-invasive hemodynamic measurements have assisted researchers to identify, localize, and interpret relations between psychiatric disease symptoms and connectivity endophenotypes. Recently, we have established a high throughput screening platform using functional ultrasound imaging (fUS) to pursue large-scale, unbiased investigation of SCHEMA (schizophrenia exome meta-analysis) mouse mutants during development. Over one thousand scanning sessions, we collected resting-state (via light sedation and physiological monitoring) hemodynamic data from wildtype (C57BL/6J, 129S1/SV1MJ, and FVB1NJ strains), as well as Grin2a, Gria3, Akap11, SP4, Zmym2, and Srrm2 mutant models. As systemic characterization of functional connectivity under the conditions of resting-date fUS had not been previously attempted, we first established that all background strains share similar, discernible connectivity patterns, with strongest connectivity signatures. C57BL/6J mice, the most common inbred strain for most SCHEMA mutants generated, show the highest count of positive correlations as well as the lowest variability, which, similar to 129S1/SV1MJ and FVB1NJ, decreases from 1 to 3 months of age regardless of their initial levels. In addition, all SCHEMA mutants, both the heterozygous (Het) knockouts and their wildtype littermates, show higher variability compared to pure C57BL/6J mice. Addressing the patterns and variability of functional connections thus allows us to pursue the pressing questions of how SCHEMA gene knockouts affect functional connectivity, whether the effects are convergent or correlate with brain-area-specific molecular and behavioral deficits. We found that, across all SCHEMA models, the most prominent differences in connectivity occur at 1 month of age, which attenuate at month 2. For Gria3, Akap11, and Srrm2, the effect returned at month 3, albeit at a lower effect size. For SP4 and Zmym2, the return of gene effect at month 3 is marked by the reversal's directionality, likely a consequence of compensatory overshoot. Despite heterogeneity of affected brain regions, the overall patterns of directionality of change across developmental time points cluster Akapp1, Zmym2, and Srrm2 against the more variable Grin2a and Gria3, and the uniquely low effect of Sp4.

Disclosures: Z. Fu: None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.07/B16

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Multimodal profiles in schizophrenia subtypes for guiding personalized treatment

Authors: *D. JANEVA[1,2], M. BREYTON[3,2,5], V. K. JIRSA[6], S. PETKOSKI[4], R. GUILHAUMOU[4];
[1]INS UMR 1106, 13005 Marseille, France; [2]Aix Marseille Univ, INSERM, INS Inst. neurosci Syst UMR 1106, Marseille, France; [4]Inst. de Neurosciences des Systèmes, [3]Aix-Marseille Univ., Marseille, France; [5]Aix Marseille Univ, APHM, INSERM, INS Inst. neurosci Syst, Service de Pharmacologie Clinique et Pharmacosurveillance, Marseille, France; [6]Aix Marseille Univ, INSERM, INS Inst. neurosci Syst UMR 1106, Marseille, France, Marseille, France

Abstract: Schizophrenia is a complex, heterogeneous disorder, with 30-50% of patients exhibiting poor treatment response. Advancing personalized interventions requires understanding multimodal interrelations. We investigated the associations in predefined data- and hypothesis-driven schizophrenia subtypes across clinical (n = 93), neuroimaging (n = 87) and pharmacodynamic (n = 87) measures from the same cohort. We identified two data-driven subtypes, Aware and Unaware, mainly separated by the Scale to Assess Unawareness in Mental Health Disorders (SUMD) with k-means clustering of a 43-dimensional clinical dataset. Hypothesis-driven subtypes were defined using Positive and Negative Symptom Scale (PANSS) scores: LPLN (Low Positive Low Negative), LPHN (Low Positive High Negative), and HPHN (High Positive High Negative), Fig. 1. (A). We computed functional features from 100 cortical and 18 subcortical regions (Schaefer 7 Networks, 100 Parcellations atlas) at regional, network, and whole-brain levels. XGBoost classifiers with SHAP values identified discriminative imaging features across the groups, Fig. 1. (B). Pharmacodynamic profiles were estimated as receptor occupancy values based on drug and dosage, and their correlations with clinical symptoms were assessed, Fig. 1. (C). The subtypes demonstrated significant differences in neuroimaging patterns, particularly at regional levels. Moreover, receptor occupancy showed distinct correlation patterns with clinical features across subtypes. These findings suggest that pharmacodynamic measures play a mediating role between brain activity and treatment response. Our approach reveals clinically meaningful schizophrenia subtypes with distinct neurobiological and pharmacodynamic profiles, driving the development of personalized, mechanism-based treatments.

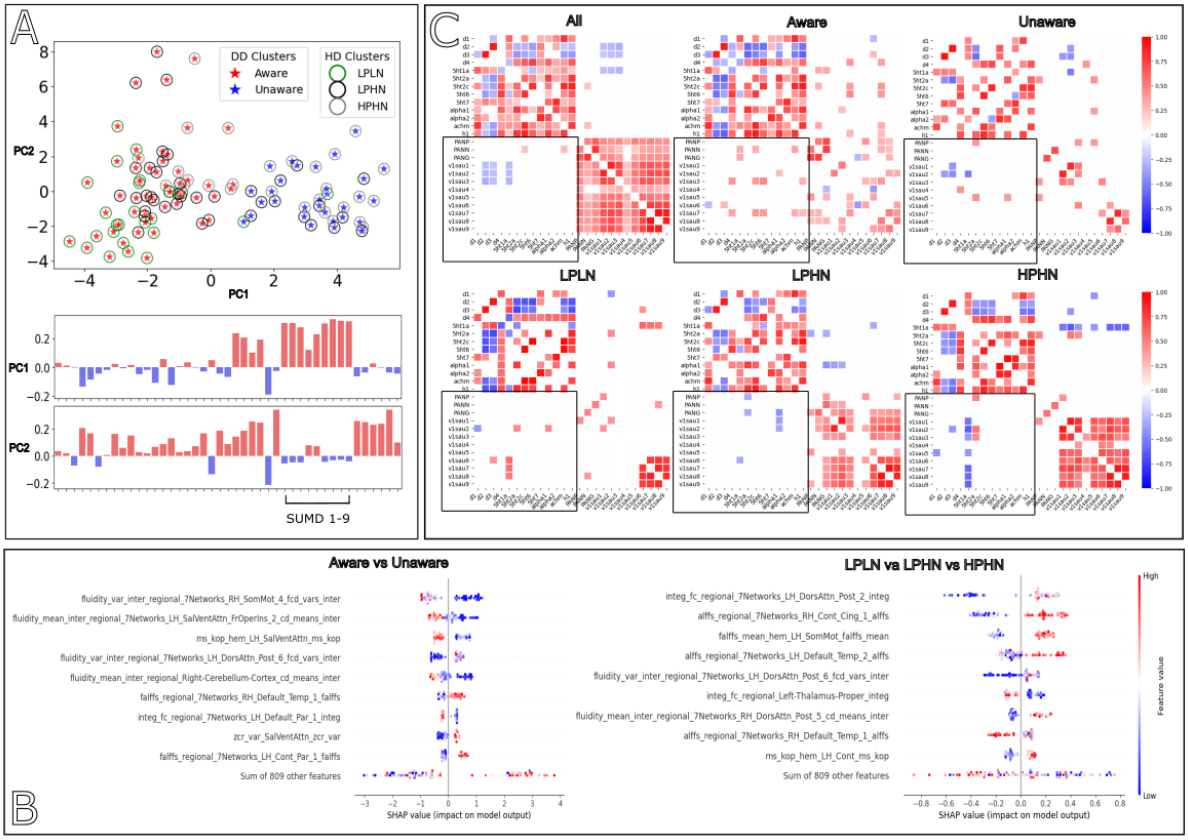


Fig 1. (A) Data- and hypothesis-driven clusters. (B) Group and subtype-specific correlations between receptor occupancy and clinical variables. (C) SHAP-based feature importance for subtype classification shows key regional imaging markers.

Disclosures: D. Janeva: None. **M. Breyton:** None. **V.K. Jirsa:** None. **S. Petkoski:** None. **R. Guilhaumou:** None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.08/Web Only

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Signant Health

Title: Clustering of Data Quality Issues in Clinical Trials of Investigational Treatments for Schizophrenia

Authors: *D. G. DANIEL[1], X. WANG[2], A. KOTT[3];
[1]Signant Hlth., McLean, VA; [2]Signant Hlth., Blue Bell, PA; [3]Sci. and Med., Signant Hlth., Prague, Czech Republic

Abstract: Research Objective:To investigate whether sources of noise in clinical testing of investigational schizophrenia treatments are concentrated in individual sites and/or regionally.
Rationale: In recent years, placebo response and non-specific variance have negatively impacted clinical trials of investigational novel treatments for schizophrenia. In this exploratory, post-hoc analysis, we investigated whether such data issues are associated with specific clinical research sites and regions.
Methods:We analyzed data quality metrics from 523 individual sites involved in 21 schizophrenia clinical trials. For each site, we recorded the number of trials participated in and the number of times the site was flagged as problematic—defined as being a significant outlier on at least one data quality indicator (such as scale administration or scoring errors, discordance within or between scales, extreme variance, inclusion issues, or suspicious data suggestive of possible tampering). We then used a binomial regression model to estimate the probability that a site in a given country would be identified as problematic.
Results:Of the 523 sites, 297 (57%) participated in only one trial, and 331 (63%) were never flagged as problematic. Sites involved in multiple trials had a higher likelihood of being identified as problematic at least once (50%) compared to those participating in only one trial (27%), $p < 0.001$. Among the 226 sites that participated in two or more trials, only 40 (18%) were flagged as problematic on multiple occasions. Although a chi-square test did not show significant regional differences in the distribution of these repeatedly problematic sites, both the US and Serbia had nearly 30% of their sites in this category. Focusing on countries with at least 10 participating sites, the binomial regression model revealed significant differences in the probability of a site being problematic. Sites in Serbia had the highest probability (66%), followed by Romania (62%) and the US (58%). In contrast, sites in Poland (13%), Ukraine (27%), and Bulgaria (33%) had the lowest probabilities.
Conclusions:This exploratory, post-hoc analysis revealed significant differences in the likelihood of sites being flagged for data quality concerns. Sites participating in multiple trials were more likely to be identified as problematic. While repeatedly problematic sites were relatively rare (8%), they accounted for 39% of all significant data quality findings. In neuroscience, confidence in the clinical testing of novel compounds might be enhanced if research sites repeatedly associated with data quality issues are identified and recalibrated.

Disclosures: D.G. Daniel: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signant Health. F. Consulting Fees (e.g., advisory boards); Signant Health, Merck. **X. Wang:** A. Employment/Salary (full or part-time): Signant Health. **A. Kott:** A. Employment/Salary (full or part-time): Signant Health. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signant Health.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.09/B17

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: WSS/2020/0036/PRCWSS

Title: Metabolomic Biomarker Signatures in Drug Naive and Risperidone Treated Schizophrenia

Authors: *S. P S[1], N. BARMAN[1], V. KUMAR[2], T. CHINNASAMY[1], N. PJ[1], R. K[1], V. SHIVAKUMAR[3], S. VARAMBALLY[2], K. GOKULAKRISHNAN[1];
[1]Neurochemistry, [2]Psychiatry, [3]Dept. of Integrative Med., Natl. Inst. of Mental Hlth. and Neuro Sci. (NIMHANS), Bengaluru, India

Abstract: Background: Schizophrenia (SCZ) is a serious, debilitating psychiatric disorder. However, the molecular mechanism of SCZ remain largely unknown, and very few studies have examined the effect of antipsychotic treatment response. We aim to study the differences in the metabolomic signatures among Drug-Naïve (DN) and Risperidone-Treated (RT) SCZ patients, compared to Healthy Controls (HCs). **Methods:** We recruited a total of 245 participants from the clinical services of a large neuropsychiatric hospital, which included DN SCZ (n=80), RT SCZ (n=90) and HCs (n=75). A liquid chromatography- mass spectrometry (LC-MS/MS) based metabolomic approach was used to identify potential metabolite biomarkers using the Biocrates AbsoluteIDQ p400 HR Kit and Metaboanalyst 6.0. **Results:** In targeted metabolomics, we observed 5 (Acylcarnitines), 8 (Amino acids), 2 (Biogenic Amines), 4 (Cholesterol esters), 10 (Glycerophospholipids), 4 (Sphingolipids) and Hexose (Sugars) metabolites that were significantly different in DN and RT SCZ compared to HCs. Notably, acylcarnitine AC (14:0) was significantly dysregulated in patients with the DN SCZ group compared to healthy controls, whereas AC (14:1) exhibited significant alterations in the RT SCZ group relative to healthy controls. **Conclusion:** Our study identified distinct metabolomic signatures that could aid in the differentiation of DN SCZ, RT SCZ, and HCs. Our findings contribute to a better understanding of the role of metabolomics signatures in SCZ pathophysiology and may facilitate the development of a laboratory-based diagnostic test for SCZ.

Disclosures: S. P s: None. **N. Barman:** None. **V. Kumar:** None. **T. Chinnasamy:** None. **N. Pj:** None. **R. K:** None. **V. Shivakumar:** None. **S. Varambally:** None. **K. Gokulakrishnan:** None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.10/B18

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Striatal Overload Causing Motor Crisis: Extrapyramidal Manifestations of Antipsychotic Excess in Clinical Profiles

Authors: *S. SAXENA;
PSYCHIATRY, Inst. of Human Behaviour and Allied Sci. (IHBAS), India, New Delhi, India

Abstract: BACKGROUND AND OBJECTIVES:Antipsychotic medications are fundamental to schizophrenia treatment, yet excessive dosing- even unintentionally- can provoke acute extrapyramidal symptoms (EPS). This case series documents the clinical features, therapeutic responses, and recovery trajectories of patients with schizophrenia who developed EPS following accidental high-dose antipsychotic intake. The study also emphasises the neurobiological relevance of dopaminergic pathway dysfunction manifesting as motor symptoms.
METHODS Three adult males diagnosed with schizophrenia were admitted to a neuropsychiatric facility in New Delhi, India, after receiving excessive doses of Risperidone, with or without other psychotropics. Comprehensive neurological evaluations, standard laboratory tests, and neuroimaging were conducted to exclude alternative diagnoses. The treatment approach included prompt discontinuation of the causative agents and administration of anticholinergic and antihistaminic medications. Patients were observed in inpatient settings for 10-14 days, and clinical progress was documented.
RESULTSCase 1: A 32-year-old received 60 mg of Risperidone along with Levosulpiride, resulting in pronounced rigidity and oculogyric crisis. Intravenous Promethazine and oral Trihexiphenidyl with Propanolol led to symptom resolution within 72 hours.Case 2: A 28-year-old developed dystonia and restlessness after ingesting 40 mg of Risperidone. Treatment with intramuscular PROMETHAZINE and oral anticholinergics resulted in significant improvement within two days. Case 3: A 35-year-old showed tremors, drooling, and stiffness after consuming an estimated 50 mg of RISPERIDONE and 30 mg of Olanzapine. Management included intravenous antihistamines, oral Trihexiphenidyl, and benzodiazepines, with full recovery by day five. All patients completed hospitalisation without complications and remained symptom-free during outpatient follow-up. Caregivers were counseled regarding safe medication practices.
SCIENTIFIC RIGOR Alternative medical explanations were ruled out through systematic assessments. Interventions followed evidence-based protocols, and symptom tracking was conducted by clinicians blinded to treatment details to minimize bias.
CONCLUSION This case series demonstrates that overdose of even second-generation antipsychotics can precipitate acute EPS. Timely identification and intervention are critical to reducing associated morbidity. Preventive strategies, including caregiver education and medication safety protocols, are essential to avoid such clinical emergencies.

Disclosures: S. Saxena: None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.11/B19

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NIH Grant U01MH130625

Title: Snr dbs for treatment-resistant schizophrenia: effects on the perception and electrophysiology of auditory-verbal hallucinations.

Authors: *K. WYSE-SOOKOO[1], Y. SALIMPOUR[3], W. S. ANDERSON[5], K. A. MILLS[4], N. G. CASCELLA[2];
[1]Biomed. Engin., [2]Psychiatry, Johns Hopkins Sch. of Med., Baltimore, MD; [3]Neurosurg., [4]Neurol., Johns Hopkins Univ., Baltimore, MD; [5]Neurosurg., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Dysfunction within the corticostriatothalamic circuit (CST) that connects the limbic and associative cortices to the substantia nigra pars reticulata (SNr) via the mediodorsal nucleus of the thalamus may underly auditory verbal hallucinations (AVH) in schizophrenia (SZ). Excess activity in the temporoparietal language areas and the left superior temporal gyrus (STG) has been associated with the presence of AVHs in functional neuroimaging studies. A novel deep brain stimulation (DBS) surgery targeting the SNr is currently being evaluated in treatment-resistant SZ patients who experience AVHs due to the SNr's functional connectivity with both of these regions. Previous work with scalp electroencephalography (EEG) has also laid the groundwork for identifying AVH biomarkers, indicating that resting state theta-gamma phase-amplitude coupling (PAC) is elevated in SZ patients compared to healthy controls. Within SZ patients, there is a transient increase in this coupling shortly before the perception of an AVH. SZ patients who experience AVHs also appear to have significantly increased beta band activity in the left inferior parietal region and left medial frontal gyrus compared to non-AVH SZ patients. This study reports the effects of SNr DBS on AVH perception and the associated electrophysiology during the first year after implantation of an SNr DBS stimulator in a clinical trial participant (NCT02361554) with treatment-resistant SZ who experiences AVHs. EEG recordings were performed before implantation, after implantation and before stimulator activation, and at each programming session after activation, including two single-blinded stimulation "on" and "off" visits. During recordings, the participant denoted the perception and duration of AVHs by holding down a pushbutton. While the rate of AVHs per minute did not appear to change significantly between the pre-implantation baseline session and the subsequent post-implantation sessions, the durations of the perceived AVHs were markedly decreased after the stimulator was turned on. Preliminary analyses of pre-AVH theta-gamma PAC have shown that significant increases can be detected before the onset of the patient-reported AVHs, and that there may be differences in the spatiotemporal pattern of these increases between stimulation off and stimulation on conditions. More detailed coupling analyses over a larger set of EEG sessions will be presented, along with results of analyses of peri-event spectral bandpower.

Disclosures: K. Wyse-Sookoo: None. **Y. Salimpour:** None. **W.S. Anderson:** None. **K.A. Mills:** None. **N.G. Cascella:** None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.12/B20

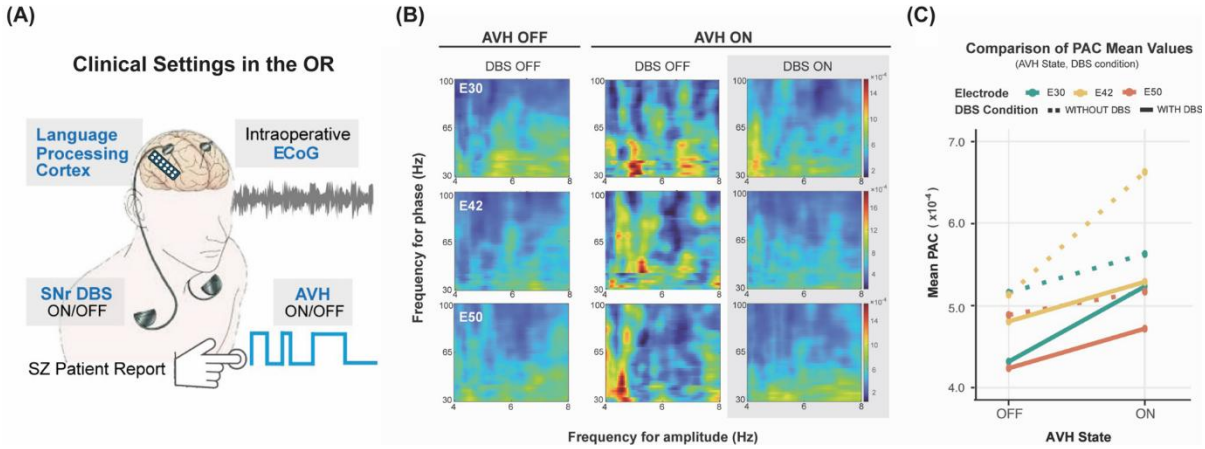
Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NIH Grant U01MH130625
NIH Grant P50MH136297

Title: Functional evidence for substantia nigra pars reticulata involvement in auditory verbal hallucinations in treatment-resistant schizophrenia

Authors: *A. SHEN[1], Y. SALIMPOUR[1], M. KIM[1], K. CHOI[2], M. J. BRAY[1], F. C. NUCIFORA[1], W. S. ANDERSON[1], M. FIGEE[2], K. A. MILLS[1], A. SAWA[1], N. G. CASCELLA[1];
[1]Johns Hopkins Sch. of Med., Baltimore, MD; [2]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Schizophrenia (SZ) is a clinically and biologically heterogeneous psychiatric disorder, with about one-third of patients being treatment-resistant (TR). Auditory verbal hallucinations (AVH) in TR SZ are a formidable challenge for pharmacologic intervention. Addressing this unmet clinical need requires individualized, mechanism-informed interventions. Deep brain stimulation (DBS) of the substantia nigra pars reticulata (SNr) has been proposed as a novel neuromodulation treatment, yet its real-time physiological effects remain unknown. In this study, we recorded the first real-time intraoperative electrocorticography (ECoG) in a patient with TR SZ during DBS electrode implantation. A 63-channel ECoG grid was placed over the left inferior parietal cortex—region implicated in language processing. The patient reported AVH events in real-time via button press across alternating DBS-on and DBS-off conditions. As a result, AVH episodes were associated with decreased gamma band-power in the angular ($p = 0.031$) and supramarginal gyri ($p = 0.027$), and an increase in theta-gamma phase-amplitude coupling (PAC), suggesting maladaptive synchronization. SNr DBS during AVH episodes shifted PAC patterns toward AVH-free baseline states. These changes implicate SNr DBS's capability in modulating cortico-striatal-thalamic-cortical circuit synchrony and suggest that its therapeutic effect may arise from disrupting pathological oscillatory coupling rather than classical inhibition. While limited to a single-subject observation, this case highlights the feasibility of capturing intraoperative cortical dynamics during DBS for TR SZ. Our findings suggest that SNr stimulation may influence AVH-related oscillatory activity and that theta-gamma PAC could serve as a biomarker for future mechanistic studies.



Disclosures: A. Shen: None. **Y. Salimpour:** None. **M. Kim:** None. **K. Choi:** None. **M.J. Bray:** None. **F.C. Nucifora:** None. **W.S. Anderson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Globus Medical. F. Consulting Fees (e.g., advisory boards); iota Biosciences. **M. Figee:** None. **K.A. Mills:** None. **A. Sawa:** None. **N.G. Cascella:** None.

Poster

PSTR427: Schizophrenia: Translational Studies and Experimental Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR427.13/B21

Topic: A.07. Development of Neural Systems

Support: JP22K15204

Title: Repetitive Neuronal Activation Regulates Cellular Maturation State via Nuclear Reprogramming

Authors: *T. MURANO[1], H. HAGIHARA[1], K. TAJINDA[2], K. KATOH[3], A. ROBISON[4], M. M. MATSUMOTO[5], M. NAMIHIRA[6], T. MIYAKAWA[1];
[1]Fujita Hlth. Univ., Toyoake, Japan; [2]Astellas Res. Inst. of America, San Diedo, CA; [3]The Exploratory Res. Ctr. on Life and Living Systems (ExCELLS), Natl. Inst. of Natural Sci. (NINS), Tsukuba, Japan; [4]Michigan State Univ., Okemos, MI; [5]Arialys Therapeutics, Inc., La Jolla, CA; [6]Mol. Biosystems Res. Inst., Tsukuba, Japan

Abstract: Neural stimulation, such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), are highly effective clinical interventions for a broad spectrum of psychiatric disorders, including depression and schizophrenia. However, their mechanism of action at the cellular level remains poorly understood. Here, we modelled ECT with repeated optogenetic neuronal stimulation in the mouse dentate gyrus, and observed ECT-like behavioral effects, including decreased depression-like behavior and increased locomotor activity. At the cellular level, we found dematuration to a long-term stable state, persisting for

more than one month, defined by changes in nuclear structure, gene expression patterns resembling the G_2/M phase of the cell cycle, and altered neural coding of navigational information. Moreover, knockout of the G_2/M master regulator Cyclin B rescued some of behavioral and cellular effects. These findings demonstrate that ECT-like brain stimulation triggers plasticity of the cellular state, revealing a form of stimulus-regulated nuclear reprogramming with potential clinical utility.

Disclosures: T. Murano: None. **H. Hagihara:** None. **K. Tajinda:** None. **A. Robison:** None. **M. Namihira:** None. **T. Miyakawa:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.01/B22

Topic: B.03. Ion Channels

Support: NICHD Intramural research program

Title: Post-synaptic scaffold protein, Preso1, regulates the A-type potassium current, hippocampal excitability and plasticity

Authors: *M. A. WELCH, J.-H. HU, K. JEROME, D. A. HOFFMAN;
NIH, Bethesda, MD

Abstract: Intellectual disability (ID) is a neurodevelopmental disorder characterized by deficits in intellectual and adaptive functioning. The onset of these deficits typically presents in childhood, with the severity ranging from mild to severe. One cause of ID is mutations in the *Preso1* (aka *FRMPD4*) gene. Preso1 is a neuronal post-synaptic scaffold protein highly expressed in the hippocampus that positively regulates excitatory synaptic transmission and spine density. In this study, we show Preso1 binds to Kv4.2, the main A-type voltage-gated potassium channel in hippocampal area CA1 dendrites. To test the functional effect of Preso1 on Kv4.2, we recorded the A-type potassium current, I_A, in out-side out patches pulled from CA1 pyramidal neurons in wild-type or Preso1 KO mice. We found I_A was significantly reduced in Preso1 KO compared to control mice. Additionally, we performed whole-cell current clamp experiments to determine if CA1 excitability was affected in Preso1 KO mice because Kv4.2 channels impact hippocampal excitability. We found a significantly increased firing rate in the Preso1 KO mice, along with a more hyperpolarized action potential (AP) threshold, higher AP amplitude, lower rheobase, and shorter latency to fire an AP. These changes in CA1 excitability are consistent with reduced Kv4.2 levels. Next, we examined NMDAR-dependent long-term depression (LTD) in Preso1 KO mice, as this form of plasticity is impacted by Kv4.2 levels. We found a 1Hz low frequency stimulation of CA3 Schaffer collateral inputs, while voltage-clamping the CA1 neuron at -40mV, produced a persistent depression of excitatory post-synaptic currents (EPSCs) in wild-type but not Preso1 KO mice. Comparing the average fold change in

EPSC amplitude between 25-30min post-LTD induction relative to baseline EPSC amplitude revealed a significant impairment in depression magnitude in Preso1 KO compared to wild-type mice. In summary, this work identifies Kv4.2 as a novel target of Preso1 and shows hippocampal excitability and plasticity are disrupted in Preso1 KO mice.

Disclosures: M.A. Welch: None. **J. Hu:** None. **K. Jerome:** None. **D.A. Hoffman:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.02/B23

Topic: B.03. Ion Channels

Support: NIH grant DC01919 to LKK

Title: Voltage-dependent opening of the Kv3.4 potassium channel triggers filopodia elongation through interactions with PCDH9

Authors: *Y. ZHANG[1], J. WU[2], H. WANG[3], L. K. KACZMAREK[1];
[1]Yale Univ. Sch. Med., New Haven, CT; [2]Pharmacol., [3]Dept. of Pharmacol., Yale Univ., New Haven, CT

Abstract: During neuronal development, the Kv3.4 voltage-dependent K^+ channel is present in growth cones of elongating axons in all major fiber tracts. Loss of Kv3.4 results in errors of migration and pathfinding. The cytoplasmic C-terminal domain of Kv3.4 directly binds PCDH9, a Ca^{2+}-dependent adhesion molecule. This prevents degradation of Kv3.4 and is essential for expression in the plasma membrane. We have now tested whether Kv3.4 simply acts a protein scaffold or if Kv3.4 voltage-dependent gating alters PCDH9-depedent actin nucleation by the WAVE complex. Expression of Kv3.4 in CHO cells hyperpolarizes their membrane potential and stimulates the outgrowth of filopodia, an effect that is reversed by PCDH9 knockout or by overexpression of a peptide that specifically blocks the interaction of PCDH9 with the WAVE complex. Expression of a Kv3.4 pore-mutant in CHO cells fails both to alter resting potential and to trigger filopodial extension. At the normal resting potential of CHO cells (~-20 mV), however, Kv3.4 would be expected be in an inactivated state. To test if the Kv3.4 pore-mutant triggers filopodial extension at more negative potentials, we co-expressed the pore-mutant with Kv3.1, a subunit that does not bind PCDH9 or alter filopodia. Co-expression the Kv3.4 pore-mutant with Kv3.1 restored the membrane potential to -60 mV and triggered filopodial extension. This suggests stimulation of actin nucleation does not require K^+ ion flux through Kv3.4 but requires the channel to be in an open or closed, but not inactivated conformation, and is supported by the finding that overexpression of the pore-mutant in Kv3.4$^{-/-}$ cerebellar ganglion neurons rescued their stunted neurite outgrowth. To further differentiate the effects of Kv3.4 open and closed states on filopodial extension, we used two- photon live-imaging of actin combined with patch clamp recording. Depolarizations that open the channel acutely stimulated filopodial extension,

while hyperpolarization had no effect and depolarizations that inactivate Kv3.4 caused retraction. Our data support the hypothesis that gating of Kv3.4 channels to the open state suggest promotes the interaction of PCDH9 with the WAVE complex to trigger actin nucleation, and that this interaction is required for normal neuronal development.

Disclosures: Y. Zhang: None. **J. Wu:** None. **H. Wang:** None. **L.K. Kaczmarek:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

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Program #/Poster #: PSTR428.03/B24

Topic: B.03. Ion Channels

Support: NIH Grant R03TR004200
NIH Grant R21NS101648
NIH Grant R01NS114210

Title: Kv2/kv6.4 heteromeric potassium channels are expressed in spinal motor neurons and localized at c-bouton synapses

Authors: T. HAMILTON[1], K. D. MURRAY[2], J. S. TRIMMER[2], J. SACK[2], ***M. J. FERNS**[1]; [1]Anesthesiol. and Pain Med., [2]Physiol. and Membrane Biol., Univ. of California Davis, Davis, CA

Abstract: Voltage-gated K^+ channels of the Kv2 family co-assemble with electrically silent KvS subunits in specific subpopulations of brain neurons, forming heteromeric Kv2/KvS channels with distinct functional properties. Little is known about the composition and function of Kv2 channels in spinal cord neurons, however. Here, we show that while Kv2.1 is broadly expressed in multiple classes of spinal cord neurons, the Kv6.4 “electrically-silent” subunit is specifically expressed in motor neurons. In motor neurons, we find that Kv6.4 protein is co-clustered with Kv2.1 and Kv2.2 subunits at endoplasmic reticulum-plasma membrane (ER-PM) junctions beneath C-bouton synapses. In Kv2.1 S590A mutant mice, in which Kv2.1 is unable to bind ER VAP proteins, Kv2.1 and Kv6.4 clustering at ER-PM junctions is severely reduced suggesting Kv2 channels are localized at ER-PM junctions by the same molecular mechanism in motor neurons and brain neurons. Moreover, clustering of Kv6.4, as well as the AMIGO-1 auxiliary subunit, are severely reduced in Kv2.1 knockout mice and moderately reduced in Kv2.2 knockout mice. Thus, expression and localization of Kv6.4 subunits is dependent on Kv2 subunits, likely through their co-assembly into heteromeric channels. Finally, we find that presynaptic C-boutons and postsynaptic clusters of the ER-resident sigma1-receptor are preserved in motor neurons of Kv2 knockout mice. Together, these findings identify a specific Kv2/KvS channel subtype expressed in motor neurons that localizes to C-bouton junctions where it could regulate neuronal excitability and signaling at ER-PM junctions.

Disclosures: T. Hamilton: None. **K.D. Murray:** None. **J.S. Trimmer:** None. **J. Sack:** None. **M.J. Ferns:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.04/B25

Topic: B.03. Ion Channels

Support: R01-MH126017

Title: The Shab family potassium channels are highly enriched at the presynaptic terminals of human neurons

Authors: O. BENNER[1], C. H. KARR[2], A. C. QUINTERO-GONZALEZ[3], M. M. TAMKUN[4], *S. CHANDA[1];
[2]Dept. of Biochem. and Mol. Biol., [3]Biochem. and Mol. Biol., [4]Biomed. Sci., [1]Colorado State Univ., Fort Collins, CO

Abstract: The Shab family voltage-gated K+ channels (i.e., Kv2.1, Kv2.2) are widely expressed in mammalian brain and regulate neuronal action-potential firing. In addition to their canonical functions, the Kv2 proteins help establish direct attachments between plasma membrane and endoplasmic reticulum (ER), also known as ER-plasma membrane junctions. However, the biochemical properties and molecular organization of these ion channels have not yet been described in human neurons. Here, we have performed a systematic analysis of endogenous expression, post-translational modification, and subcellular distribution of the major components of Kv2 complex in neurons derived from human stem cells. We found that both Kv2.1, Kv2.2, and their auxiliary subunit AMIGO1 are significantly upregulated during early neurogenesis, localize at the cell surface, and already begin to assemble with each other. Human Kv2.1 and AMIGO1, but not Kv2.2, undergo substantial post-translational modification including phosphorylation and/or N-linked glycosylation. Acute pharmacological inhibition with Kv2 blockers also revealed their functional activation in human neurons. These proteins formed prominent clusters at cell bodies, dendritic branches, and axon initial segments. Interestingly, a large fraction of them also exhibited considerable accumulation at human presynaptic terminals, where they aggregated with the local ER network. This synaptic localization of Kv2 subunits was primarily restricted to presynaptic regions, as they demonstrated limited enrichment at postsynaptic densities. These results were highly reproducible in multiple stem cell lines used and alternative differentiation protocols tested, confirming that human presynaptic compartments can actively recruit the Shab family K+ ion channels.

Disclosures: O. Benner: None. **C.H. Karr:** None. **A.C. Quintero-Gonzalez:** None. **M.M. Tamkun:** None. **S. Chanda:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.05/Web Only

Topic: B.03. Ion Channels

Title: De Novo Design of Selective Kv1.3 Inhibitors for Targeted Neuroinflammation Therapy

Authors: *H. M. NGUYEN[1], D. LOPEZ MATEOS[2], K. HUANG[1,3], K. NARANG[2], M. MARQUIS[1], H. WULFF[1], V. YAROV-YAROVOY[2];
[1]Pharmacol., [2]Physiol. and Membrane Biol., [3]Univ. of California, Davis, CA

Abstract: Neuroinflammation, driven by activated microglia, is a pervasive and perpetuating factor in numerous neurodegenerative and neuroinflammatory diseases. Current treatments, such as steroids or calcineurin inhibitors, offer some relief but broadly target microglial activity, often leading to severe immune-compromising side effects that preclude long-term use. The voltage-gated potassium channel Kv1.3 is consistently upregulated in activated, pro-inflammatory (M1-like) microglia across diverse neurological disorders and critically mediates key microglial inflammatory responses, including calcium signaling, neurotoxic cytokine production (e.g., IL-1β, TNF-α), reactive oxygen species generation, microglial proliferation, and neurotoxicity. We leveraged a suite of deep-learning methods—RoseTTAFold Diffusion, Protein Message-Passing Neural Network, and AlphaFold—to *de novo* design novel peptide inhibitors specifically targeting the extracellular pore domain of Kv1.3. We generated two classes of miniproteins: completely *de novo* pore blockers designed from the apo Kv1.3 experimental structure alone, and "toxin-inspired" designs grafting the key lysine from ShK into *de novo* scaffolds to replicate its inhibitory mechanism. From thousands of *in-silico* designs, we successfully expressed, purified, and functionally tested a preliminary set using whole-cell patch-clamp electrophysiology. Both completely *de novo* and toxin-inspired approaches yielded designs that exhibited nanomolar inhibitory potency against Kv1.3. Crucially, these founder designs demonstrated a favorable selectivity profile over Nav1.5, hERG, and other closely related Kv1 family members, and effectively depolarized microglial membrane potential and suppressed calcium signaling. Our approach using advanced deep-learning methodologies represents a highly promising therapeutic strategy to mitigate neuroinflammation and associated neurodegeneration by preventing detrimental microglial activation without broad immune suppression, thus avoiding the systemic side effects of current therapies.

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Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.06/B26

Topic: B.03. Ion Channels

Support: R01-ES031407

Title: Channel-forming BKα subunits in a binary lipid bilayer suffice to support channel inhibition by toluene levels reached in blood during acute intoxication.

Authors: *A. SHAW[1], A. BUKIYA[2], A. DOPICO[3];
[1]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [2]The Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [3]Pharmacol., The Univ. of Tennessee HSC, Col. of Medici, Memphis, TN

Abstract: Toluene acute intoxication by inhalation and brain ischemia share many neurological and psychological outcomes. Cerebral artery constriction is well-known to cause brain ischemia, and our group has recently documented that toluene at concentrations reached during acute intoxication following inhalation constricts cerebral arteries, an action that is blunted by genetic ablation or selective pharmacological block of big conductance Ca^{2+}/voltage-gated K^+ (BK) channels (*Shaw et al., 2025*). Consistent with such involvement, 0.1 mM toluene inhibits BK channels when probed in their native cerebrovascular smooth muscle (SM) membranes (*Shaw et al., 2025*). Here, we set to determine whether BK channels in absence of the complex proteolipid environment of native SM membranes are functional targets of toluene. Thus, we evaluated the effect of acute toluene exposure on the function of BK channel homotetramers made of α subunits cloned from rat cerebral artery SM (cbv1 channels) following channel reconstitution into 3:1 (w/w) phosphatidylethanolamine:phosphatidylserine planar bilayers. Toluene induces a dose-dependent inhibition of cbv1 channels, reaching up to a 37.5% reduction in open channel probability (Po) at 0.1 mM, without evoking any significant change in average unitary current amplitude. These data indicate that BK α subunits inserted into a bare lipid environment suffice to support channel inhibition by toluene concentrations found in blood upon human acute intoxication. Since native cerebrovascular BK channels inhibited by toluene with eventual cerebral artery constriction (*Shaw et al., 2025*) include regulatory β1 subunits, current studies are being conducted to determine whether these regulatory subunits affect toluene-induced inhibition of BK channel activity.

Disclosures: A. Shaw: None. **A. Bukiya:** None. **A. Dopico:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.07/B27

Topic: B.03. Ion Channels

Title: Neuronal membrane expression of potassium channel Kv4.2 and sodium channel SCN1beta in the amygdala and hippocampus following auditory fear conditioning.

Authors: *P. KAUR[1], S. VERMA[2], K. E. COLE[3], R. G. PARSONS[3];
[1]Stony Brook Univ., Stony Brook, NY; [2]Stony Brook Univ., Stony Brook University, NY;
[3]Psychology, Stony Brook Univ., Stony Brook, NY

Abstract: Prior studies from our lab have shown that an initial auditory fear conditioning session can facilitate subsequent fear learning within a time window beginning an hour after initial learning and lasting approximately 24 hours. While we have identified cellular mechanisms engaged in the amygdala soon after learning that are necessary for this facilitation effect, whether there are unique downstream cellular events that support the longer-lasting aspect of facilitation is unknown. Furthermore, we have not tested the involvement of the hippocampus, which is known to be involved in various aspects of aversive learning. This study investigated the expression of Kv4.2 and SCN1beta ion channels in the amygdala and hippocampus following auditory fear conditioning at specific time points corresponding to two time points at which facilitation is observed (i.e. 1 hour, 1 day) and at 7 days when the facilitatory effect has waned. We were interested in the expression of these proteins given their involvement in regulating membrane excitability, which is a plausible mechanism of our behavioral facilitation effects. Separate groups of male Sprague-Dawley rats underwent auditory fear conditioning or an equivalent period of context exposure and were sacrificed either 1 hour, 1 day, or 1 week later. Tissue samples were taken, and membrane fractions were subjected to western blot analysis for Kv4.2 and SCN1beta. In both the amygdala and hippocampus, Kv4.2 levels were significantly decreased in rats that had been trained compared to context exposed rats and these rats were consistent across time points. An analysis of SCN1beta expression did not yield any significant differences across conditions or groups in the amygdala or hippocampus. These findings indicate that auditory fear conditioning reduces the neuronal membrane expression of Kv4.2 in the hippocampus and amygdala, suggesting that learning results in the internalization and/or degradation of Kv4.2. The absence of a differential effect of time suggests that expression of Kv4.2 is unlikely to be a specific mechanism underlying the facilitation of subsequent learning by auditory fear conditioning, but rather a possible mechanism of long-term memory storage.

Disclosures: P. Kaur: None. **S. Verma:** None. **K.E. Cole:** None. **R.G. Parsons:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.08/B28

Topic: B.03. Ion Channels

Support: NICHD intramural research program

Title: Impaired DPP6-Kv4.2 dynamics and Kv4.2 dendritic gradient in Angelman syndrome model mice

Authors: *J.-H. HU[1], Y. LIU[2], D. A. HOFFMAN[3];
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Abstract: Angelman syndrome (AS) is a severe neurological disorder characterized by intellectual disability, absence of speech, spontaneous seizure, and motor dysfunction. The absence of functional maternally derived UBE3A protein is considered the primary cause of AS, yet the downstream signaling pathways remain elusive. We previously identified the voltage-gated K^+ channel Kv4.2 as an activity-dependent substrate for UBE3A and showed that UBE3A primarily targets DPP6 containing Kv4.2 complex and ubiquitinates Kv4.2 at residue K103. This process is required for activity-induced Kv4.2 protein loss in cultured hippocampal neurons. Here we show that UBE3A binds to the internalized Kv4.2 rather than the surface Kv4.2 when co-expressed with DPP6 in HEK293T cells. Kv4.2-DPP6 association is significantly decreased upon PTZ-induced seizure in wild-type mice. However, in a mouse model of AS, Kv4.2-DPP6 association is reduced and not regulated by PTZ-induced seizure. As DPP6 established Kv4.2 dendritic gradient in hippocampal pyramidal neurons, we also showed impaired dendritic gradient of Kv4.2 in both basal and apical dendrites in a mouse model of AS. These findings provide additional information on Kv4.2 as a substrate of UBE3A contributing to certain phenotypes of AS.

Disclosures: J. Hu: None. **Y. Liu:** None. **D.A. Hoffman:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

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Program #/Poster #: PSTR428.09/B29

Topic: B.03. Ion Channels

Support: the National Natural Science Foundation of China (32071040 to BL, 82071241 and 81871048 to LH)
Guangdong Basic and Applied Basic Research Foundation (2023B1515040019 to BL)
Guangdong Project (2017GC010590 to BL)

Title: An optogenetic toolbox for tunable control of endogenous voltage-gated ion channels

Authors: *L. CHEN[1], X. ZHANG[4], L. HUANG[2], B. LI[3];
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Abstract: Ion channels mediate ions flow through the membrane and play a key role in neuronal signaling transduction. States of ion channels change dynamically under different physiological and pathological conditions. However, fast and genetically encoded tools to regulate endogenous ion channels are lacking. To address this bottleneck, we developed two optogenetic tools for the

BK channel: (1) BK-LIICA (Light Induced Ion Channel Activator) and (2) BK-lumi. BK-LIICA significantly amplified BK current following blue light illumination, whereas BK-lumi specifically blocked BK channels upon expression and unblocked channels in a light-dependent manner. Both BK-LIICA and BK-lumi significantly reduced the firing rate of pyramidal neurons after blue light illumination. In behavioral test, our tools could optically control mice locomotion without affecting motor ability. Furthermore, BK-LIICA successfully rescued social deficits in a mouse model exhibiting BK channel downregulation. Critically, our approach is generalizable to other ion channels. Leveraging some cutting-edge deep learning methods, we successfully devised an optogenetic tool by computational de novo design. Collectively, we demonstrate that our optogenetic tools are versatile and generalizable. These tools can modulate endogenous ion channels in molecular, cellular, and behavioral levels, offering a powerful approach to investigate the function of endogenous ion channels.

Disclosures: L. Chen: None. **X. Zhang:** None. **L. Huang:** None. **B. Li:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.10/B30

Topic: B.03. Ion Channels

Support: NS102239

Title: Slack (KCNT1) potassium channels regulate the structure of the inner mitochondrial membrane of neurons

Authors: *H. WANG[1], S. WU[3], Y. ZHANG[4], J. WU[2], E. A. JONAS[5], L. K. KACZMAREK[6]; [2]Pharmacol., [1]Yale Univ., New Haven, CT; [3]Biogen, Cambridge, MA; [4]Pharmacol., Yale Univ. Sch. Med., New Haven, CT; [5]Yale Univ. Sch. Med., Hamden, CT; [6]Yale Univ. Sch. Med., New Haven, CT

Abstract: The Slack channel (KCNT1, $K_{Na}1.1$) is a sodium-activated potassium channel expressed in neurons of the cerebral cortex, as well as in multiple other brain regions where gain-of-function mutations cause several forms of childhood epilepsy and intellectual disability. Slack regulates synaptic plasticity, and its cytoplasmic C-terminus interacts with mRNA translation machinery, including FMRP and CYFIP1, to modulate local protein synthesis. Here, we report a novel role for Slack in mitochondrial bioenergetics and cristae morphogenesis. Proteomic analysis of Slack knockout (KO) mice, as well as mice bearing the Slack-R455H gain-of-function mutation, revealed elevated levels of the cristae-regulating proteins MIC60 and OPA1, as well as levels of other inner mitochondrial membrane proteins in the cerebral cortex of both strains compared to those in wild type mice. These results were confirmed by western immunoblotting. Strikingly, visual inspection and quantitative analysis of electron micrographs of mitochondria in pyramidal cortical neurons revealed significantly increased numbers and

density of mitochondrial cristae in both Slack KO and Slack-R455H mice. Functional assays demonstrated enhanced mitochondrial respiration (OCR) in synaptoneurosomes from Slack-R455H animals, suggesting that Slack activity tunes bioenergetic capacity. We propose that Slack channels act as metabolic sensors, coupling neuronal activity to mitochondrial plasticity via ion-sensitive structural remodeling. Dysregulation of this pathway may contribute to the metabolic pathophysiology of Slack-associated epilepsies.

Disclosures: H. Wang: None. **S. Wu:** None. **Y. Zhang:** None. **J. Wu:** None. **E.A. Jonas:** None. **L.K. Kaczmarek:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

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Program #/Poster #: PSTR428.11/B31

Topic: B.03. Ion Channels

Support: NIH grant NS102239

Title: Block of Slack (KCNT1) ameliorates loss of non-synaptic mitochondrial function after traumatic brain injury

Authors: V. GOPAL VISWANATHAN[1], F. MEREDITH[2], E. SULLIVAN[2], J. WU[4], ***L. K. KACZMAREK**[5], P. G. SULLIVAN[3];
[1]Dept. of Neurosci. and SCoBIRC, Univ. of Kentucky, Lexington, CT; [2]Dept. of Neurosci. and SCoBIRC, [3]SCoBIRC and Dept. of Neurosci., Univ. of Kentucky, Lexington, KY; [4]Pharmacol., Yale Univ., New Haven, CT; [5]Yale Univ. Sch. Med., New Haven, CT

Abstract: Genetic mutations that increase the activity of Slack sodium-activated potassium channels (also termed KCNT1, $K_{Na}1.1$ channels) lead to intractable early onset epilepsy. Alterations in Slack expression or activity also result in changes in mitochondrial composition and structure. Recent studies have suggested that the expression of Slack channels is increased in an animal model of traumatic brain injury (TBI) and that the increased activity of these channel may promote the occurrence of seizures following injury. Because TBI causes prolonged changes in mitochondrial function of cortical neurons, and these changes are likely to determine cell survival, we tested the effects of a pharmacological inhibitor of Slack channels, PRX-2904, on mitochondrial function following controlled TBI in mice. Mice (10-12 weeks old; n=5-6/group) were subjected to a 1 mm (moderate-severe) controlled injury directly to the surface of the brain using a 3mm flat-tip pneumatic impactor at 3.5m/s and were sacrificed 24 hours post-injury. Synaptic and non-synaptic mitochondria were prepared from the cerebral cortex and oxygen consumption rates (OCR) were analyzed in the presence of mitochondrial substrates, inhibitors and uncouplers of the electron transport chain. We found that treatment of animals PRX-2904 (30mg/kg) 15 minutes after injury significantly reversed changes in OCR on non-synaptic mitochondria (State III, State V complex-I and State V complex-II) produced by the

injury, but did not reverse the decrease in OCR produced in synaptic mitochondria. In another cohort of mice (n=6-8/group), tissue sparing and behavior were assessed using the same dosage. Compared to sham animals, injured animals exhibited a significant loss of cortical tissue volume. Although PRX-2904 treatment markedly improved mitochondrial function, it did not result in the expected preservation of cortical tissue. Behavioral experiments indicated that pharmacological treatments targeting Slack potassium channels may ameliorate at least some of the effect of traumatic brain injury. Ongoing experiments will investigate PRX-2904 repeated dosing and the therapeutic window of intervention further.

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Poster

PSTR428: Voltage-Gated Potassium Channels

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Program #/Poster #: PSTR428.12/B32

Topic: B.03. Ion Channels

Support: NS102239
UL1 TR001863 from the National Center for Advancing Translational Sciences

Title: Antisense oligonucleotide-mediated gene therapy corrects defects in neuronal excitability and mRNA translation in KCNT1 epilepsy

Authors: *J. WU[1], S. GOLINSKI[3], S. GILLIAT[2], R. S. SMITH[3], Y. ZHANG[2], H. WANG[2], T. YU[4], L. K. KACZMAREK[2];
[2]Pharmacol., [1]Yale Univ., New Haven, CT; [3]Pharmacol., Northwestern Univ., Chicago, IL; [4]Div. of Genet. and Genomics, Boston Children's Hosp., Boston, CT

Abstract: Gain-of-function (GOF) mutations in the *KCNT1* gene, which encodes the sodium-activated potassium channel Slack (KCNT1, $K_{Na}1.1$), lead to network hyperexcitability, refractory seizures, and severe intellectual disability. Antisense oligonucleotides (ASOs) have emerged as promising therapeutic agents for KCNT1 epilepsy, although their mechanisms and broader effects remain unclear. In a mouse model of KCNT1 epilepsy with the *Kcnt1-R455H* mutation, we demonstrate that knockdown of *Kcnt1* with an ASO targeting the core domain of the channel reduces both Na^+-activated K^+ (K_{Na}) currents and voltage-dependent sodium (Na_V) currents, alleviating mutation-induced hyperexcitation in excitatory neurons and restoring inhibition in interneurons. Moreover, *Kcnt1* knockdown releases its binding proteins FMRP (Fragile X Mental Retardation Protein) and CYFIP1 (Cytoplasmic FMR1 Interacting Protein 1)

from the channel to eIF4E (Eukaryotic Initiation Factor 4E), where they normally function to inhibit cap-dependent translation initiation. As a result, ASO treatment reduces the synthesis of Na_V channels, specifically $Na_V1.1$, $Na_V1.2$ and $Na_V1.6$, and their localization to the axon initial segment (AIS), further contributing to the reduction in Na_V currents. Finally, we show that the interactions of FMRP and CYFIP1 with KCNT1 are present in mid-gestation human cortical plate neurons, and that ASO treatment similarly regulates the distribution of these proteins in human neurons. Our findings provide new insights into the mechanism by which KCNT1 regulates mRNA translation and highlight the role of ASOs in modulating both neuronal excitability and mRNA translation, supporting their potential as therapeutic interventions for refractory epilepsies and developmental disorders.

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Poster

PSTR428: Voltage-Gated Potassium Channels

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Program #/Poster #: PSTR428.13/B33

Topic: B.03. Ion Channels

Support: GR114663

Title: Neuronal excitability of bipolar disorder mimicked by ATP synthase c subunit overexpression in rat neurons

Authors: *L. LIU[1], P. LICZNERSKI[2], Y. ZHANG[5], R. CHEN[3], L. SHEN[4], L. K. KACZMAREK[6], E. A. JONAS[7];
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Abstract: Neuronal excitability of bipolar disorder mimicked by ATP synthase c-subunit overexpression in rat neurons Liman Liu, Licznerski Pawel, Yalan Zhang, Rongmin Chen, Lei Shen, Kaczmarek Leonard, Elizabeth A. Jonas Yale School of Medicine, New Haven, CT Disclosures: Liman Liu: None. Licznerski Pawel: None. Yalan Zhang: None. Rongmin Chen: None. Lei Shen: None. Kaczmarek Leonard: None. Elizabeth A. Jonas: None. Abstract Mitochondrial ATP synthase c-subunit leak channel (ACLC) activity is implicated in the bioenergetic regulation of cell metabolism and in formation of the mitochondrial permeability transition pore (mPTP). Mitochondrial dysfunction has been associated with bipolar disorder (BD), a disease characterized by altered mood and energy states. Human brain organoids derived from BD patients exhibit elevated ATP synthase c-subunit expression, increased glycolytic and TCA cycle activity, increases in inner mitochondrial membrane ion channel conductance and markedly altered transcription and translation, including aberrantly elevated increases in

transcription/translation of certain ion channels. This project aims to elucidate the mechanisms of how increased c-subunit expression affects neuronal plasma membrane ion channel transcription/translation and/or causes post translational ion channel modifications. In neurons isolated from BD patients' brain organoids, electrophysiological recordings revealed an increase in the percentage presence of action potentials at low current injection and a trend toward increased firing rate compared to healthy controls. Treatment with lithium and dexpramipexole-agents known to reduce mitochondrial membrane leak by binding to the ATP synthase directly—partially reversed this hyperexcitability in the isolated neurons and reversed neuronal activity as measured by calcium transients in the intact organoids. To study the mechanism of how increased ACLC activity might cause these abnormalities, we overexpressed the ATP synthase c-subunit in isolated rat cortical neurons via AAV (AAV c-sub) and compared them to AAV-GFP controls. Primary neurons from embryonic day 18 rats were infected on day in vitro 5, and whole-cell patch clamp recordings were conducted on days 15-21 in both current-clamp and voltage-clamp modes. Collectively, our study will provide mechanistic insight into how elevated ACLC expression and activity drive neuronal excitability and contribute to cortical network dysfunction in BD.Keywords:mitochondrial dysfunction; ATP synthase c-subunit; cortical neuron excitability; whole-cell patch clamp, neuropsychiatric disease, human brain organoids.

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Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.14/B34

Topic: B.03. Ion Channels

Title: Role of cerebellar spreading depression in the pathophysiology of episodic ataxia type 1

Authors: *M. PESSIA[1], F. M. HAIDAR[2], M. D`ADAMO[3];
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Abstract: Episodic ataxia type 1 (EA1) is a neurologic channelopathy due to *loss-of-function* mutations in the gene coding for the Kv1.1 channel subunit, and characterized by interictal myokymia and episodic attacks of generalized ataxia. The neurologic defect causing the "*episodicity*" of the attacks is unknown. Given that in other episodic neurological disorder, like migraine with aura, attacks are thought to be triggered by cortical spreading depression (CSD)—a wave of neuronal and glial depolarization followed by sustained inhibition—we hypothesized that EA1 may similarly result from an increased susceptibility to cerebellar spreading depression (CeSD), driven by impaired Kv1.1 channel activity and increased cerebellar excitability. To induce a CSD-like event *in vitro*, we perfused sagittal cerebellar slices with aCSF containing 30 mM KCl while monitoring light transmittance and Ca^{2+} dynamics. The high K^+ aCSF evoked

a wave of increased light transmittance with biphasic peaks, primarily along the molecular layer, and triggered a robust Ca^{2+} wave in the same region, confirming CeSD initiation and propagation. Next, we recorded the extracellular potential changes associated with the propagation of a CeSD wave. In most cerebellar slices, CeSD-associated hyperpolarization consistently exhibited a single peak with an amplitude of ~4 mV, a duration of ~20 seconds, and a propagation speed of 1-4 mm/min. Moreover, extracellular recordings from Purkinje cells revealed that the passage of a CeSD wave caused a transient cessation of firing. To investigate the role of neurotransmitter receptors in CeSD, we tested the pharmacological effect of AP-5 (NMDA receptor antagonist), CNQX (AMPA receptor antagonist) and Gabazine (GBZ, $GABA_A$ receptor antagonist). CeSD was inhibited by CNQX (10 μM) but not by AP-5 (10 μM). In addition, we found that the CeSD could not be elicited in the presence of either GBZ (10 μM) or the voltage-gated Na^+ channel blocker TTX (1 μM). Notably, we found that the CeSD recorded from cerebellar slices dissected from a rodent model of EA1 (*Kv1.1*$^{V408A/+}$) spreads at higher velocity and invades a wider area of the molecular layer than that recorded from WT mice, indicating that the *loss-of-function* mutation V408A in Kv1.1 channel can alter the properties of CeSD. Overall, these findings suggest that CeSD plays a critical role in the pathogenesis of EA1.

Disclosures: M. Pessia: None. **F.M. Haidar:** None. **M. D`Adamo:** None.

Poster

PSTR428: Voltage-Gated Potassium Channels

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Topic: B.03. Ion Channels

Support: NIH Grant NS093073
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Title: Axon-dendrite targeting of SCA13-linked K^+ channel in central neurons requires a microtubule-stabilizing protein

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Abstract: Kv3.3 voltage-gated K^+ (Kv) channels are highly concentrated in Purkinje neuron dendrites and hippocampal mossy fibers, consistent with motor and cognitive deficits characterized in spinocerebellar ataxia 13 (SCA13) caused by Kv3.3 mutations. However, the channel targeting mechanism remains poorly understood. Here we report that the microtubule-associated protein 6 (MAP6) is required in proper axon-dendrite targeting of Kv3.3 channels. MAP6 deletion reduces Kv3.3 channels in Purkinje cell dendrites and hippocampal mossy fibers. MAP6's 1st and 2nd Mn modules directly bind the external surface of the Kv3.3 N-terminal T1 tetramer, while its 3rd Mn module indirectly associates with Cav2 voltage-gated Ca^{2+} (Cav) channels. Knocking down MAP6 markedly reduces the somatodendritic level of Kv3.3 and

Cav2.1 (lined to SCA6) in Purkinje neurons, whereas Mn1/2-GFP expression reduces the axon-dendrite levels of Kv3.3 but not Cav2.1, but both reduce Purkinje neuron burst firing. Thus, our findings provide new insights into Purkinje neuron targeting of two important ion channels whose genes are linked to SCAs.

Disclosures: C. Gu: None.

Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

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Topic: B.03. Ion Channels

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Title: Role of Kv7 channels in the disruption of the blood-brain barrier induced by angiotensin II

Authors: C. CELENTANO[1], G. SCHIPANI[1], R. VITALE[1], S. IERVOLINO[1], F. MICELI[1], M. TAGLIALATELA[1], ***V. BARRESE**[2];
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Abstract: The blood-brain barrier (BBB) plays a pivotal role in maintaining brain homeostasis and neuronal function; disruption of the BBB causes alterations of the balance of ions and solutes, and contributes to several neurological disorders such as epilepsy and stroke. Interestingly, the renin-angiotensin system (RAS) is a crucial regulator of BBB permeability, and accumulating evidence suggest that increased RAS activity is associated with late-onset epilepsy. Moreover, angiotensin II (Ang II) regulates the expression and function of several classes of ion channels, which play a crucial role in the homeostasis of the BBB. Among them, we have recently shown that voltage-gated Kv7 potassium channels (Kv7.1-Kv7.5) are expressed in brain endothelial cells (EC), where they regulate BBB integrity in both physiological conditions and during seizures. Therefore, in the present work we investigated the role of Kv7 channels in Ang II-induced alteration of the BBB. Clonal (BEND-3) and primary brain ECs, as well as brain ECs derived from human induced pluripotent stem cells (iPSCs) were co-cultured with pericytes and astrocytes in the Transwell system, to reproduce in vitro the neurovascular unit. Cells were exposed to Ang II (100 nM) in presence of Kv7 activators such as retigabine and ML213 (both used at 10 μM), and the effects on permeability of ECs and structure of tight junctions (TJs) were assessed by means of Trans-Endothelial Electrical Resistance (TEER) measurement, immunofluorescence, Western blot and Proximity Ligation Assay (PLA). Incubation of ECs with

Kv7 channel activators prevented the decrease in TEER induced by Ang II, and reduced the disruption of Zonula Occludens 1 (ZO-1), a key regulator of TJ integrity. Moreover, opening of Kv7 channels prevented the increase of intracellular Ca^{2+} levels caused by Ang II, and the consequent enhanced phosphorylation of ZO-1, that is associated to its redistribution from the TJs to the intracellular space. Interestingly, Ang II did not affect EC viability, but selectively downregulated endothelial Kv7.5, an effect that was reduced by the proteasome inhibitor MG-132. Our results suggest that the degradation of Kv7.5 protein might participate in the Ang II-induced damage of the BBB. In particular, the depolarization prompted by reduced Kv7.5 levels might lead to calcium accumulation and phosphorylation of ZO-1, which, in turn, cause the rearrangement of TJs and the increase of the permeability of the BBB. Overall, these results highlight activation of Kv7 channels as a potential strategy to prevent BBB disruption caused by an overactive RAS.

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Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.17/B37

Topic: B.03. Ion Channels

Support: Clinical Research Priority Program (CRPP) Praeclare

Title: Probing KCNQ2 Variant-Specific Effects on Channel Function, Neuronal Excitability and Gene Expression

Authors: *A. KAPNULINA[1], G. SIEGEL[2], A. FREI[2], L. HEINRICH[1], K. SCHMIDT[1], A. RAUCH[2], M. MUELLER[1];
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Abstract: *KCNQ2* encodes a subunit of voltage-gated K^+ channels that mediate the neuronal M-current. Variants in *KCNQ2* are linked to a broad spectrum of developmental conditions, including neonatal epilepsy and intellectual disability (ID) of varying severity. Although many pathogenic *KCNQ2* variants have been reported, the relationship between genotype and patient phenotype, as well as the underlying disease mechanisms remain largely unclear. Here, we aimed to bridge this knowledge gap by investigating the effects of *de novo KCNQ2* variants on KCNQ channel function, neuronal excitability and gene expression. The patient cohort comprised four patients diagnosed with benign familial neonatal epilepsy (BFNE), three with developmental and epileptic encephalopathy (DEE), and one with ID. To study KCNQ channels in isolation, we expressed human *KCNQ2* constructs in CHO cells and recorded the resulting M-current using whole-cell patch-clamp. At the level of the M-current properties, most variants resulted in loss-

of-function (LOF) phenotypes impacting ion channel function and/or functional channel density. DEE variants produced more pronounced LOF phenotypes than BFNE variants, whereas the ID variant resulted in a GOF at the level of channel conductance. One BFNE and two DEE variants were further evaluated in CRISPR/Cas9-edited human iPSC-derived neurons. We first characterized the effects of acute M-current block in control neurons using the KCNQ antagonist XE991, which decreased neuronal K^+ current density, resulting in a depolarized resting membrane potential and a decreased afterhyperpolarization. Additionally, XE991-treated neurons exhibited a decreased propensity for repetitive action potential firing upon sustained depolarization, suggesting an early depolarization block. While the effect of the BFNE variant most closely resembled that of an acute M-current block in neurons, additional changes in the passive membrane properties were observed in association with this variant, which may be part of neuronal adaptation to chronic M-current loss. Despite their link to a more severe clinical phenotype, DEE variants displayed milder or no detectable phenotypes at the level of neuronal currents and excitability. Intriguingly, preliminary bulk RNA-sequencing data from these cultures point towards decreased expression of an auxiliary K^+ subunit-encoding gene, which could be indicative of compensation for KCNQ impairment. Together, our data suggest variant-specific phenotypes in KCNQ2-channel function and density that correlate with patient phenotype, which may not be directly discernible in neurons owing to potential compensatory mechanisms.

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Poster

PSTR428: Voltage-Gated Potassium Channels

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR428.18/Web Only

Topic: B.03. Ion Channels

Title: Mechanistic insights into lipopolysaccharide-induced cellular membrane potential modulation: quantifying ionic contributions through computational modeling

Authors: *Y. KIM[1], M. HADJISAVVA[2], R. L. COOPER[3];
[1]Western Kentucky Univ., Gatton Acad. of Mathematics & Sci., Richmond, KY; [2]Biol., Univ. of Kentucky, Richmond, KY; [3]Biol., Univ. of Kentucky, Lexington, KY

Abstract: It has recently been demonstrated that lipopolysaccharide (LPS) from Serratia marcescens results in a transient hyperpolarization of the membrane potential followed by a subsequent depolarization in larval Drosophila muscle (Hadjisavva and Cooper, 2025). The mechanisms of action appear to be that LPS transiently activates K2P (i.e., two-pore-domain K+ channel) channels followed by action on the NALCN (i.e., Na+ leak channels) channels. Substitution of the ionic composition and concentrations of ions in the bathing media as well as genetic overexpression of dORK1 (i.e., a Drosophila form of K2P channel) helped to substantiate

the proposed mechanisms. However, the effects on the overall permeability of the ions in the varied conditions have yet to be estimated. With the use of the Goldman-Hodgkin-Katz (i.e. GHK) equation and the known concentrations of ions in the bathing media as well as empirical data of the membrane potential the focus is now to estimate the permeability of the ions with computational simulations.

Disclosures: Y. Kim: None. **M. Hadjisavva:** None. **R.L. Cooper:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.01/B38

Topic: B.05. Synaptic Plasticity

Support: NIH R21NS136976

Title: Transcription factor CREB is activated at synapses after induction of long-term potentiation

Authors: *N. M. ALVAREZ[1], E. E. MOSES[2], D. T. PAK[3];
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Abstract: Long-term potentiation (LTP) is a form of synaptic plasticity important for memory formation in the hippocampus that is impaired across many neurodegenerative disorders. The phosphorylation of transcription factor CREB (cAMP responsive element binding protein) and the subsequent CREB-induced gene transcription that characterizes later stages of LTP is greatly reduced under neurodegenerative conditions, resulting in synaptic dysfunction. Therefore, it is important to further elucidate the mechanisms by which CREB contributes to processes of LTP in hippocampal neurons. The role of nuclear CREB in LTP has already been well-characterized, but our lab's preliminary data indicates that there is also a subpopulation of CREB localized to the synapse under both basal and LTP conditions. The function of synaptically localized CREB in LTP has not yet been studied. We have shown that the amount of phosphorylated "activated" CREB at the synapse increases immediately after LTP induction and then gradually decreases, suggesting possible dephosphorylation or trafficking of synaptic CREB. Furthermore, through mass spectrometry, we have identified novel phosphorylation sites and CREB-interacting proteins which indicate that synaptic CREB may regulate various local synaptic processes, such as actin-based transport and post-synaptic scaffolding. These results indicate that CREB may play a direct role in synapses in addition to being an important LTP-induced nuclear transcription factor, and these findings may modify current canonical understandings of LTP and other forms of synaptic plasticity.

Disclosures: N.M. Alvarez: None. **E.E. Moses:** None. **D.T. Pak:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.02/B39

Topic: B.05. Synaptic Plasticity

Title: Intensity and localization of pCREB in inhibitory and excitatory neurons.

Authors: *I. SHARMA[1], D. T. PAK[2];
[1]Dept. of Pharmacol. and Physiol., Georgetown Univ., Washington, DC; [2]Pharmacol., Georgetown Univ. Med. Sch., Washington, DC

Abstract: Abstract: Long-term potentiation (LTP), the persistent strengthening of synaptic connections, is critical for memory formation and maintenance. Cyclic AMP response element-binding protein (CREB), when phosphorylated (pCREB), regulates genes essential for LTP maintenance. Our lab previously found novel synaptic localization of pCREB in excitatory neurons post-LTP, prompting this study to investigate whether excitatory synapses on inhibitory neurons show similar pCREB dynamics, potentially revealing cell-type-specific mechanisms underlying memory maintenance. Primary hippocampal neurons from E17-19 Sprague-Dawley rats (mixed-sex cultures) were cultured on glass coverslips until DIV21. They were subjected to chemical LTP (cLTP) induction using a buffer of strychnine (1uM), forskolin (27uM), and rolipram (3.6uM) in Neurobasal media (Gibco, cat no 21103049) at 1-5 sec, 30 sec, 1 min, 3 min, and 5 min. pCREB localization was assessed via immunocytochemistry with n=10 neurons per condition quantified by fluorescence intensity. Inhibitory neurons were identified by glutamic acid decarboxylase (GAD) expression and postsynaptic density protein 95 (PSD95) morphology. Experiments were blinded, with APV treatment as a control. Analysis (One-way ANOVA, Dunnett's Multiple Comparisons, $p<0.05$) revealed that pCREB within excitatory synapses of inhibitory neurons dramatically increased following LTP stimulation, but did not decrease to the same degree as the synapses of excitatory neurons. These findings suggest a cell-type-specific pCREB response, suggesting distinct synaptic plasticity mechanisms in inhibitory neurons. This differential regulation may underpin memory maintenance by modulating excitatory-inhibitory balance in hippocampal circuits, advancing our understanding of cell-type contributions to cognitive processes.

Disclosures: I. Sharma: None. **D.T. Pak:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.03/B40

Topic: B.05. Synaptic Plasticity

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Title: Local sustained Ca^{2+} influx triggered by high-frequency glutamate inputs at cerebellar Purkinje cell dendrites

Authors: *R. OKAWA, S.-Y. KAWAGUCHI;
Kyoto Univ., Kyoto, Japan

Abstract: Neuronal activity-driven Ca^{2+} signaling plays an important role in a variety of neural function including synaptic plasticity. In cerebellar Purkinje cells, for example, strong elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) induces long-term depression (LTD), which underlies motor learning in animals. Generally, Ca^{2+} signal reflects the temporal profile of its upstream signaling event. To monitor the spatiotemporal dynamics of $[Ca^{2+}]_i$ upon high-frequency glutamatergic inputs, we transfected a fluorescent Ca^{2+} probe protein GCaMP7f to cultured Purkinje cells and uncaged 4-Methoxy-7-nitroindonyl (MNI)-glutamate by 405 nanometer laser illumination on its dendritic branch. Strong $[Ca^{2+}]_i$ increase as inducing LTD in Purkinje cell was caused by 80 Hz glutamate uncaging (5 sets of 80 stimuli at 0.5 Hz), decaying in several seconds. Surprisingly, tens of seconds after the decay, $[Ca^{2+}]_i$ again started to rise around the stimulated point. This second $[Ca^{2+}]_i$ rise persisted for at least 5 minutes and occasionally over 30 minutes, and was kept confined to ~10 micrometer around the stimulated location. This local sustained $[Ca^{2+}]_i$ elevation was also observed in the cerebellar acute slice upon the repetitive parallel fiber stimulation. The induction of the local sustained $[Ca^{2+}]_i$ elevation was suppressed by an agonist of the metabotropic glutamate receptor 1 (mGluR1) CPCCOEt, but not by depleting Ca^{2+} store of the endoplasmic reticulum with thapsigargin treatment, suggesting that mGluR1 activation by repetitive glutamate inputs somehow activate the Ca^{2+} influx continuously. Supporting this idea, increase of external Ca^{2+} concentration affected the intensity of the local sustained $[Ca^{2+}]_i$ elevation. We next attempted to identify the Ca^{2+}-conducting ion channels mediating the local sustained Ca^{2+} influx. Inhibition of either P/Q-type voltage-gated Ca^{2+} channels by ω-agatoxin IVA, or transient receptor potential canonical (TRPC) channels by SKF96365, did not fully suppress the sustained $[Ca^{2+}]_i$ elevation. As an alternative candidate, we focused on arachidonate-regulated Ca^{2+} (ARC) channel, which is composed of Orai1/3 subunits as the store-operated Ca^{2+} channel, but its activation is independent of the store depletion. Exogenous expression of a dominant negative mutant of Orai3 significantly abolished the sustained $[Ca^{2+}]_i$ rise, indicating a critical role of Orai3 channel in the local sustained $[Ca^{2+}]_i$ elevation in a Purkinje cell dendrite. In this poster, we will show the spatiotemporal dynamics and molecule mechanism of this unprecedented Ca^{2+} signaling in neuronal dendrites.

Disclosures: R. Okawa: None. **S. Kawaguchi:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.04/B41

Topic: B.05. Synaptic Plasticity

Support: R37 MH057068
R01 MH115304

Title: Strong high-frequency synaptic stimulation facilitates formation of persistent KIBRA-PKMζ accumulation in activated spines marked by phosphorylated cofilin during long-term potentiation (LTP)

Authors: *P. TSOKAS[1], K. D. ALLEN[6], D. CANO[2], C. HSIEH[3], J. E. COTTRELL[4], A. A. FENTON[7], T. C. SACKTOR[5];
[1]Physiol. and Pharmacology; Anesthesiology; The Furchgott Ctr. for Neural and Behavioral Sci., [2]Col. of Med., [3]Dept of Physiol. and Pharmacology, The Furchgott Ctr. for Neural and Behavioral Sci., [4]Anesthesiol., [5]Dept Physiol. & Pharmacol, Anesthesiol, Neurology, The Furchgott Ctr. for Neural and Behavioral Sci., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [6]Ctr. for Neurosci. and Behavior, Medgar Evers College,, Brooklyn, NY; [7]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Introduction: Protein kinase Mzeta (PKMζ) is a seminal memory molecule (https://doi.org/10.1038/nrn2949). It is a persistently active, neural tissue-specific atypical protein kinase C isoform, whose synthesis in response to synaptic activation is critical for the maintenance of late-phase long-term potentiation (late-LTP), and for the consolidation and maintenance of long-term memory. We recently showed that kidney/brain-expressed protein/WWC1 (KIBRA), a postsynaptic scaffolding protein genetically linked to human memory performance, complexes with PKMζ, anchoring the kinase's potentiating action to maintain late-LTP (https://doi.org/10.1126/sciadv.adl0030). Here we examine the molecular mechanisms that target the kinase to activated synaptic spines. We performed immunohistochemistry to examine the distribution of PKMζ, KIBRA, and the early-LTP marker of activated spines, phospho-cofilin (serine 3, P-cofilin). Phosphorylation at this LIM-kinase site inactivates the actin depolymerization factor, cofilin, promoting actin filament formation in early-phase LTP. We found that LTP induction facilitates the colocalization of KIBRA and PKMζ in activated spines marked by P-S3-cofilin. **Methods:** Acute hippocampal slices (400 μm) were prepared from 2-4-month-old male mice. Extracellular field recordings: LTP was induced by two 100 Hz tetani, delivered to CA3-CA1 synapses of stratum radiatum. Slices were fixed in 4% PFA for 48 hrs, and 20 μm sections were prepared. Immunofluorescence (IF) was performed with anti-PKMζ, anti-KIBRA, and anti-P-S3-cofilin antibodies. PKMζ, KIBRA, and P-S3-cofilin colocalization was examined by laser confocal microscopy. **Results:** Schaffer collateral/commissural stimulation persistently increases amounts and colocalization of KIBRA and PKMζ in CA1 pyramidal cells in st. radiatum. At 30 min post-tetanization, a transition

period between early-LTP and induction of late-LTP, these increases in KIBRA and PKMζ colocalize with the early-LTP marker of activated spines, P-S3-cofilin. **Conclusion:** At 30 min post-tetanization, increased KIBRA/PKMζ immunoreactivity in CA1 st. radiatum colocalizes with the key activity-dependent component of early-LTP, P-S3-cofilin, that marks activated synapses. Future experiments will determine whether P-S3-cofilin colocalizes with KIBRA-PKMζ complexes, directly measured by proximity ligation assay (PLA).

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Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.05/B42

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 1F31NS143354-01
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Title: Trafficking of AMPA receptor subunits in Par1c (MARK1) knockout mice

Authors: *R. A. SHEAR[1], E. KELLY[4], R. TANG[2], M. SUN[5], I. MIETUS[1], L. RUNNELS[1], P.-Y. PAN[6], H. ZHANG[3];
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Abstract: Dendritic spines are sites of postsynaptic excitatory input that are critical for learning and memory. Abnormalities in dendritic spine dynamics and morphology have been linked to neurodevelopmental disorders such as autism spectrum disorder (ASD). Our laboratory has recently generated a forebrain-specific conditional knockout (cKO) of partitioning defective 1 c (Par1c), also known as microtubule affinity regulating kinase 1 (MARK1), which is a serine/threonine kinase linked to ASD and bipolar disorder. Importantly, genetic evidence supports that Par1c functions in higher level cognition. Furthermore, *MARK1* is highly expressed in forebrain pyramidal neurons and exhibits human-specific accelerated evolution, suggesting its importance in the development of cognition. We found that Par1c cKO mice show dendritic spine and behavioral abnormalities *in vivo*. To examine how loss of Par1c affects the postsynaptic receptors and scaffolding proteins, we performed Western blot analysis of synaptosomes. Interestingly, we found a significant increase in synaptic levels of the AMPA receptor subunit GluR2. To probe for the underlying mechanisms, we performed phosphoproteomic analysis of WT and Par1c cKO hippocampi. We discovered a significant

decrease in the phosphorylation of S843 of RalGAPα1 in Par1c cKO hippocampi, which is a site that matches the Par1 phosphorylation consensus sequence. Preliminary *in vitro* kinase assay data support that RalGAPα1 is a direct Par1c substrate. RalGAPα1 is appreciated for its role in neurodevelopmental disorders and is known to regulate membrane trafficking. Interestingly, preliminary data suggest expression of a nonphosphorylatable (S843A) RalGAPα1 significantly increases surface GluA2 in primary hippocampal neurons and N2a cells. Thus, our current experiments are aimed at better establishing RalGAPα1 as a Par1c substrate, and determining whether RalGAPα1 regulates GluA2 trafficking downstream of Par1. Additionally, we have generated a photoactivatable Par1c to understand the role of Par1c in GluA2 trafficking and synaptic plasticity.

Disclosures: R.A. Shear: None. **E. Kelly:** None. **R. Tang:** None. **M. Sun:** None. **I. Mietus:** None. **L. Runnels:** None. **P. Pan:** None. **H. Zhang:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.06/B43

Topic: B.05. Synaptic Plasticity

Title: Studying the effects of ketamine on neuronal activity and ERK signaling at single neuron resolution in cortical neuron cultures

Authors: *I. M. J. ANNALA[1], S. KOHTALA[2], T. P. RANTAMAKI[3];
[1]Div. of Pharmacol. and Pharmacotherapy, Fac. of Pharm., Univ. of Helsinki, Helsinki, Finland; [2]Univ. of Helsinki, Helsinki, ; [3]Div. of Pharmacol. and Pharmacotherapy, Fac. of Pharm., Univ. Helsinki, Helsinki, Finland

Abstract: Ketamine has antidepressant effects at subanesthetic doses. These doses are associated with paradoxical increase in the activity of glutamatergic neurons in the cortex, which has been explained by inhibition of N-methyl-D-aspartate receptors (NMDARs) in GABAergic interneurons. At the molecular level, preclinical studies have suggested the activation of synaptic plasticity-related signaling pathways such as TrkB (tropomyosin receptor kinase B) and ERK1/2 (extracellular signal-regulated kinase 1 and 2) as key components in ketamine's antidepressant mechanism. However, a cohesive understanding of its actions across mechanistic levels and dose ranges remains incomplete. Here we aimed to bridge the electrophysiological and molecular-level responses to ketamine at individual neuron resolution in mouse cortical neuron cultures. Specifically, we have set up an experimental pipeline to study concentration-dependent effects of ketamine on neuronal activity using imaging with genetically encoded indicators combined with RNA-fluorescence in situ hybridization (FISH) and immunocytochemical stainings from the same cultures. By correlating the electrophysiological response of each neuron to its p-TrkB/p-ERK/*c-fos* expression as well as to its baseline activity and neuronal subtype, we can now elucidate the interplay between these modalities upon ketamine exposure. Markedly, we

demonstrate how the selection of media (Neurobasal media versus physiologically more relevant culture media) affects the experimental setting and outcomes. Next, we will use our setup to explore the interplay between ketamine and neuronal networks, which we believe will advance understanding of ketamine's mechanism of action and potentially reveal novel approaches to antidepressant development.

Disclosures: I.M.J. Annala: None. **S. Kohtala:** None. **T.P. Rantamaki:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.07/B44

Topic: B.05. Synaptic Plasticity

Title: Metabolic and Metabotropic Convergence: Lactate Enhances NMDA Receptor Function via Redox and CD38-PKC Signaling

Authors: *G. HERRERA-LÓPEZ[1], H. FIUMELLI[2], P. J. MAGISTRETTI[2];
[1]KAUST, Thuwal, Saudi Arabia; [2]BESE, King Abdullah Univ. of Sci. and Technol., Thuwal, Saudi Arabia

Abstract: Astrocyte-derived lactate is increasingly recognized as both a metabolic substrate and a signaling molecule capable of modulating plasticity, synaptic transmission and memory. Recently, we demonstrated that lactate enhances NMDA receptor (NMDAR) currents via a redox-sensitive mechanism that targets GluN2B-containing receptors. Here, we build on those findings by identifying a complementary signaling cascade that contributes to the potentiation of NMDAR by lactate in primary cortical neurons. Whole-cell patch-clamp recordings revealed that lactate enhanced NMDAR currents evoked by glutamate, but had a much smaller effect when NMDA was used as agonist instead of glutamate, implicating a role for other glutamate receptor subtypes. Pharmacological analysis identified group II mGluRs (mGluRII) as essential for the effect of lactate, and co-application of the selective mGluRII agonist DCG-IV and NMDA mimicked the glutamate-mediated potentiation of NMDAR responses in the presence of lactate. Downstream of mGluRII, we identified a Gi/o protein-dependent cascade involving α and βγ subunits, PI3K and protein kinase C (PKC). Inhibition of PKCα/β and PKCζ isoforms abolished lactate's effects. We further show that CD38, a NAD^+-dependent ADP-ribosyl cyclase known to promote Ca^{2+} release, is required for both PKC activation and NMDAR potentiation. Western blot analysis confirmed a lactate-mediated and CD38-dependent increased in PKC phosphorylation. Given that lactate shifts the NAD^+/NADH ratio, these findings reveal a dual mechanism: a metabolic shift that engages redox-sensitive sites on NMDARs, and a mGluRII-mediated one activating a Ca^{2+}/NAD^+-linked signaling cascade involving CD38 and PKC. Together, our results demonstrate that astrocyte-derived lactate enhances NMDAR function through the convergence of redox modulation and metabotropic signaling, providing mechanistic insights into how metabolic cues regulate synaptic plasticity.

Disclosures: G. Herrera-López: None. **H. Fiumelli:** None. **P.J. Magistretti:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.08/B45

Topic: B.05. Synaptic Plasticity

Title: Pkc participates in ltp-associated reductions of calcium-activated k^+channel activities of hippocampal synaptosomal membranes

Authors: *J. FARLEY;
Indiana Univ. Program in Neurosci., Bloomington, IN

Abstract: Hippocampal LTP is a widely-studied form of synaptic plasticity that may mediate some forms of memory. Because potassium ion (K^+) channels in presynaptic terminals regulate neurotransmitter release at many synapses and are targets for modulation by many second-messenger and other signaling molecules, I examined the possibility that their activities changed and might contribute to LTP. K^+ channels were incorporated from adult rat brain hippocampal synaptosomal membranes into planar lipid bilayers on the tips of patch-clamp electrodes. As in previous work using cortical synaptosomes (Farley & Rudy, 1991, *Biophys. J.*) several large-conductance (> 50 pS) voltage- and calcium-dependent K^+ channel types (I-III) were routinely observed in synaptosomal membranes prepared from hippocampi of unstimulated (sham-operated) and low-frequency stimulation (LFS) controls. In contrast, little channel activity was observed in membranes from animals ~1 hr following *in vivo* widespread induction of LTP at perforant path - dentate gyrus (pp-dg) synapses. To maximize the hippocampal regions affected by LTP-stimulation, stimulating electrodes were positioned at the “bottleneck of Lomo" (Lomo, 1971, *Exp Brain Res*). High-frequency stimulation (HFS) involved 8 trains, spaced 30 sec apart. Each train consisted of eight 0.4 msec pulses at 400 Hz. LFS entailed 8 trains of 8 pulses at 0.1 Hz. Test stimuli used to activate pp-dg synapses were constant voltage, 0.1 msec monophasic pulses, delivered at 0.1 Hz continuously, except during HFS periods. Synaptic strength within pp-stimulated pathways was monitored by measurement of field potentials of dg granule cells. Robust LTP was observed in 6 different animals from which synaptosomal membranes were subsequently prepared. LTP (measured as a % increase of baseline spike population amplitude 5 min following HFS) ranged from 178 - 287%. Potentiation was not observed in any of the six LFS control animals. K^+ channel activity of LTP-stimulated synaptosomes was increased by: alkaline phosphatase, the non-specific S/T kinase-inhibitor, H-7, as well as by a polyclonal antibody (goat anti-rat; Huang & Huang, 1986, *J Biol Chem*) that neutralizes PKC activity. Additionally, for membranes from sham-controls, bath addition of 1-2 units of heterogenous PKC (purified from rat brain) decreased K^+ channel activities (in the presence of co-factors required for PKC activation (10^{-4} M Ca^{2+}, low mM Mg/ATP, uM diolein). The results suggest that a PKC-phosphorylation-mediated reduction in Ca^{2+}-activated K^+ channel activities in

presynaptic terminals may contribute to (intermediate term) maintained expression of LTP at excitatory pp-dg synapses.

Disclosures: J. Farley: None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.09/B46

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

Support: GR1055502

Title: Disruption of the SYNGAP1 PDZ ligand motif accelerates maturation of human iPSC-derived GABAergic neurons

Authors: *Y. FENG[1], V. CLEMENTEL[2], I. FLORES[3], M. P. COBA[4];
[1]Univ. of Southern California Zilkha Neurogenetic Inst., Los Angeles, CA; [2]Zilkha Neurogenetic Inst. USC, Los Angeles, CA; [3]Neurosci., [4]USC, Los Angeles, CA

Abstract: SYNGAP1 haploinsufficiency is a leading genetic cause of neurodevelopmental disorders (NDD), including intellectual disability and epileptic encephalopathy. While most studies on SYNGAP1 function have focused on glutamatergic neurons, its role in GABAergic neurons and during early neuronal development is unclear. Using human iPSC-derived GABAergic neurons, we demonstrate that SYNGAP1 haploinsufficiency accelerates neuronal maturation, characterized by increased dendritic length, synaptic density, and maturation of synaptic structures. Disruption of the isoform-specific SYNGAP1 PDZ binding motif reproduces these phenotypes, highlighting the critical role of PDZ-mediated interactions in regulating GABAergic neuronal maturation. Proteomic and phosphoproteomic analyses reveal significant dysregulation of synaptic proteins, RNA processing, and transcriptional control, with a significant increase in postsynaptic density proteins content. Co-culture studies with glutamatergic neurons show that SYNGAP1 mutations dysregulate network activity by increased inhibitory GABAergic tone. These findings establish that SYNGAP1 acts as a key regulator of neuronal maturation across both excitatory and inhibitory neurons. Our work underscores the importance of the SYNGAP1 PDZ ligand motif for normal neuronal development and suggests translational strategies targeting SYNGAP1 alpha1 isoform levels to mitigate SYNGAP1-related NDD.

Disclosures: Y. Feng: None. **V. Clementel:** None. **I. Flores:** None. **M.P. Coba:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.10/B47

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

Support: GR1069090

Title: The SYNGAP1 family of RASGAP proteins and the emergence of the PDZ protein interaction function

Authors: V. CLEMENTEL[1], Y. FENG[2], I. FLORES[3], G. RUMBAUGH[5], *M. P. COBA[4]; [1]Zilkha Neurogenetic Inst., Los Angeles, CA; [2]Univ. of Southern California Zilkha Neurogenetic Inst., Los Angeles, CA; [3]Neurosci., [4]Psychiatry and Neurosci., USC, Los Angeles, CA; [5]Scripps Florida, Jupiter, FL

Abstract: SYNGAP1 belongs to the RASGAP family of proteins, however the relationship between other family members, paralogues and their common ancestor, have not been well characterized. In particular, the set of molecular characteristics they share and how their differences might impact signaling networks associated to neurodevelopmental disease remain unclear. Here, we show that SYNGAP1 belongs to a family of RASGAP proteins, along with DAB2IP and RASAL2, which share a common ancestor in Placozoa. These proteins share the domain architecture of PH, C2, RASGAP, and DUF3498. Towards the C-terminal region and within the DUF3498 domain, SYNGAP1 has a coil-coil region with the capacity to form SYNGAP1 trimers. SYNGAP1 family members DAB2IP and RASAL2 and their common ancestor also share homology in their coil-coil region. Suggesting that the capacity to form this RASGAP trimers have been conserved as an essential feature of the family.

Disclosures: V. Clementel: None. **Y. Feng:** None. **I. Flores:** None. **G. Rumbaugh:** None. **M.P. Coba:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.11/B48

Topic: B.05. Synaptic Plasticity

Support: NIH Grant AG056622
NIH Grant AG055581

Title: Activation of neuronal AMPK impairs cognitive function and long-term synaptic plasticity in mice

Authors: *T. LI[1], Q. SU[2], T. MA[3];
[1]Wake Forest Univ., Winston Salem, NC; [2]Wake Forest Univ. Sch. of Med., Winston Salem, NC; [3]Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston Salem, NC

Abstract: AMP-activated protein kinase (AMPK) is the key sensor in cell to regulate energy homeostasis. It is composed of catalytic unit α (α1 and α2), scaffolding unit β (β1, and β2), and regulatory unit γ (γ1, γ2, and γ3). Emerging evidence has linked AMPK dysregulation to diverse neurological diseases characterized by cognitive impairments. However, the effects of neuronal AMPK activation on cognitive and synaptic function remain unknown. The γ1 subunit is mainly expressed in neurons and plays an important role in AMPK regulation in response to cellular energy levels. The D316A mutation in γ1 subunit has been identified to lead to a gain of function in AMPK activity. Here, we generated heterozygous (AMPKγ1^{het}) and homozygous (AMPKγ1^{homo}) excitatory neuronal AMPKγ1D316A mutation mice to investigate the effects of neuron-specific activation of AMPK in mice on cognition and synaptic plasticity. Multiple behavioral tests were used to test the cognitive behavior of mice. Hippocampal synaptic plasticity was measured by in vitro electrophysiological technique. Moreover, hippocampal de novo protein synthesis was assessed by the surface sensing of translation (SUnSET) assay, and the AMPK-related signaling were measured via Western blot. In behavioral tests, we found that both AMPKγ1^{het} and AMPKγ1^{homo} mice showed recognition memory impairment in novel object recognition test, working memory deficit in Y-maze test, and impaired long-term spatial learning and reference memory ability in Morris water maze test. Furthermore, hippocampal late-phase long-term potentiation (L-LTP) was impaired in AMPKγ1^{het} and AMPKγ1^{homo} mice. Moreover, overall hippocampal de novo protein synthesis was significantly decreased in the AMPKγ1^{het} and AMPKγ1^{homo} mice. Together these results suggest that neuron-specific AMPK activation could result in impaired translational capacity and impairments of cognitive function and long-term synaptic plasticity.

Disclosures: T. Li: None. **Q. Su:** None. **T. Ma:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.12/B49

Topic: B.05. Synaptic Plasticity

Support: NIH Grant AG082388

Title: Inhibition of glucose transporter receptors impairs cognitive function and hippocampal synaptic plasticity in mice

Authors: *Q. SU[1], T. LI[2], T. MA[2];
[1]Dept. of Intrnl. Medicine, Gerontology and Geriatric Med., Wake Forest Univ. Sch. of Med.,

Winston Salem, NC; [2]Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Disturbance of brain glucose metabolism is linked to cognitive impairment, as well as a pathological hallmark of Alzheimer's disease (AD). The molecular mechanisms underlying impaired brain glucose metabolism and cognitive deficit remain unclear. In this study, we reported that intranasal administration of mice with KL-11743 (1.2 mg/mL, 10 μL per day, 14 days), an inhibitor of glucose transport receptors (GLUTs), resulted in glucose metabolism disorders in neurons, inhibition of hippocampal long-term potentiation (LTP), and learning and memory deficits. Furthermore, KL-11743 treatment induced activation of AMP-activated protein kinase (AMPK), autophagy upregulation, andreduced postsynaptic density 95 (PSD95) in hippocampus. These findings suggest that GLUTs inhibition of KL-1174 could induce cognitive deficits and synaptic plasticity impairments in mice. It indicates the potential of targeting GLUTs to ameliorate neurocognintive dysfunction induced by GLUTs deficiency and glucose metabolism dysregulation in the brain.

Disclosures: Q. Su: None. **T. Li:** None. **T. Ma:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.13/B50

Topic: B.05. Synaptic Plasticity

Support: DFG grant Kr1321/9-1

Title: Variants in the LRRC7 gene lead to intellectual disability, autism, obesity and aggressive behaviour

Authors: J. WILLIM[1], ***H.-J. KREIENKAMP**[2];
[1]Huamn Genet., Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [2]UKE Hamburg, Hamburg, Germany

Abstract: Densin-180, encoded by the *LRRC7* gene, is a postsynaptic scaffold protein at glutamatergic synapses, linking cytoskeletal elements with signalling proteins such as the α-subunit of Ca^{2+}/calmodulin-dependent protein kinase II (αCaMKII). Densin-180 deficient mice have been reported to exhibit a wide variety of abnormal behaviors, including anxiety, aggression and autism, as well as impaired short term memory. We have identified a larger cohort of human patients carrying heterozygous variants in the *LRRC7* gene. The clinical spectrum involves intellectual disability, autism, ADHD, aggression and, in several cases, hyperphagia-associated obesity. Most patients carry loss-of-function (e.g. frameshift, splice site or nonsense) variants, which occurred mostly *de novo* but were in some cases also inherited from apparently healthy parents. Furthermore, we identified missense variants altering the N-terminal leucine rich repeats (LRRs) or the C-terminal PDZ domain. Four of the missense variants in

conserved positions of the LRRs disrupt binding to newly identified interaction partners, which include protein phosphatase 1 (PP1α). Thus, these variants interfere with the capacity of Densin-180 to act as a scaffold for phosphatase/kinase signalling pathways. Furthermore, a variant in the C-terminal PDZ domain of Densin-180 interferes with binding to δ-catenin and with synaptic targeting of Densin-180 in primary cultured neurons. We conclude that *LRRC7* encodes a major determinant of intellectual development and behaviour; the aggression phenotype observed in patients validates Densin-180/Lrrc7 deficient mice as a model for aggression in humans; in addition, hyperphagia observed in some patients points to a role of LRRC7 in appetite control.

Disclosures: J. Willim: None. **H. Kreienkamp:** None.

Poster

PSTR429: Long-Term Synaptic Plasticity: Intracellular Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR429.14/B51

Topic: B.05. Synaptic Plasticity

Support: NIH T32 MH016880
NIH R01 NS086933
ABNexus Pilot Support Funding Program

Title: Akt1 plays a sex-specific role in endocannabinoid signaling, plasticity, and behavior

Authors: *M. GRIFFIOEN[1], C. BORSKI[1], S. ZOU[1], J. K. KUSHNER[1], C. HOEFFER, Jr.[2]; [1]Inst. for Behavioral Genet., Univ. of Colorado Boulder, Boulder, CO; [2]Integrated Physiol., Univ. of Colorado Boulder, Lousiville, CO

Abstract: AKT is a central protein kinase essential for various neuronal processes. AKT is present in most cell types in the brain, with three structurally similar isoforms (AKT1, AKT2, AKT3) encoded by different genes. Of these, AKT1 and AKT3 are expressed in excitatory neurons, with only AKT1 expressed in interneurons. Importantly, these isoforms have isoform- and cell-specific roles in synaptic plasticity, as well as sex-dependent effects on behavior. Because AKT function plays a role in memory formation and anxiety expression, AKT is implicated in many neurological disorders, such as Alzheimer's disease (AD), autism spectrum disorder (ASD), generalized anxiety disorder (GAD), and schizophrenia. Interneuronal dysfunction has been proposed to contribute to the pathophysiology of neuropsychiatric disorders. The removal of *Akt1* alters anxiety-like behavior, extinction learning, and the extinction of long-term memory (LTM), as well as the renewal of extinguished memory, making it crucial to elucidate AKT1's function in interneuronal regulation. Using genetic mouse models that selectively remove AKT1 from interneurons, our studies revealed AKT1 interneuron-specific and sex-dependent effects on anxiety-like behaviors. Because endocannabinoid (eCB) signaling is known to modulate IN activity and affect behavior and fear extinction, we investigated eCB signaling in the context of AKT1 function. We found that cannabinoid receptor

(CR) activation promoted AKT1 activation, *Akt1* deficiency altered CR-dependent signaling, and long-term depression (LTD) in a sex-specific manner. To investigate the mechanisms by which AKT1 mediates these effects, we employed a transcriptomic and protein synthesis measurement approach. Pathways related to endocannabinoid signaling and GABAergic function, as well as sex differences between knockouts, revealed potential targets that AKT1 may use to regulate these functions. Using these genetic mouse models to interrogate the role of interneuronal AKT1 in neurological disorders, we will identify new therapeutic targets for treating and diagnosing diseases such as schizophrenia and AD. These data will also contribute valuable information about AKT1 function in the context of biological sex, a variable that plays a significant role in the manifestation of mental health disorders.

Disclosures: M. Griffioen: None. **C. Borski:** None. **S. zou:** None. **J.K. Kushner:** None. **C. Hoeffer:** None.

Poster

PSTR430: Oscillations and Synchrony: Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR430.01/B52

Topic: B.07. Network Interactions

Support: Vetenskapsrådet 2021-01769
Vetenskapsrådet 2018-02717
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Magnus Bergvall Foundation
Olle Engkvist Foundation

Title: Differential effects of psychedelic and non-psychedelic 5-HT2AR agonists on high-frequency oscillations in cortical and subcortical structures

Authors: S. A. BARRIENTOS[1], R. J. ALVAREZ[1], P. PETERSSON[2,1], ***P. HALJE**[1];
[1]Med. faculty, Lund Univ., Lund, Sweden; [2]Exp.Med. Sci., Umeå Univ., Umeå, Sweden

Abstract: Serotonergic psychedelics exert their acute effects mainly through agonism on serotonin 2A receptors (5-HT2AR). However, some 5-HT2AR agonists, such as lisuride, do not produce psychedelic effects. While several mechanistic differences between psychedelic and non-psychedelic 5-HT2AR agonists have been identified - such as imbalanced activation of 5-HT1A vs. 5-HT2A receptors, biased signaling downstream of the 5-HT2A receptor, and selective activation of intracellular 5-HT2Ars - it remains unclear how these differences relate to the perceptual and cognitive alterations characteristic of the psychedelic state.To identify neuronal activity patterns specific to the psychedelic state, we compared the effects of the non-psychedelic 5-HT2AR agonist lisuride to those of two classic serotonergic psychedelics (LSD

and DOI) as well as the psychostimulant amphetamine. We recorded local field potentials from multiple cortical and subcortical regions - including the orbitofrontal cortex, prefrontal cortex, olfactory cortex, ventral striatum and septum - using 128-channel microelectrode arrays in freely moving rats.Consistent with prior findings, both LSD and DOI markedly increased the prevalence (detection rate) and amplitude of high-frequency oscillations (HFOs) across the cognitive-limbic cortex-basal ganglia network. In contrast, lisuride produced a more modest enhancement of HFO amplitude in select regions and did not significantly alter their prevalence in any structure. Notably, lisuride induced a pronounced shift in HFO frequency, reducing it from 139 ± 9 Hz at baseline to 103 ± 15 Hz at peak effect. A similar down-tuning of HFO frequency has been observed with the antipsychotic clozapine, suggesting a link between HFO frequency and hallucinations.

Disclosures: S.A. Barrientos: None. **R.J. Alvarez:** None. **P. Petersson:** None. **P. Halje:** None.

Poster

PSTR430: Oscillations and Synchrony: Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR430.02/B53

Topic: B.07. Network Interactions

Title: Spatiotemporal mechanisms governing oscillation generation and interaction during absence seizures

Authors: *B. BUCKLEY[1], E. DULKO[2], S. KILIANSKI[3], M. P. BEENHAKKER[3];
[2]Pharmacol., [1]Univ. of Virginia, Charlottesville, VA; [3]Univ. of Virginia, Charlottesville, VA.

Abstract: Understanding how the brain generates electrical signals is of fundamental importance. Neural oscillations have gained considerable attention for their role in coordinating neuronal activity and, ultimately, behavioral outputs, including movement, higher order thinking, and sleep. Oscillation abnormalities have also been observed in pathological conditions, including Alzheimer's Disease (AD), Parkinson's Disease (PD), and epilepsy. Despite the long-standing consensus that neural oscillations reflect coordinated neuronal activity that drives functional output, our understanding regarding how oscillations spontaneously and rapidly arise remains poorly understood.
Here, we leverage the C3H/HeJ mouse model of absence epilepsy to understand how the brain generates widespread neural oscillations. Absence epilepsy is associated with global ~3 Hz neural oscillations that are driven by thalamocortical circuits. Our lab has recently established that several thalamic nuclei—and, surprisingly, the CA3 region of the hippocampus—are engaged during these oscillations. Given the established hippocampal role in the generation of several neural oscillations, we aim to resolve how the hippocampus contributes to the generation of global, seizure-related oscillations.
Notably, neural oscillations that support a specific function may either suppress or facilitate the generation of oscillations underlying other functions. Our preliminary data indicate that

hippocampal sharp wave ripples decrease the production of absence seizures. To better resolve this interaction, we are recording the activity of single neurons with Neuropixel recording electrodes chronically implanted in the C3H/HeJ mouse. By simultaneously recording the activity of single neurons in the hippocampus, cortex, and thalamus—structures implicated in the generation of sharp wave ripples and seizures—we aim to understand the interaction between distinct oscillatory circuits.

Disclosures: B. Buckley: None. **E. Dulko:** None. **S. Kilianski:** None. **M.P. Beenhakker:** None.

Poster

PSTR430: Oscillations and Synchrony: Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR430.03/B54

Topic: B.07. Network Interactions

Support: NIH Grant 5R01NS126594
UVA Wagner Fellowship

Title: Circuit degeneracy in absence epilepsy

Authors: *E. DULKO[1], S. KILIANSKI[2], A. CARNS[1], I. LESMANA[3], A. RAJESH[1], M. PIKUS[1], M. P. BEENHAKKER[2];
[2]Pharmacol., [1]Univ. of Virginia, Charlottesville, VA; [3]Univ. of California, Los Angeles Interdepartmental Ph.D. Program In Neurosci., Los Angeles, CA

Abstract: Background: Absence epilepsy (AE) is the most common pediatric epilepsy of idiopathic origin. Currently available anti-seizure medications reduce seizure occurrence but are associated with unacceptable freedom from treatment failure rates (~50%) due to intolerable side effects. The spike-wave discharge (SWD) is the electrographic hallmark of AE. Understanding the neuronal mechanisms of SWD generation is a necessary step for developing better, targeted treatments. The polygenic nature—and yet stereotypical presentation—of SWDs suggests that many diverse mechanisms drive SWDs. If true, then this possibility indicates that SWDs are produced by degenerate circuit mechanisms. We aim to resolve this possibility. **Methods:** 27 C3H/HeJ ("Gria4") and 21 Stargazer ("STG") mice, two common models of spontaneous SWDs, were used in this study. Using simultaneous single-unit and electrocorticographic (ECoG) recordings in awake head-fixed mice, we examined firing patterns of ~2,000 individual neurons across 20 brain structures including somatosensory cortex, most thalamic nuclei, and the hippocampus. **Results:** We found that STG mice had more frequent and prolonged SWDs, relative to those observed in Gria4 mice. However, the cycle period of STG and Gria4 SWDs was indistinguishable, suggesting that similar SWD networks are engaged in the two mouse models. Cross-correlation analyses revealed that three medial thalamic nuclei serve as possible synchrony hubs, as these presented with the highest increase in synchrony measures during seizures in both mouse models. By contrast, other brain structures were either not firing

synchronously or their synchrony increase varied between STG and Gria4 mice. Importantly, hippocampal recruitment during SWDs was observed exclusively in Gria4 mice. Analysis of neuronal firing rates revealed heterogeneous, and in some cases opposing, seizure-related activity changes. For instance, neuronal firing in the lateral posterior nucleus of the thalamus increased during Gria4 seizures but decreased during STG seizures. Collectively, these findings suggest that SWDs can emerge from distinct, possibly degenerate, circuit mechanisms, and underscore the importance of genetic background when resolving ictogenic mechanisms.

Disclosures: E. Dulko: None. **S. Kilianski:** None. **A. Carns:** None. **I. Lesmana:** None. **A. Rajesh:** None. **M. Pikus:** None. **M.P. Beenhakker:** None.

Poster

PSTR430: Oscillations and Synchrony: Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR430.04/B55

Topic: B.07. Network Interactions

Support: Raynor Cerebellum Project

Title: Synchronous Bursting in the Basal Ganglia-Thalamic Circuit: Evidence of Seizure-Like Dynamics in Human Dystonia

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Abstract: Synchronous activity has long been associated with epileptic seizures, yet its presence and functional role in movement disorders like dystonia remain underexplored. In this study, we investigated whether seizure-like population dynamics exist within the thalamo-basal ganglia loop in humans with dystonia. We recorded local field potentials and multi-unit spiking activity from over ten pediatric patients diagnosed with dystonia who were undergoing deep brain stimulation (DBS) procedure. Each patient was implanted with up to ten temporary stereoelectroencephalography (sEEG) electrodes targeting the Globus pallidus internus (GPi) and subthalamic nucleus (STN) of the basal ganglia, ventral oralis anterior-posterior (VoaVop), ventral intermediate (VIM), centromedian (CM), and centrolateral (CL) nuclei of the thalamus, and pedunculopontine nucleus (PPN). Analysis of the spike trains revealed robust episodes of synchronous bursting that co-occurred across multiple nodes of the network. These bursting events are not restricted to individual regions but instead involve temporally aligned activity across multiple brain regions. This suggests a form of hypersynchronous network behavior that may be overlooked when evaluating nodes in isolation. These findings support a model in which dystonia involves hypersynchronous neuronal activity akin to epileptic seizure dynamics, challenging traditional views that emphasize only firing rate or pattern abnormalities. To further

characterize this synchronous activity, we present results that examine inter-regional burst propagation patterns and the spectral features of these bursts using connectivity analyses. Together, these results provide compelling evidence that dystonia may be fundamentally a disorder of pathological neural synchronization within the motor network.

Disclosures: A. Seyyed Mousavi: None. **S. Javadzadeh No:** None. **T. Chang:** None. **T.D. Sanger:** None.

Poster

PSTR430: Oscillations and Synchrony: Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR430.05/B56

Topic: B.07. Network Interactions

Support: 1R61NS125568-01A1

Title: Network Characteristics and Responsive Neurostimulation (RNS) Treatment Response in Epilepsy

Authors: *K. C. NIX[1], N. SINHA[2], E. CONRAD[3];
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Abstract: Background: Epilepsy is increasingly understood as a disorder of brain network organization. Patients often exhibit abnormal connectivity patterns, including atypical distribution of highly connected regions known as network hubs. Responsive Neurostimulation (RNS) is a neuromodulatory treatment option for individuals with drug-resistant epilepsy who are not candidates for resective surgery. Although approximately 70% of patients experience clinical improvement with RNS, treatment response varies considerably, and predictors of outcome remain limited. One possible factor is hubness, a network measure reflecting nodes that are highly connected to other central nodes. While prior work has demonstrated differences in hub organization between epilepsy patients and healthy controls, its role in predicting neuromodulation outcomes is unclear.
Objective:To investigate whether interictal network hub properties are associated with clinical response to RNS therapy.
Methods: We retrospectively studied 95 patients with drug-resistant epilepsy who underwent intracranial EEG (iEEG), RNS implantation (NeuroPace), and at least two years of clinical follow-up across three centers (HUP, UCSF, NYU). Functional brain networks were constructed from interictal coherence, and nodal metrics of hubness—eigenvector centrality and node strength—were computed across canonical frequency bands. Seizure onset and spread regions were annotated using a semi-automated detection pipeline. For each patient, we examined the distance between top hub nodes and seizure-related electrodes and compared distributions between responders and nonresponders using Mann-Whitney U-tests.

Results: Analysis is ongoing. Preliminary observations suggest that spatial relationships between interictal hubs and seizure-involved regions may differ by treatment response. We hypothesize that closer proximity between RNS leads and interictal hubs is associated with improved clinical outcomes.
Conclusion: Network metrics derived from interictal iEEG may offer insight into variability in RNS response. This work could support improved patient selection and targeting strategies in neuromodulation for epilepsy.

Disclosures: K.C. Nix: None. **N. Sinha:** None. **E. Conrad:** None.

Poster

PSTR430: Oscillations and Synchrony: Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR430.06/B57

Topic: B.07. Network Interactions

Support: NRF Grant RS-2022-NR070151
NRF Grant RS-2024-00402116
MOTIE Grant RS-2024-00419358
MOHW Grant HI23C0156

Title: The effects of transcutaneous auricular vagus nerve stimulation (taVNS) at different stimulation sites on fronto-central EEG and cardiac parameters

Authors: S. LEE[1], Y. NAM[1], J. SUNG[2], *S. JUN[1,3];
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Abstract: Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive technique that targets the vagus nerve through specific areas of the outer ear. Compared to invasive vagus nerve stimulation (VNS), taVNS offers a higher safety profile and fewer side effects, making it well-suited for both clinical and research applications. VNS has been applied to treat drug-resistant epilepsy, depression, chronic pain, migraines, obesity, and to enhance cognitive function. In our previous study, we observed that VNS reduced absolute theta power and increase absolute alpha power in fronto-central electroencephalogram (EEG), suggesting neuromodulatory effects. This aligns with the findings in cognitive impairment, where EEG features reflect disease severity. For example, Alzheimer's disease (AD) patients show elevated theta power compared to those with mild cognitive impairment (MCI), and higher alpha1 and beta power in fronto-central regions are associated with better Mini-Mental State Examination (MMSE) scores. Some studies also report VNS-related reductions in heart rate and oxygen saturation, indicating potential autonomic modulation. Despite the growing interest in taVNS, various studies have targeted different stimulation sites within the outer ear to activate the auricular branch of the vagus nerve. To address this variability, the present study investigated the

site-specific effects of taVNS at different auricular locations—left and right cymba concha, tragus, and earlobe—to determine whether the stimulation site influences EEG and cardiac responses, and ultimately, to identify the most effective site for modulating brain and autonomic activity. Healthy, right-handed female participants received taVNS at each site over a six-week period, with sessions conducted at the same day and time each week. Resting-state EEG and pulse oximetry were recorded immediately before and after 10 minutes of stimulation at each site, using a non-randomized, within-subject design. EEG signals were analyzed for absolute power in the delta, theta, alpha1, alpha2, and beta frequency bands across fronto-central channels (F3, F4, Fz, FC1, FC2, Cz). Heart rate and peripheral oxygen saturation (SpO_2) were assessed using pulse oximetry. Stimulation at the cymba concha appears to elicit relatively stronger effects compared to other auricular sites.

Disclosures: S. Lee: None. **Y. Nam:** None. **J. Sung:** None. **S. Jun:** None.

Poster

PSTR430: Oscillations and Synchrony: Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR430.07/B58

Topic: B.07. Network Interactions

Title: Temporal Dynamics of Thalamo-Cortical Beta-Gamma Phase-Amplitude Coupling During Rest

Authors: *C. E. LEE[1,2], E. OPRI[1,3];
[1]Biomed. Engin., [2]Mathematics, [3]Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: The coupling of neural oscillations across brain regions is crucial for communication. Low frequency oscillations (LFO) are believed to facilitate cognitive functions like visual and motor tasks, attention, and sleep, and may originate within subcortical regions such as the thalamus (ventral intermediate nucleus, VIM). Meanwhile, high broadband activity (HBA) in cortical potentials reflects local processing, which has been shown in motor control within the primary motor cortex (M1). Previous work from our group (Opri *et al*., 2019) has proposed how *beta-gamma* phase-amplitude coupling (PAC) is the manifestation of a gating mechanism within the thalamo-cortical loop. Here, we hypothesized that the PAC during rest is not composed of a single entrainment state, but instead it is also representing state-specific temporal changes between VIM-M1 regions during rest inspired by Zhang *et al*. (2019). We leveraged a previously published dataset from our group (Opri *et al.,* 2019). Intraoperative local field potentials (LFP) from VIM and electrocorticography (ECoG) from M1 were recorded from 9 essential tremor (ET) patients (4 males and 5 females) at the University of Florida, while patients were at rest. After preprocessing, coupling measures were computed with a variation of Tort method (2010). Short-time palettes (mean amplitude distributions) were calculated at the frequency which coupling is the highest. To quantify similarities across patients, palettes were multi-step normalized. After dimension reduction with UMAP 3D, they were clustered using consensus *k*-

means clustering. Based on elbow method, three clusters/states were identified. Each mean palette per cluster exhibited different patterns, with different preferred frequency for amplitude at 198Hz, 114Hz, and 54Hz for cluster 1, 2, and 3, respectively. Each pattern had a distinct maximum modulation index (MI) at 0.0102, 0.0259, and 0.0371 for cluster 1, 2, and 3, respectively. To understand the structure of temporal dynamics, compounded Markov chain was calculated across patients. The compounded Markov chain suggests evenly distributed transition probabilities between three distinct states. This will improve our understanding of thalamo-cortical loop interactions, and how we can tailor neuromodulation therapies to optimize state-specific behaviors. **Citations**: 1. Opri, E., Cernera, S., Okun, M. S., Foote, K. D., & Gunduz, A. (2019). The Functional Role of Thalamocortical Coupling in the Human Motor Network. *Journal of Neuroscience*, 39(41), 8124-8134.; 2. Zhang, L., Lee, J., Rozell, C., & Singer, A. C. (2019). Sub-Second Dynamics of Theta-Gamma Coupling in Hippocampal CA1. *eLife*, 8, e44320.

Disclosures: C.E. Lee: None. **E. Opri:** None.

Poster

PSTR430: Oscillations and Synchrony: Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR430.08/B59

Topic: B.07. Network Interactions

Title: A Comparison of Methods to Localize Local Field Potential Features From Deep Brain Stimulation Recordings

Authors: *F. MAPAR[1,2], M. BEAUZILE[3], F. CHINEA[1], T. HERRINGTON[1,2];
[1]Neurol., Massachusetts Gen. Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Sensing-enabled deep brain stimulation (DBS) systems allow chronic recording of intracranial local field potentials (LFP). Beta band (13-30 Hz) power in subthalamic nucleus (STN) LFPs correlates with Parkinsonian motor symptom severity and may help select effective stimulation sites. Current commercial DBS systems record bipolar signals (potential difference between two electrode contacts on the same electrode) to reduce volume conduction and stimulation artifacts, limiting precise localization of LFP features. Several methods have been proposed to identify the electrode contact with the largest local beta amplitude, presumed closest to the beta "source." These include assuming that beta power will be largest for contacts spanning the beta power source ("sandwich"), ranking contacts by modeling signal attenuation with distance (DETEC), and using the contralateral DBS electrode as a common reference (Medtronic Electrode Identifier). We also assessed the performance of beta LFP phase reversal between adjacent bipolar montages, an approach commonly utilized to localize spectral features on scalp EEG. In this approach, a reversal of the instantaneous phase (calculated by Hilbert transformation) between consecutive bipolar pairs of contacts signifies that the shared contact is

the source. We analyzed ambulatory Medtronic Percept LFP recordings from 40 DBS electrodes (hemispheres) from 29 patients with Parkinson's to compare these methods. Electrode Identifier (contralateral referencing) was available for 13 of these hemispheres. The beta source electrode contact identified by Electrode Identifier agreed with the phase reversal method in 92% ($p=0.004$, permutation test), sandwich method in 7% ($p=0.997$), and DETEC method in 38% ($p=0.257$). Notably, phase reversal and sandwich methods were discordant in 92% of cases. Beta source contacts within STN were more consistently mapped to the dorsolateral STN for the phase reversal method, especially for the more anterior portion of sensorimotor STN. Sandwich and DETEC methods identified more ventromedial STN contacts with less spatial specificity. In summary, investigators and clinicians should be cautious in interpreting the location of beta power from the amplitude of bipolar referenced recordings. When only bipolar data are available, phase reversal is the most reliable method for identifying the beta source.

Disclosures: F. Mapar: None. **M. Beauzile:** None. **F. Chinea:** None. **T. Herrington:** None.

Poster

PSTR430: Oscillations and Synchrony: Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR430.09/B60

Topic: B.07. Network Interactions

Support: NIH K12 00153370

Title: Premotor Cortico-Subcortical Synchrony During Speech Perception and Production

Authors: *D. A. PEREZ[1], T. DAVIS[2], A. D. DORVAL[1], S. RAHIMPOUR[2];
[1]Biomed. Engin., [2]Neurosurg., Univ. of Utah, Salt Lake City, UT

Abstract: Speech perception and production rely on the dynamic coordination of information across premotor, motor, and sensory cortices, including cortico-subcortical networks. Prior studies have established the involvement of these regions in articulatory and acoustic processing, but the precise temporal and spatial mechanisms by which speech sounds are encoded across cortical-basal ganglia and thalamic networks during speech perception and production remain poorly understood. In this study, we recorded from high-density electrocorticography and deep brain stimulation (DBS) electrodes during a triplet syllable repetition task performed by four patients undergoing awake DBS implantation. Patients heard and repeated consonant-vowel (CV) syllable triplets while cortico-subcortical neural activity was sampled at 1 kHz. Power was extracted using Morlet Wavelet Transformation in 200-ms windows centered on the transition zone of each syllable. A generalized linear model (GLM) was used to model power as a function of phonological features or syllable position. By repeatedly fitting the GLM to shuffled data for permutation testing, we identified electrodes and power bands with statistically significant encoding. From significant contacts, we can narrow down our contact pairs to inspect the phase locking value (PLV) across regions during speech perception and production as a measure of

synchronization. In the premotor cortex (Brodmann area 6), we observed significant spatiotemporal encoding of perception onset and production offset across frequency bands. In the subthalamic nucleus (STN), increased beta band power was positively associated with perception onset and production offset and negatively associated with perception offset and production onset. Based on GLM premotor and STN contacts, we were able to see significant increases in PLV in the beta band at perception onset and production offset. Given previous studies on encoding start and stop of speech perception and production, this study adds support to the combined synchronization that occurs across the premotor cortex and STN, suggesting a coordinated gating of speech transitions. These results support a model in which cortico-subcortical networks encode the temporal structure of speech and may guide future decoding strategies focused on the timing of speech sounds.

Disclosures: D.A. Perez: None. **T. Davis:** None. **A.D. Dorval:** None. **S. Rahimpour:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.01/C1

Topic: B.08. Epilepsy

Title: Evaluation of anti-epileptic mechanisms in the entorhinal cortex (EC) ex vivo using different convulsant models and analysis methods

Authors: S. A. NEALE[1], E. C. O'CONNOR[2], ***T. E. SALT**[1];
[1]Neurexpert Limited, Newcastle Upon Tyne, United Kingdom; [2]Roche Pharma Res. and Early Development, Neurosci. and Rare Diseases, Roche Innovation Ctr. Basel, Basel, Switzerland

Abstract: Preclinical evaluation of potential anti-epileptic drugs remains an important toolset in the development of novel medications. We compared effects of several compounds (with known mechanisms of action) on different measures of epileptiform activity induced by either the $GABA_A$ antagonist gabazine, or the potassium channel blocker 4-aminopyridine (4-AP). Epileptiform activity was recorded from adult mouse EC brain slices using extracellular electrodes. Slices were maintained in an interface chamber at 32C and were preincubated for 75 minutes in test compounds including a WNK-kinase inhibitor (WNK463, 1 μM), a K_V7 channel enhancer (retigabine, 20 μM), a $GABA_A$ receptor positive allosteric modulator (diazepam, 50 μM), a $mGlu_{2/3}$ receptor agonist (LY354740, 3μM), or vehicle. Test compound incubation was maintained throughout a subsequent 60 minute application of either 4-AP (100 μM) or gabazine (10 μM). Recordings were evaluated at several timepoints during the 4-AP or gabazine application with a variety of analyses.
Latency to the first epileptiform event was not significantly changed by any of the test compound treatments. However, coastline analysis revealed that 4-AP-evoked activity was reduced by diazepam (by 67±8%) and retigabine (by 95±9%) at 15-60 minutes after 4-AP, whereas WNK463 and LY354740 had no effect. By contrast, only retigabine was effective against

gabazine-evoked activity (59±9% reduction). Similarly, counts of epileptiform events or high-frequency spiking revealed efficacy of diazepam and retigabine against 4-AP, but only retigabine reduced gabazine-evoked activity. Power spectrum analysis of activity in delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz), beta (13-30Hz), low gamma (30-48Hz) and high gamma (52-100Hz) bands showed that both 4-AP and gabazine were able to increase power in these ranges. However, only retigabine had significant effects on these actions, and only on 4-AP-induced power changes. Retigabine appeared to enhance delta band power (124±7% increase) but reduced other frequency bands' power (73±21% decrease).
Taken together, these results show that different analysis methods can reveal distinct facets of epileptiform activity and their modulation by anti-convulsant mechanisms. In particular, coastline analysis and power-spectrum analysis appear to reveal the most detail of a compound's action.

Disclosures: S.A. Neale: A. Employment/Salary (full or part-time): Neurexpert Limited. **E.C. O'Connor:** A. Employment/Salary (full or part-time): F. Hoffmann-La Roche Ltd. **T.E. Salt:** A. Employment/Salary (full or part-time): Neurexpert Limited.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.02/C2

Topic: B.08. Epilepsy

Title: Antiseizure effects of hydro-ethanolic extracts of artemisia afra, in an in vitro in an entorhinal cortex hippocampal slices of rat.

Authors: *T. E. KEDISO;
Physiol., Addis Ababa Univ., Addis Ababa (gpo), Ethiopia

Abstract: Epilepsy is a chronic neurological disorder that affects people of all ages. Many synthetic anti-epileptic drugs are available; however, their effectiveness is a significant challenge. Herbal medicines are widely used across the globe due to their broad applicability and therapeutic efficacy coupled with the least side effects, which has accelerated the scientific research regarding anti-epileptic activity. In Ethiopia, traditionally, the aqueous extract of the whole plant of Artemisia Afra is used for the treatment of epilepsy. The study aimed to investigate the anti-seizure effects of the 70% ethanol extract of A. afra in an in vitro animal model. A comparison of the mean latency to onset of the seizure-like event, delay, or increase in the mean latency between seizure-like events was made in an in vitro entorhinal cortex-hippocampal brain slice of Wistar Rat in a low magnesium model of epilepsy. Pharmacological experiments were performed with bath application of 70% ethanol A. afra crude extract (100µL), vehicle control (100µL), and control (1.2mL/m of mACSF). Data were presented as the mean ± standard error of the mean and analyzed using a one-way analysis of variance (ANOVA) and followed by post-hoc Tukey's multiple comparisons test. $P < 0.05$ was considered statistically

significant. A. afra crude extract showed significant delay or increase [46.300 ± 2.309 min $p<0.05$*;] in latency to the onset of the seizure-like event, delay or increase [2.438±0.139 min $p<0.05$*] in the mean latency between seizure-like event, against the low magnesium models of epilepsy compared to the control [35.231±0.795 min.; 1.671±0.0512 min.] and vehicle [39.444±0.886 min; 1.712±0.0473 min.]. Also, it showed a significant delay or increase [2.353±0.132* min. $p<0.05$*] in the mean latency between the seizure-like event of the same slices as compared to the control [1.638±0.0361sec] and washout [1.684±0.0903 sec] in the low magnesium model of epilepsy. In summary, 70% ethanolic extract of the plant A. afra, alleviates low magnesium-induced seizure-like events in brain slices of rats.

Disclosures: T.E. Kediso: None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.03/C3

Topic: B.08. Epilepsy

Support: Research without animaltests (Forska Utan Djurförsök) Project-ID: N2023-0007

Title: From spikes to fields: human-PSC-derived 3D neural in vitro assays for epileptogenic and anti-seizure drug assessment

Authors: *E. ARTHURSSON[1], S. THEISS[2], N. JAISUPA[1], S. ILLES[3,1];
[1]Inst. of Neurosci. and Physiol., Univ. of Gothenburg, Gothenburg, Sweden; [2]Inst. of Clin. Neurosci., Univ. of Duesseldorf, Duesseldorf, Germany; [3]Oscillution AB, Gothenburg, Sweden

Abstract: Human pluripotent stem cell (PSC)-derived 3D neural in vitro models serve a dual purpose: to identify potential epileptogenic effects of compounds on human brain function as part of neurotoxicity assessment, and to evaluate the potency and efficacy of anti-seizure drugs (ASDs).
While most studies have focused on spiking activity extracted from extracellular recordings, the role of local field potentials (LFPs) in assessing drug effects remains underexplored.
To address this, we developed a high-capacity assay platform using 3D PSC-derived neural cultures integrated with microelectrode arrays (MEAs) in a 96-well format. This system enables simultaneous recording of spiking activity and LFPs, and thereby combines the electrophysiological depth of brain slice models with the scalability of cell culture systems, providing a human-relevant alternative to animal-based assays.
Using this platform, we monitored and analyzed network-level electrophysiological activity to evaluate the efficacy and potency of established ASDs in modulating seizure-like events in human 3D neural cultures. Our findings demonstrate that integrating LFP analysis with spiking data offers deeper insights into the mechanisms of action of compounds and their effects on

neuronal excitability and synaptic regulation—both excitatory and inhibitory.
In conclusion, our 3D human neural models offer a comprehensive and translational platform for predicting ASD efficacy and safety across diverse epileptiform conditions, representing a valuable alternative to traditional animal-based systems.
Related Poster: ***Assessing Cannabidiol's Efficacy and Neurotoxicity in Human 3D Neural Models of Seizure Activity*** Stephan Theiss, Nattapon Jaisupa, Erik Arthursson, Sebastian Illes

Disclosures: E. Arthursson: None. **S. Theiss:** None. **N. Jaisupa:** None. **S. Illes:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder and holds a position at Oscillution AB. Oscillution AB were not involved in the study, and all experiments and data analyisis were conducted at the University of Gothenburg.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.04/C4

Topic: B.08. Epilepsy

Title: Preparation and evaluation of a modified ketogenic diet for seizure suppression and associated neurobehavioral comorbidities in rat model of status epilepticus.

Authors: *A. KUMAR[1], P. SHARMA[2], S. KUMARI[1], S. RAHMATKAR[2], A. RANA[1], P. SHARMA[3], S. SHARMA[2], V. PATIAL[1], V. SRIVATSAN[1], D. SINGH[2];
[2]Dietetics and Nutr. Technol., [1]Council of Scientific and Industrial Res., Palampur, India; [3]West Virginia Univ., Morgantown, WV

Abstract: Epilepsy is a chronic neurological disorder affecting over 70 million individuals globally, with approximately one-third of patients experiencing drug-resistant epilepsy (DRE). While the classical ketogenic diet (KD) is clinically recognized for its anti-seizure efficacy, its poor tolerability, associated metabolic side effects, and lack of effect on epilepsy-related comorbid conditions limit its widespread therapeutic use. In this study, we formulated a modified ketogenic diet (mKD) enriched with plant-derived omega-3 polyunsaturated fatty acids (PUFAs), to offer a safer and more sustainable alternative. The oil component of the mKD was extracted via hexane and analyzed using fatty acid methyl ester (FAME) profiling, revealing a high ALA content and an optimal ω-6:ω-3 ratio. The therapeutic potential of the mKD was evaluated in the lithium-pilocarpine (Li-Pilo) model of status epilepticus in adult rats. After the latent phase, the diet was introduced to assess its effects during the chronic epileptic period. The mKD significantly reduced seizure severity based on behavioral seizure scores compared to standard and MCT-based ketogenic diets. Additionally, neurobehavioral comorbidities were assessed using the Morris Water Maze (MWM) for cognitive function, Open Field Test for anxiety-like behavior, and Forced Swim Test for depression-like symptoms. mKD-fed animals exhibited improved cognitive performance, reduced anxiety-like behavior, and decreased depressive-like

symptoms. These findings highlight the anti-seizure and neurobehavioral benefits of an omega-3 enriched mKD and support its potential as an effective dietary intervention for managing drug-resistant epilepsy and its associated comorbidities.

Disclosures: A. Kumar: None. **P. Sharma:** None. **S. Kumari:** None. **S. Rahmatkar:** None. **A. Rana:** None. **P. Sharma:** None. **S. Sharma:** None. **V. Patial:** None. **V. Srivatsan:** None. **D. Singh:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.05/C5

Topic: B.08. Epilepsy

Title: Anti-inflammatory effect of EGF-FGF exosome in epileptic mice

Authors: B. HONGYE WANG[1], L. ZHI[1], X. WANG[2], X. LIU[1], *Y. WANG[2];
[1]Zhongshan Hospital, Fudan Univ., Shanghai, China; [2]Fudan Univ., Shanghai, China

Abstract: Epilepsy is a common disorder of the central nervous system (CNS), which manifests as recurrentepisodes of brain dysfunction caused by large-scale synchronous abnormal discharges of neurons.Neuroinflammation is a pathological stimulation which plays a critical role in epileptogenesis.Thus, targeted adjunctive therapies aimed at neuroinflammation offer promising new approacheson epilepsy. Recent findings indicate that members of the FGF family influence epilepsyregulation. However, the protective effects of EGF and FGF on neuroinflammation followingepilepsy remain underexplored. In this study, we applied engineering enhanced EGF and FGFexpression 293T-exosome (EGF-FGF.Exos) as treatment agent to investigate its protection onneuroinflammation during the occurrence of the seizures. In PTZ seizure mice model,EGF-FGF.Exos exhibited strong inhibitory effect on microglial activation and regulated microglialpolarization towards the M2 phenotype while suppressing M1 polarization. RT-qPCR resultsdemonstrated that EGF-FGF.Exos reduced the mRNA expression of central pro-inflammatoryfactors IL-1β, IL-6, and TNF-α in the animal model. HE staining showed that EGF-FGF.Exospretreatment prevented neuronal loss in both the CA1 and CA3 regions of the hippocampus.Further experiment demonstrated that the inhibitory effects of EGF-FGF.Exos onpro-inflammatory factor expression, microglial activation, and M1 polarization pre-activation iscaused by inhibiting the NF-κB pathway, and this inhibitory effect on after-seizure inflammationwas reversed by PMA (NF-κB pathway agonist). In conclusion, this current study demonstratedthat EGF-FGF enhancing exosomes (EGF-FGF.Exos) inhibit inflammatory responses in PTZseizure mice model by suppressing NF-κB pathway.

Disclosures: B. Hongye wang: None. **L. Zhi:** None. **X. Wang:** None. **X. Liu:** None. **Y. Wang:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.06/C6

Topic: B.08. Epilepsy

Support: ISF Grant 1976/20

Title: Neuron-targeted Nrf2 gene therapy confers long-term antioxidant and neuroprotective effects in refractory epilepsy

Authors: *A. SAADI[1], M. GROYSMAN[3], T. SHEKH-AHMAD[2];
[1]Sch. of Pharm., [2]Dept. of Pharmaceutics, Hebrew Univ. of Jerusalem, Jerusalem, Israel; [3]The Edmond and Lily Safra Ctr. for Brain Sci. (ELSC), The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Epilepsy affects over 65 million people worldwide, with nearly one-third of patients suffering from drug-resistant forms, particularly temporal lobe epilepsy (TLE), in which conventional antiepileptic drugs fail to prevent ongoing seizures or modify disease progression. Oxidative stress (OS) is a key driver of epileptogenesis, contributing to disease onset, progression, and chronic maintenance. However, systemic antioxidant therapies have shown limited clinical success due to poor targeting and transient efficacy. Here, we developed a neuron-specific gene therapy platform using adeno-associated virus serotype 9 (AAV9) to deliver the transcription factor Nrf2 under the control of the excitatory neuron-specific CaMKIIα promoter. *In vitro* validation demonstrated a high transduction efficiency (~71%) and selective expression in excitatory neurons, with no colocalization in GABAergic populations. Under seizure-like conditions induced by picrotoxin and 4-aminopyridine, Nrf2 overexpression reduced calcium hyperexcitability, suppressed ROS accumulation, and decreased neuronal death. These effects were accompanied by robust upregulation of Nrf2 and its downstream antioxidant targets (NQO1 and HO-1), as confirmed by Western blotting, RT-PCR, and FACS analyses. *In vivo*, AAV9-CaMKIIα-Nrf2 was stereotaxically delivered to the dorsal and ventral hippocampus of rats. Kainic acid (KA)-induced status epilepticus (SE) was used to model temporal lobe epilepsy. Continuous real-time monitoring of cortical activity was achieved using electrocorticographic (ECoG) and video recordings over an 18-week period. Across three intervention models—prophylactic (pre-SE), early therapeutic (1 day post-SE), and chronic (established epilepsy)—Nrf2 gene therapy significantly reduced seizure burden, oxidative DNA damage (8-OHdG), neuroinflammation, and hippocampal neuron loss. Notably, in the preventive model, 4 of 9 animals remained entirely seizure-free, and in the chronic phase, Nrf2 delivery significantly decreased seizure frequency and severity—highlighting its disease-modifying potential. In conclusion, neuron-targeted Nrf2 gene therapy provides durable antioxidant and neuroprotective effects across multiple stages of epilepsy. By enhancing endogenous defense pathways in excitatory neurons, this strategy holds promise as a preventive and disease-modifying treatment for drug-resistant epilepsy.

Disclosures: A. Saadi: None. **M. Groysman:** None. **T. Shekh-Ahmad:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.07/C7

Topic: B.08. Epilepsy

Title: A high-throughput in vitro functional platform for anti-epileptic drug screening in genetic and chemically induced seizure models

Authors: L. CHEN[1], S. ZHANG[1], J. XU[1], *Y. PIN[2];
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Abstract: Rodent brain slice assay has been regarded as the "gold standard" of ex vivo preclinical evaluation and screening for CNS drug discovery. However, this conventional electrophysiology technique has very limited throughput in screening large numbers of compounds. We developed a multi-well, multi-electrode array (mwMEA) platform to create a high-throughput in vitro functional assay for modeling neurological diseases and accelerating drug screening. We established a chemically induced seizurogenic model by applying traditional pro-seizurogenic compounds with different mechanisms of action - picrotoxin (PTX), 4-aminopyridine, and pentylenetetrazol - as well as elevated extracellular K^+ concentrations, to rat hippocampal neurons cultured on mwMEA plates. Then, we evaluated the anti-seizurogenic effects of valproate (VPA) and retigabine (RTG), which act on different molecular targets. For the genetic seizurogenic model, we developed a Dravet syndrome (DS) model of human severe epileptic encephalopathy characterized by recurrent and prolonged seizures. DS is caused by mutations on the SCN1A gene, which encodes the voltage-gated Nav1.1 channel. We extracted the hippocampal neurons from WT/DS mice at an early age and cultured them long-term on mwMEA recording plates. For our chemically induced seizurogenic model, we confirmed that the primary rat hippocampal neurons exhibited a firing pattern that switched from increased interictal spike firing to synchronized network ictal burst firing with longer duration and higher regularity. Then, we confirmed the anti-seizurogenic effect of VPA, which inhibited the synchronized burst firing pattern in a concentration-dependent manner. In addition, we applied RTG, a KCNQ potassium ion channel agonist, which significantly reversed the increase in spike firing frequency and synchronized burst firing patterns at 3 μM, and even suppressed spike firing at 10 μM, which suggested that RTG might have inhibited the action potentials in individual neurons. In the cell-based DS model evaluation, the susceptibility to PTX-induced burst firing patterns was notably increased in the DS group. Furthermore, VPA exhibited a more pronounced concentration-dependent inhibition in the DS group. Based on our study, the in vitro, cell-based mwMEA assay provides a novel approach for high-throughput screening and evaluation of antiepileptic drug candidates in both chemically induced and genetic defect models, potentially accelerating the discovery of new therapies for neurological disorders.

Disclosures: L. Chen: None. **S. Zhang:** None. **J. Xu:** None. **Y. Pin:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.08/Web Only

Topic: B.08. Epilepsy

Support: PE501082200-2023-PROCIENCIA

Title: A Novel FAAH Inhibitor (MCH02) Modulates the Expression of the Hippocampal Endocannabinoid System and Maxi-K Potassium Channel α-Subunit in Chronic Epileptic Rats

Authors: C. BECERRA FLORES[1], Y. YAURI HUAMAN[1], R. CÁCERES ROBLES[1], B. GUZMAN PARO[1], G. E. PARDO[1], C. MEDINA-SALDIVAR[1], *L. F. PACHECO[2];
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Abstract: Epileptogenesis involves lasting molecular and synaptic changes leading to increased neuronal hypersynchrony and epilepsy. The endocannabinoid system (ECS) and large-conductance calcium-activated potassium (BK) channels are potential antiseizure targets due to their modulatory role in presynaptic processes. In this context, N-(8Z-Heptadecen-1-yl)-O-(3-pyridylmethyl) carbamate (MCH02), a fatty acid amide hydrolase (FAAH) derived from *Lepidium meyenii*, emerges as a potential anti-epileptogenic drug because it enhances ECS signaling by increasing anandamide levels. This study evaluated the behavioral and molecular effects of intraperitoneally administering MCH02 in a chronic pentylenetetrazol (PTZ) kindling model in rats. Sprague-Dawley rats were assigned to vehicle-saline, vehicle-PTZ, MCH02-saline, or PTZ+MCH02 groups. Kindled animals received sub-convulsant PTZ injections (35 mg/kg, i.p.) every other day for 17 sessions, while treated animals received MCH02 (1 mg/kg, i.p.) 30 minutes before PTZ. Seizures were scored using a modified Racine scale, and long-term memory was assessed using the Barnes maze and novel object recognition (NOR) tests. The hippocampus was dissected for RT-qPCR (*Cnr1, Faah, Napepld, and Kcnma1*) and Western blot (CB1, FAAH, and BK channel α-subunit) analyses in the CA1, CA3, and dentate gyrus (DG) regions. Although MCH02 tended to increase animal survival, it also promoted reduced weight gain. Additionally, MCH02 did not alleviate seizure severity, as scores did not differ between the PTZ and PTZ+MCH02 groups. While PTZ kindling impaired object recognition, which was prevented by MCH02, neither PTZ nor MCH02 significantly affected spatial memory in the Barnes maze. At the molecular level, PTZ and MCH02 had region-specific effects. PTZ increased CB1 protein in CA1, however, this effect was attenuated by MCH02, though no mRNA changes were observed. In CA3, PTZ increased FAAH, CB1r, and BKα1 proteins—effects prevented by MCH02. mRNA levels tended to rise for all targets except Faah. PTZ elevated CB1r and BKα1 proteins in DG, and MCH02 increased FAAH, but transcript levels remained unchanged. Based on the results, the administration of MCH02 has multiple effects on the behavioral and molecular impact of the PTZ kindling model. While it can increase animal

survival, it does not appear to interfere with the epileptogenic process. This was also reflected in the intricate effects of the drugs on different hippocampal regions.

Disclosures: C. Becerra Flores: None. **Y. Yauri Huaman:** None. **R. Cáceres Robles:** None. **B. Guzman Paro:** None. **G.E. Pardo:** None. **C. Medina-Saldivar:** None. **L.F. Pacheco:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.09/Web Only

Topic: B.08. Epilepsy

Support: Section of Postgraduated Studies and Research, Academic Secretary of National polytechnic Institute, México

Title: Effect of induction of nitric oxide synthesis on glutamic acid decarboxylase activity

Authors: *L. A. VEGA RASGADO;
BIOQUIMICA, ESCUELA NACIONAL DE CIENCIAS Biológicas, INSTITUTO, CDMX, Mexico

Abstract: Nitric oxide (NO) is a neurotransmitter/neuromodulator synthesized from the oxidation of L-Arginine (L-Arg) by one of the isoforms of the enzyme NO Synthase (NOS): endothelial (e-NOS), neuronal (n-NOS) and inducible (i-NOS). The role of NO in epileptogenesis is still a matter of controversy, with reports showing either pro or anticonvulsant effects. Previous results of different indirect studies employing distinct NOS inhibitors suggest that a possible explanation of these paradoxical properties could be on the NOS isoform involved and their effects on glutamic acid decarboxylase (DAG), a key enzyme on glutamate and/or gamma aminobutyric acid (GABA) metabolism. To continue exploring this hypothesis the direct effect of NO on DAG activity was investigated, by inducing its synthesis with L-Arg and studying its effects on GAD activity from mouse brain (CD1 strain, 20-25 g of body mass) *in vitro* as well as *in vivo*. With this aim a spectrophotometric method described by Sasaki et al (Eur. J. Pharmacol. 367, 165-173, 1999) was employed. Experiments were conducted accordingly with the Helsinki Guide for Laboratory animals (Results $\pm$ SEM, $n \geq 4$, $p < 0.05$). Different concentrations of L-Arg decreased DAG activity (especially at low concentrations), which increased as L-Arg concentrations was higher; in any case it reached control levels. Such decreases in DAG activity reach their minimum after 20 or 30 minutes of treatment, increasing slowly after that; only with concentration 1×10^{-3} M and after 1 hour, GAD activity was reestablished. *In vivo* effects of L-Arg on DAG activity presented a valley at the dose of 30 mg/Kg (decrease of 10%) and a peak (increase of 10%) at 60 mg/kg. Higher doses of L-Arg decreased DAG activity reaching about 75%. Together, results suggest that NO modulate DAG activity, thus neuronal excitability. Concentration, time of treatment and dose are very important

factors in these studies and increases as well as decreases in DAG activity are considered to represent the effects caused by NO generated by the different NOS isoforms. These results contribute to a better understanding of the role of NO in epileptogenesis and represent a base to the development of new antiepileptic drugs.

Disclosures: L.A. Vega rasgado: None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.10/C8

Topic: B.08. Epilepsy

Support: PROSNI 2024
Fortalecimiento 2024

Title: Evaluation of Bee Venom's Effects on Convulsive Seizures Induced by 4-Aminopyridine in Rats

Authors: *F. ROMERO-AVILA[1], C. VENTURA[2], L. G. MEDINA-CEJA[3], O. VARGAS[4]; [1]Cell. and Mol. Biol., Univ. de Guadalajara, Guadalajara, Mexico; [2]Dept. de Biología Celular y Molecular, CUCBA, Univ. de Guadalajara, Zapopan, Jalisco, Mexico; [3]Dept. of Cell. and Mol. Biol., Univ. de Guadalajara, Guadalajara, Mexico; [4]Univ. de Guadalajara, Zapopan, Mexico

Abstract: Epilepsy is a neurological disorder marked by persistent, synchronized neuronal discharges and often resistant to conventional antiseizure treatments. Animal models, such as those using 4-aminopyridine (4-AP), a potassium channel blocker that induces seizures by enhancing synaptic transmission, are essential for studying seizure mechanisms. Bee venom from Hymenoptera insects contains bioactive compounds with neuroprotective and anti-inflammatory properties, offering potential for novel therapeutic approaches in epilepsy and related neurodegenerative diseases.In this study, we evaluated the effects of bee venom on convulsive seizures in male Wistar rats. Seizures were induced by intracerebroventricular administration of 4-AP, followed 30 minutes later by subcutaneous administration of bee venom. For this purpose, animals were implanted with a guide cannula for drug delivery and superficial electrodes for EEG recording. Rats were randomly assigned to one of three groups: (1) control (0.9% NaCl), (2) 4-AP (20 mM), and (3) 4-AP + bee venom (10 μg). Convulsive behavior was assessed using the Racine scale, with stages 3 to 5 considered indicative of convulsive seizures. Behavioral monitoring was conducted for 3 hours post-administration. EEG recordings were subsequently analyzed to corroborate epileptiform activity.Animals treated with bee venom showed significantly less severe convulsive behavior, corresponding to stages 1-2 on the Racine scale, compared to the 4-AP group, which observed more intense seizures (stages 4-5). Additionally, the duration of convulsive seizures was markedly reduced in the bee venom-treated group (32.5 ± 9.57 minutes) relative to the 4-AP group (152.5 ± 22.17 minutes). EEG recordings

over a four-hours period—including 30 minutes of baseline, 30 minutes post-4-AP administration, and 180 minutes following bee venom treatment—showed mean frequencies of 43.92 ± 20.77 Hz in the control group, 43.82 ± 20.80 Hz in the 4-AP group, and 43.46 ± 21.62 Hz in the 4-AP + bee venom group, with no statistically significant differences among the groups.These findings suggest that bee venom has the potential to attenuate both the severity and duration of convulsive seizures. Although bee venom has not yet been widely explored as a treatment for epilepsy, its effects on seizure modulation requires further investigation, particularly regarding its mechanisms of action within the nervous system. Supported by University of Guadalajara (PROSNI 2024, CVM/LMC, Fortalecimiento 2024, LMC).

Disclosures: F. Romero-Avila: None. **C. Ventura:** None. **L.G. Medina-Ceja:** None. **O. Vargas:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.11/C9

Topic: B.08. Epilepsy

Support: NHRI-EX110-11006NC (National Health Research Institutes, Taiwan)

Title: Effects of Levetiracetam on hippocampal glutamate transporter 1 loss and dendritic defect in a pentylenetetrazole-induced epilepsy mouse model and drug-resistant epilepsy patients

Authors: W.-C. TING[1,2], S. CHANG[2], P.-C. HSU[2], L. CHEN[2], T.-L. TSAI[2], Y.-H. CHEN[5], C.-C. HUNG[2], Y.-J. HUANG[3], *Y.-L. GAN[6], H.-H. CHEN[5], C.-F. LIN[5], C.-C. CHOU[7], H.-Y. YU[7], C.-C. LEE[5,1,4], Y.-H. Y. LEE[2,4];
[1]Sch. of Medicine, Col. of Med., [2]Inst. of Physiology, Col. of Med., [4]Brain Res. Ctr., [3]Natl. Yang Ming Chiao Tung Univ., Taipei City, Taiwan; [5]Dept. of Neurosurg., Taipei Veterans Gen. Hosp., Taipei City, Taiwan; [6]Taipei Veterans Gen. Hosp., Taipei city, Taiwan; [7]Dept. of Neurol., Taipei Veterans Gen. Hosp., Taipei City, Taiwan

Abstract: Levetiracetam (LEV), a first-line anti-seizure medication, is widely used in modern clinical neurology. Previous studies have demonstrated that synaptic vesicle protein 2A is the primary binding site of LEV, mediating several downstream neuronal processes. However, the anticonvulsant's effects on astrocytic activity remain relatively underexplored. Since epilepsy is associated with excessive synaptic glutamate release, and glutamate transporter 1 (GLT1) on astrocytes plays a key role in reuptaking excessive glutamate, the astrocyte-mediated glutamate homeostasis is essential for maintaining normal neurophysiology. Therefore, we investigated the effect of LEV on astrocytic and neuronal features in the hippocampus in the epilepsy mouse model and human hippocampus tissue. To model acute seizure striking events, we used C57BL/6 mice subjected to a single pentylenetetrazol (PTZ) injection for seizure induction. Behavioral assessments and hippocampal tissue collection were performed at 24 hours and 7 days post-

induction. Behavioral assessments included multiplex seizure severity indices, open field test, nest building test, and free-rolling horizontal bar test. Histological analysis of mouse hippocampus was conducted using immunofluorescence staining for NeuN, GFAP, MAP2, GLT1, and DAPI. Neuronal and astrocytic features were quantified accordingly. Additionally, human hippocampal tissue samples were collected from drug-resistant epilepsy patients undergoing lobectomy at Taipei Veterans General Hospital, allowing for cross-validation and comparison of pathological findings in the rodent model. Current data demonstrated that, first, dendritic integrity was compromised in PTZ-induced acute seizure mice, which was reversed by LEV administration, indicating a dendritic protective effect. Furthermore, neuronal loss began on day 7 but not at 24 hours, suggesting that this process occurs after the dendritic defects; LEV tends to attenuate this condition. Moreover, GLT1 loss in the mouse hippocampal tissue was observable, particularly in the pyramidal and lucidum layers, and this reduction was also reversed by LEV treatment. Finally, analysis of human hippocampal tissue supported the correlation of LEV administration and dendritic histological findings mentioned above. In summary, these results suggest that LEV treatment in an epilepsy animal model has beneficial effects for the preservation of astrocytic glutamate transporters and dendritic integrity, which support its clinical application in improving therapeutic strategies to protect neuroglial functions in patients.

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Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.12/C10

Topic: B.08. Epilepsy

Support: UK Ministry of Defence

Title: The utility of larval zebrafish for assessment of the seizuregenic potential and treatment options for materials of defence and security concern

Authors: J. KEARN, *C. WHITMORE;
Defence Sci. and Technol. Lab., Salisbury, United Kingdom

Abstract: Chemically induced seizure activity is incapacitating and can result in long term neuropathology with consequent cognitive decrements. Control of these seizures is particularly important in the context of defence and security science as chemical warfare agents such as the organophosphorus nerve agents (OPNAs) and certain pesticides, pharmaceuticals and toxins can cause seizure activity that is difficult to control. Here we have assessed the utility of 4 days post-fertilization (dpf) zebrafish larvae as a means of assessing seizure activity and its treatment.

AChE inhibitors (the carbamate donepezil and OPNAs) and $GABA_A$ receptor ($GABA_A$-R) targeted compounds (including picrotoxin and the rodenticide tetramethylenedisulfotetramine) were used to initiate seizure activity. The benzodiazepines diazepam and/or midazolam were examined for their ability to prevent or control the seizures. CNS neuronal activity was measured directly by confocal microscopy in elavl3:GCaMP6s zebrafish larvae and the behavioural effect of the compounds were examined using movement tracking (Zantiks automated behavioural research system). The AChE inhibitors and the $GABA_A$R-targeted compounds caused seizure-like co-ordinated neuronal activity in elavl3:GCaMP6s zebrafish larvae. Single-plane confocal microscopy showed some differences in regional activity with the different classes of compound. In behavioural tests, AChE inhibitors reduced movement in a light-dark assay in a concentration-dependent way. Donepezil, unlike the OPNAs caused an initial hyperactivity at the lowest concentrations tested. In contrast, the $GABA_A$R-targeted compounds caused a marked and concentration-dependent increase in movement in assays conducted in the light phase. Initial studies showed that benzodiazepines could reduce seizure activity caused by both OPNA and $GABA_A$R-targeted compounds. This work shows that zebrafish larvae, at 4 dpf, can be used in combined behavioural and neuronal imaging-based assays to assess seizure activity caused by different classes of compound. Moreover, preliminary results with benzodiazepines suggest that these seizures are sensitive to anticonvulsant treatments, thus demonstrating the utility of zebrafish larvae for screening of both seizure potential and treatment. © Crown copyright (2025), Dstl. This information is licensed under the Open Government Licence v3.0. To view this licence, visit https://www.nationalarchives.gov.uk/doc/open-government-licence/. Any enquiries regarding this publication should be sent to: centralenquiries@dstl.gov.uk.

Disclosures: J. Kearn: A. Employment/Salary (full or part-time): Defence Science & Technology Laboratory. **C. Whitmore:** A. Employment/Salary (full or part-time): Defence, Science & Technology Laboratory.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.13/C11

Topic: B.08. Epilepsy

Support: NIH Grant R01NS139468

Title: Disease correcting antisense oligonucleotides improve survival and reduce seizures in Scn8a mouse model

Authors: *H. B. DAME[1], C. G. DULLA[2], M. OUDIN[1];
[1]Tufts Univ., Medford, MA; [2]Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Mutations in the SCN8A gene coding for the Nav1.6 sodium channel are responsible for up to 1% of developmental epileptic encephalopathy (DEE), causing not only refractory

seizures, but also global developmental delays and movement disorders. Currently there are no specific treatments available for patients with SCN8A DEE. SCN8A undergoes developmentally-regulated alternative splicing, yielding a neonatal isoform, exon 5N, or an adult isoform, exon 5A. There are 50 patients with pathogenic mutations in the 5N or 5A exon, and we hypothesize that developing splice-switching antisense oligonucleotides (ASOs) that can induce a switch from the mutated exon to a corrected exon could offer a novel therapeutic approach for SCN8A patients.
First, we developed a novel mouse model of Ser217Pro mutation in the 5N exon in C57BL/6 mice. The heterozygous S217P(+/-) mutation in mice induces early onset seizures within the first 15 days of life and an average life expectancy of 19 days. Using EEG and video analysis we were able to capture seizures occurring in the S217P(+/-) mice in early life and adulthood. Second, we designed for ASOs that could induce the exclusion of a mutated exon 5N and inclusion of the non-mutated *Scn8a* exon 5A. We identified several ASOs able to induce the exclusion of *Scn8a* exon 5N and increased inclusion of exon 5A in neuroblastoma cell lines, ND7/23 and SH-SY5Y, as well as by gymnotic uptake in primary neurons from P0 mice. Some of these ASOs have no impact on the alternative splicing of other sodium ion channel genes and *Scn8a* transcript levels. Lastly, we have confirmed that one of the ASOs can induce splice-switching *in vivo*, after ICV injection in P1 pups, and increase survival while decreasing seizures of S217P(+/-) treated animals. These ASOs are the first treatment strategy with the goal of correcting a mutated protein for patients with SCN8A DEE.

Disclosures: H.B. Dame: None. **C.G. Dulla:** None. **M. Oudin:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR431.14/C12

Topic: B.08. Epilepsy

Support: Research without animaltests (Forska Utan Djurförsök) Project-ID: N2023-0007

Title: Assessing Cannabidiol's Efficacy and Neurotoxicity in Human 3D Neural Models of Seizure Activity

Authors: *S. ILLES[1,2], E. ARTHURSSON[3], S. THEISS[5], N. JAISUPA[4];
[1]Oscillution AB, Gothenburg, Sweden; [2]Inst. for Neuroscience, Gothenburg, Sweden, The Sahlgrenska Acad. at Gothenburg University,, Göteborg, Sweden; [3]Univ. of Gothenburg, Göteborg, Sweden; [4]Univ. of Gothenburg, Gothenburg, Sweden; [5]Inst. of Clin. Neurosci., Univ. of Duesseldorf, Duesseldorf, Germany

Abstract: Cannabidiol (CBD), a non-psychoactive compound derived from *Cannabis sativa*, has emerged as a promising treatment for drug-resistant epilepsies, including Dravet syndrome and

Lennox-Gastaut syndrome. Its therapeutic effects are thought to involve modulation of neuronal excitability and interactions with non-cannabinoid receptors. Since its approval for certain clinical indications, next-generation CBD derivatives are under development to enhance potency, efficacy, and pharmacokinetics.
While CBD has been extensively studied in rodent brain slices and primary neuronal cultures, its impact on seizure-like activity in human neurons remains underexplored.
To bridge this gap, we used a high-capacity assay platform using 3D PSC-derived neural cultures integrated with microelectrode arrays (MEAs) in a 96-well format. This system enables simultaneous recording of spiking activity and LFPs, and thereby combines the electrophysiological depth of brain slice models with the scalability of cell culture systems, providing a human-relevant alternative to animal-based assays. Using this platform, we assessed the efficacy and potency of CBD in modulating seizure-like events in human 3D neural networks.
Our results show that CBD suppressed seizure-like activity at concentrations comparable to those effective in animal-based *in vitro* models. Additionally, we identified a dose-dependent neurotoxic effect at concentrations previously reported as anticonvulsive in rodent brain slice preparations, underscoring the importance of defining the therapeutic window in human-relevant models.
In conclusion, our 3D human PSC-derived neural assay provides a translationally relevant platform for evaluating anti-seizure drug efficacy, potency, and safety—particularly for compounds with complex mechanisms of action.
Related Poster:
From Spikes to Fields: A Human-Relevant Assay for Epileptogenic and Anti-Seizure Drug Assessment Erik Arthursson, Stephan Theiss, Nattapon Jaisupa, Sebastian Illes

Disclosures: S. Illes: A. Employment/Salary (full or part-time): Oscillution AB. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oscillution AB. **E. Arthursson:** None. **S. Theiss:** None. **N. Jaisupa:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR431.15/C13

Topic: B.08. Epilepsy

Support: U.S. Government Other Transaction number W15QKN-16-9-1002

Title: A novel M1 selective muscarinic antagonist (AD-229) reverses acute effects of organophosphates on respiratory rate and intracranial EEG

Authors: *J. S. THINSCHMIDT[1], S. W. HARDEN[1], J. D. TALTON[2], C. J. FRAZIER[1]; [1]Univ. of Florida, Gainesville, FL; [2]Alchem Labs., Alachua, FL

Abstract: Effective medical countermeasures (MCMs) for organophosphate (OP) poisoning remain a critical need due to the severe and often rapid neurotoxic effects of OP exposure. Traditional therapies are limited by off-target interactions and poor CNS bioavailability, largely due to inadequate penetration of the blood-brain barrier (BBB). To address these limitations, there is ongoing interest in identifying novel acetylcholinesterase (AChE) reactivators, muscarinic antagonists, and other agents with broad-spectrum efficacy and enhanced CNS activity. Our group has previously established a rat basolateral amygdala (BLA) brain slice assay to characterize the efficacy of such compounds in counteracting acute toxicity from the OP analog 4-nitrophenyl isopropyl methylphosphonate (NIMP) (Thinschmidt et al. 2022). To complement this ex vivo approach, we developed an anesthetized in vivo model that enables simultaneous assessment of the BLA EEG and respiratory responses following intravenous OP challenge (Thinschmidt et al 2024). In this model, 0.5 mg/kg NIMP (IV & SQ) reliably induces seizure-like discharges in the BLA and progressive respiratory depression. When administered intravenously, test compounds can be evaluated for CNS efficacy based on their ability to mitigate these effects, thereby providing insight into BBB permeability and pharmacodynamic action. Using this platform, we previously demonstrated that intravenous administration of atropine (5 mg/kg), a non-selective mAChR antagonist, effectively prevented and reversed NIMP-induced seizure activity and respiratory depression. In contrast, the M1-selective antagonist pirenzepine failed to provide protection or reversal, consistent with its poor CNS penetration. Here, we evaluated AD-229, a novel M1-selective muscarinic antagonist currently in preclinical development, with an in vitro IC_{50} of 16-32 nM. In both intravenous and subcutaneous NIMP challenge models (0.5 mg/kg), AD-229 rapidly reversed BLA EEG hyperactivity and respiratory depression, restoring both measures to near-baseline levels. These results align with pharmacokinetic data showing a half-life of 2.4 hours and robust CNS penetration, reflected in high brain-to-plasma partitioning. Additional preclinical characterization of AD-229 reveals favorable properties, including an LD_{50} > 50 mg/kg (single-dose, mice) and aqueous formulation stability exceeding four months at room temperature. Although GLP-compliant toxicity studies are pending, the current data strongly support AD-229 as a promising lead compound with potential utility as an alternative or adjunct to atropine in the treatment of OP poisoning.

Disclosures: J.S. Thinschmidt: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TRON group. Other; TRON group BOD. **S.W. Harden:** None. **J.D. Talton:** A. Employment/Salary (full or part-time): CEO and owner of Alchem. **C.J. Frazier:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.16/C14

Topic: B.08. Epilepsy

Support: R01 NS126418

Title: Investigating the pharmacoresponsiveness of interictal spikes and myoclonic jerks in the kcna1-null mouse model of temporal lobe epilepsy

Authors: *V. ALONSO[1], S. A. MATTHEWS[2], K. A. SIMEONE[3], T. SIMEONE[4]; [2]Pharmacol., [1]Creighton Univ., Omaha, NE; [3]Dept. of Pharmacol., [4]Pharmacol., Creighton Univ. Sch. of Med., Omaha, NE

Abstract: *Kcna1*-null mice are a model of temporal lobe epilepsy that exhibit a wide array of seizure types and epileptiform activity - including interictal spikes, myoclonic jerks, and convulsions - both focal and generalized. Previously, we evaluated the efficacy of conventional antiseizure medications (ASMs) against generalized convulsions and concluded that *Kcna1*-null mice have pharmacoresistent epilepsy. Clinically, myoclonic jerks are notoriously difficult to treat and the interplay between interictal spikes, ASM responsiveness, and seizure EEG dynamics remains elusive. Thus, in this exploratory study, we sought to determine the effect of ASMs on the incidence of myoclonic jerks and interictal spikes of *Kcna1*-null mice. *Kcna1-null* mice were surgically implanted with 2 ipsilateral subdural cortical electrodes in the medial parietal and medial frontal regions and EMG wires in the nuchal muscles. Mice were injected intraperitonially with either carbamazepine, phenytoin, phenobarbital, or levetiracetam for 2 days at high therapeutic doses following 2 days of appropriate vehicle treatment beginning at postnatal day 42. Simultaneous video-EEG recordings were collected during the 4 days of treatment. EEG spikes were identified using SPIKE software automatic spike detection and were manually categorized as interictal, myoclonic, or artifacts with video verification. Preliminary analyses suggest myoclonic jerks have a diurnal rhythm, whereas interictal spikes do not. Analyses of drug treatments is ongoing; thus far, phenobarbital has no significant effect on myoclonic jerks or interictal spikes. Determining the pharmacoresponsivesness of myoclonic jerks and interictal spikes may support the *Kcna1*-null mouse as a moderate throughput model of multiple drug-resistant seizure types useful in determining mechanisms and testing novel therapeutic strategies.

Disclosures: V. Alonso: None. **S.A. Matthews:** None. **K.A. Simeone:** None. **T. Simeone:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.17/C15

Topic: B.08. Epilepsy

Support: NIH grant P20GM109089-06

Title: Induction of REM sleep via midbrain stimulation reduces seizure burden in a rat model of temporal lobe epilepsynduction of REM sleep via midbrain stimulation reduces seizure burden in a rat model of temporal lobe epilepsy

Authors: *A. L. SOMMER[1], D. GREGG[2], N. MAHTO[3], S. A. MCKENZIE[4];
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Abstract: The proportion of patients with drug-resistant epilepsy has remained stubbornly fixed at around 30% despite a generation of drug development. Mesial temporal lobe epilepsy (MTLE) is the most common type of focal epilepsy and one of the most difficult to treat with existing pharmacology. For patients with pharmacoresistant MTLE, deep brain stimulation may be an option. A number of stimulation targets have been explored to treat MTLE such as the temporal lobe seizure onset zone, the anterior nucleus of the thalamus, and the cerebellum. Though existing neuromodulation strategies significantly decrease seizure rate in the majority of patients, a minority achieve seizure freedom. Inspired by the close relationship between sleep and seizure onset, and the observation that generalized seizures are rare during rapid eye movement (REM) sleep, we tested whether experimental induction of REM could treat seizures in rodent models of MTLE. To model acquired MTLE, we adopted the rat intrahippocampal kainic acid (IHKA) model in which spontaneous seizures develop in the weeks following status epilepticus induced by the chemoconvulsant. Monopolar electrical stimulation of the midbrain increased the rate and duration of a REM-like state, as measured by increases in limbic theta power in the absence of movement or arousal. This stimulation also decreased the rate of spontaneous seizures by 30% and decreased the incidence of interictal epileptiform discharges (IEDs) bilaterally in the neocortex, hippocampus, and amygdala. Decreases in IED rate were well explained by changes in sleep structure and not changes in theta power or movement. No changes in REM, seizure rate, or IED rate were observed during within-subject control sessions in which stimulation was withheld, or in subjects with electrodes outside of the midbrain. We next tested whether pre-conditioning the midbrain with electrical stimulation (1-hr monopolar stimulation at ~0.1-Hz) would reduce the severity of electrically evoked seizures (10-Hz monopolar hippocampal stimulation for 10-s). We found that if hippocampal stimulation was delivered upon a background of high theta power, the evoked seizures tended to remain focal, while those seizures triggered on a low theta background tended to generalize. These findings suggest that midbrain stimulation reduces seizures and other epileptiform activity across the brain by inducing a neuroprotective state defined by a lower likelihood of seizure onset and secondary generalization. Our findings motivate further development of DBS strategies that target REM-promoting regions for the treatment of drug-resistant epilepsy.

Disclosures: A.L. Sommer: None. **D. Gregg:** None. **N. Mahto:** None. **S.A. McKenzie:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.18/C16

Topic: B.08. Epilepsy

Support: R01 NS126594-01

Title: Closed-loop optogenetic modulation of thalamic nuclei in childhood absence epilepsy

Authors: *S. HE[1], S. KILIANSKI[2], Y. ZHANG[3], E. WU[3], J. SANCHEZ[3], A. CARNS[3], G. NAIK[3], M. P. BEENHAKKER[2];
[1]Univ. of Virgina, Charlottesville, VA; [2]Pharmacol., [3]Univ. of Virginia, Charlottesville, VA

Abstract: Generalized seizures are defined as epileptic events that engage both hemispheres of the brain from the onset, leading to widespread disturbances in neural activity. Absence seizures associated with a pediatric form of generalized epilepsy are characterized by brief interruptions in consciousness, accompanied by the concurrent electroencephalographic (EEG) pattern of synchronized 3 Hz spike-wave discharges (SWDs) lasting a few seconds. With advancements in epilepsy treatment, responsive neurostimulation (RNS) represents a closed-loop stimulation strategy that monitors brain activity and delivers electrical stimulation (ES) only when abnormal patterns are detected, resulting in increased precision and reduced unnecessary stimulation. However, the exact structures contributing to seizure control remain unclear due to the limitations of ES, wherein the stimulating current often spreads across multiple brain regions. Here, we evaluate the utility of RNS in reducing seizures associated with the C3H/HeJ mouse model of absence epilepsy. By integrating electrocorticography (ECoG) recording with closed-loop optogenetic inhibition, we aim to identify nuclei within the thalamus that initiate or terminate absence seizures. Six thalamic nuclei were selectively tested, including the thalamic reticular nucleus (RT), the ventrobasal (VB) thalamus, the posteromedial thalamic nucleus (POm), the centromedian thalamic nucleus (CM), the laterodorsal nucleus (LD), and the anterior nucleus of the thalamus (ANT). We employed a voltage amplitude-based seizure detection algorithm with a limited delay of 3 ms between spike detection and light stimulation. Our results reveal that among all the nuclei, RT inhibition aborts seizures with the shortest duration (within 500 ms), whereas other structures like POm have little or no effect on seizure maintenance. Our research ultimately aims to provide better targets for clinical applications and to resolve seizure generating circuits associated with childhood absence epilepsy.

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Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.19/Web Only

Topic: B.08. Epilepsy

Title: Insights into Seizure Induced Disruptions in Neonatal Rat Hippocampal Neurons and the Role of Cannabidiol in Functional Recovery

Authors: *H. AHSAN[1], F. IQBAL[1], M. YACOUB[1], Z. KHAN[1], N. I. SYED[2];
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Abstract: Epilepsy is one of the most common chronic neurologic conditions, affecting almost 15 million women of child-bearing age worldwide. Although anti-seizure medications (ASMs) remain the primary treatment option for epilepsy, increasing evidence suggests that the risk of adverse birth outcomes and neurodevelopmental disorders in exposed children is higher. These include adverse effects on the hippocampus, which is the region of the brain responsible for learning and memory. Recently a new ASM, Cannabidiol (CBD), derived from the non-psychoactive component of *Cannabis stavia* was approved for patients ≥ 2 years of age with epilepsy. Preclinical research has suggested CBD may influence neurodevelopment; however, its impact on the development of the fetal brain remains poorly understood. Given that cannabis use during pregnancy is on the rise, and with one in every four pregnant women believing cannabis use is harmless, it is crucial to deduce how this may impact the development of the fetal brain. Our research investigates the impact of seizure-like activity (SLA) on functional network connectivity and the modulatory effects of CBD in an epilepsy-in-a-dish model by leveraging primary P0 Sprague-Dawley rat hippocampal neurons.We first validate an *in vitro* low [Mg^{2+}] seizure induction model and quantitatively assess changes in synaptic density through two key postsynaptic markers, postsynaptic density protein 95 (PSD-95) and AMPA receptor subunit GluA1 (GluR1), which play essential roles in synaptic plasticity and excitatory neurotransmission. We found that transient CBD exposure does not significantly alter PSD-95 or GluR1 fluorescence under SLA conditions in developing neonatal networks. We then applied computational network analysis to electrophysiological recordings by leveraging micro-electrode arrays, elucidating how CBD transiently restores network topology by normalizing node-level graph metrics, reducing SLA-induced disruptions. In particular, we see metrics such as node strength, betweenness centrality, and participation coefficient transiently return to normative levels following CBD exposure. We also find that CBD transiently modulates node cartography by increasing globally connected nodes and enhancing edge strength, thereby mitigating SLA-induced hub isolation. By leveraging computational modeling and molecular analysis, our research provides novel insights into the effects of CBD on seizure-induced network reorganization, advancing our understanding of seizure pharmacology *in vitro*.

Disclosures: H. Ahsan: None. **F. Iqbal:** None. **M. Yacoub:** None. **Z. Khan:** None. **N.I. Syed:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.20/C17

Topic: B.08. Epilepsy

Title: Activity dependent antioxidant gene therapy for epilepsy

Authors: *P. SINGH, T. SHEKH-AHMAD;
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Abstract: Epilepsy affects approximately 1% of the global population, with over 30% of patients resistant to currently available antiseizure medications (ASMs). While ASMs manage symptoms, they fail to address the underlying mechanisms of epileptogenesis. This therapeutic gap highlights the urgent need for interventions that not only suppress seizures but also prevent the development of epilepsy and modify its progression. We present an activity-dependent gene therapy approach using cfos-driven expression of Nrf2, a key regulator of cellular antioxidant defenses, to provide targeted, on-demand neuroprotection in a rat model of epilepsy. Following status epilepticus, cfos-Nrf2 expression was rapidly upregulated, peaking at 24 hours, and was selectively localized to excitatory neurons, ensuring spatial and temporal targeting of hyperexcitable circuits involved in epileptogenesis. Functional activation of the Nrf2 pathway was confirmed by the upregulation of downstream targets such as NQO1, accompanied by a progressive reduction in seizure severity during repeated PTZ-induced challenges, indicating a transient but effective neuroprotective window. Long-term video-ECoG monitoring confirmed long-lasting seizure suppression, reduction in interictal activity over 12 weeks, supporting the disease-modifying potential of this therapy. Moreover, cfos-Nrf2-treated animals exhibited improvements in spatial working memory and reduced anxiety-like behavior, addressing a major unmet need in epilepsy treatment. Compared to conventional gene therapy and pharmacological approaches, the cfos-Nrf2 system is fully autonomous, leveraging endogenous seizure activity to trigger therapeutic expression. This confers precise temporal control of neuroprotection, reduces the risk of tolerance, and ensures sustained therapeutic efficacy over time.

Disclosures: P. Singh: None. **T. Shekh-Ahmad:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.21/C18

Topic: B.08. Epilepsy

Support: NICHD grant HD101642
NINDS training grant T32 NS04554

Title: Postnatal oxytocin treatment reduces seizure susceptibility evident in male, but not female, Fragile X Syndrome model mice.

Authors: *J. CHAVEZ[1], G. LYNCH[2], C. M. GALL[3];
[1]Anat. and Neurobio., Univ. of California, Irvine, Irvine, CA; [2]Univ. California, Irvine, Irvine, CA; [3]Dept. of Anat. and Neurobio., Univ. of California at Irvine, Irvine, CA

Abstract: Fragile X syndrome (FXS) is the leading inherited cause of intellectual disability, and is frequently accompanied by seizures. Early-life treatment with the hormone oxytocin (OXT)

reportedly improves social behavior in rodent models of autism including FXS, but the possibility that OXT treatment may also attenuate seizure susceptibility is not known. Moreover, despite FXS impacting both males and females, the majority of preclinical studies and tests of therapeutics have focused on males. In the present study, we used the Fmr1-Knockout (KO) mouse model of FXS to test if intranasal treatment with OXT, as compared to saline (SAL), daily from postnatal day (P) 7 to P13 influences the predisposition for audiogenic seizures (AGS) in male and female mice tested in adulthood. Both wildtype (WT) and Fmr1-KO mice (FVB sighted background) were assessed at 3-4 months of age for the incidence and severity of AGS. After a brief (45s) acoustic stimulation at 120 dB, male WT mice (given OXT or SAL) displayed no seizure activity. In contrast, SAL-treated male KOs exhibited robust AGS, in many cases leading to death. Seizure activity was significantly reduced in male KOs given early OXT treatment with many exhibiting no seizure activity at all. In contrast, female KOs given SAL had markedly lower seizure severity scores as compared to SAL-treated Fmr1-KO males, and OXT treatment did not alter seizure outcome in females. Similar to the males, both female WT groups (± OXT treatment) did not exhibit any seizure behavior. To determine if the effect of OXT in Fmr1-KO males is developmentally constrained, a separate cohort of mice received OXT or SAL treatment from P30-P36. With these later treatments, both SAL- and OXT-treated KOs exhibited robust seizure activity, indicating that the protective effects of oxytocin treatment may be limited to early stages of postnatal development. Overall, these findings reveal dramatic male/female differences in the propensity for audiogenic seizures in Fmr1-KO mice and indicate that in FXS males early-life OXT treatment could eliminate seizure susceptibility with beneficial effects lasting well into adulthood.

Disclosures: J. Chavez: None. **G. Lynch:** None. **C.M. Gall:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.22/C19

Topic: B.08. Epilepsy

Title: Progression of hippocampal pathology in a mouse model of chronic focal epilepsy and its alteration by inhibitory interneuron cell therapy (NRTX-1001)

Authors: *E. T. SEVILLA[1], A. B. VOGEL[1], M. B. PAREKH[1], A. BATES[1], F. PORKKA[1], P. HAMPEL[1], B. DE HARO[1], M. BERSHTEYN[2], G. SUBRAMANYAM[2], M. SEZAN[2], A. BULFONE[3], G. BANIK[3], C. A. PRIEST[3], C. R. NICHOLAS[3];
[1]Preclinical, [2]Discovery Res., [3]Neurona Therapeut., South San Francisco, CA

Abstract: One-third of people with mesial temporal lobe epilepsy (MTLE) have drug-resistant seizures. NRTX-1001 is a cell therapy in clinical development for the treatment of MTLE comprising GABAergic, post-mitotic, medial ganglionic eminence-derived, pallial-type interneurons. Previous studies demonstrated the efficacy of NRTX-1001 in reducing seizure

frequency and altering epileptic histopathology in a chronic model of MTLE in immunocompromised (NOG) mice. Hippocampal sclerosis and granule cell dispersion (GCD) in the dentate gyrus are pathological hallmarks of MTLE; both observations are less extensive in mice at 8 months post transplantation (MPT) of NRTX-1001.

Here, we asked the question: does transplantation of interneurons *prevent* or *repair* hippocampal histopathology? The following studies establish a timeline of hippocampal pathology in the focal kainate model of MTLE over 9 months and examine the intervention of NRTX-1001 on this timeline.

The MTLE model was generated by intrahippocampal injection of kainic acid in NOG mice to induce status epilepticus, which leads to chronic recurrent seizures and sclerosis. Hippocampal histology was subsequently examined at multiple timepoints up to 9 months post status epilepticus (MPSE). Experimental groups of epileptic mice received a one-time intrahippocampal administration of NRTX-1001 at either 1 week post status epilepticus ("Early"), 1 MPSE ("Mid"), or 4 MPSE ("Late"). For these groups, hippocampal histology was examined at 5 MPT. Corresponding control groups had no cell transplants.

To assess sclerosis, a hematoxylin and eosin stain was used to assign qualitative scores of hippocampal damage. To assess GCD, antibodies against PROX1, a granule cell marker, were used to measure the area of the granule cell layer (GCL). Sclerosis and GCD gradually increased in severity over time through 9 MPSE in the control groups without cell transplant. However, in the Early- and Mid-transplant groups, sclerosis scores were lower than at 4 MPSE without transplant. Interestingly, Late-transplant mice had significantly smaller GCL area compared to non-transplanted mice examined at 4 MPSE (time of transplant). These data suggest that NRTX-1001 transplantation into epileptic mice limits the progression of sclerosis and additional dispersion of the GCL, demonstrating prevention and potential partial repair of epileptic histopathology. In future studies, the mechanism of action for reduction of the GCL area will be investigated.

The results of these preclinical studies support ongoing clinical trials (NCT05135091, NCT06422923) to evaluate NRTX-1001 in people with drug-resistant temporal lobe epilepsy.

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Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.23/C20

Topic: B.08. Epilepsy

Support: TRAN1-11611
CLIN2-13355

Title: Preclinical characterization of a human inhibitory interneuron cell therapy candidate for drug-resistant epilepsy in the intrahippocampal kainate mouse model

Authors: *A. B. VOGEL[1], M. B. PAREKH[1], M. BERSHTEYN[2], P. HAMPEL[1], E. T. SEVILLA[1], F. A. PORKKA[1], A. A. BATES[1], G. SUBRAMANYAM[2], M. SEZAN[2], R. ZHOU[2], L. C. FUENTEALBA[2], C. A. PRIEST[1], C. R. NICHOLAS[3];
[1]Preclinical, [2]Discovery Res., [3]Neurona Therapeut., South San Francisco, CA

Abstract: Epilepsy is one of the most common neurological disorders worldwide, characterized by spontaneous recurrent seizures and network hyperexcitability. About one-third of patients have drug-resistant seizures, presenting an unmet need for new therapeutic strategies. Surgical lobectomy to remove or ablate the seizure focus can be an option for some patients with

refractory focal epilepsy but is not indicated or effective for all and can cause cognitive impairment. As a non-tissue-destructive alternative, an investigational cellular therapeutic candidate, NRTX-1001, was developed from human pluripotent stem cells comprising GABAergic postmitotic pallial interneurons. An intrahippocampal (IH) kainate mouse model of drug-resistant mesial temporal lobe epilepsy (MTLE) was used to investigate NRTX-1001 persistence, distribution, fate, and composition. Epileptic mice received a single IH transplantation of NRTX-1001 during the chronic phase of the model, which resulted in pronounced suppression of focal electrographic seizures and reduced hippocampal pathology. Across several preclinical studies, approximately two-thirds of epileptic mice that received NRTX-1001 were stably seizure-free 8 months post-transplantation. Single nucleus RNA sequencing (snRNAseq) analyses of the grafted cells enabled bioinformatic identification of human interneuron subtypes. NRTX-1001 grafts persisted long-term with stable subtype composition. No ectopic tissues, tumors, or teratomas were observed following transplantation of NRTX-1001, and no deleterious effects were observed in behavioral testing. NRTX-1001 is being evaluated for safety and efficacy in two ongoing phase I/II clinical trials (NCT05135091, NCT06422923) for drug-resistant MTLE.

Disclosures: **A.B. Vogel:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **M.B. Parekh:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **M. Bershteyn:** A. Employment/Salary (full or part-time): Neurona Therapeutics. **P. Hampel:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **E.T. Sevilla:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **F.A. Porkka:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **A.A. Bates:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **G. Subramanyam:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **M. Sezan:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **R. Zhou:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **L.C. Fuentealba:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **C.A. Priest:** A. Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **C.R. Nicholas:** A.

Employment/Salary (full or part-time): Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.24/C21

Topic: B.08. Epilepsy

Support: 5R21NS132071-02 (RG, CAG)
Summer Undergraduate Research Experience (VF)

Title: Adeno-associated viral vectors with Prox1 regulatory elements enable granule-cell-specific expression in the mouse dentate gyrus

Authors: *V. SUN[1], V. FLEGEANCE[1], E. ACERBO[1], N. SUBRAMANIARAO[1], K. BERGLUND[1], R. E. GROSS[2], C.-A. N. GUTEKUNST[1];
[1]Dept. of Neurosurg., Emory Univ. Sch. of Med., Atlanta, GA; [2]Dept Neurosurg., Rutgers Univ., New Brunswick, NJ

Abstract: Temporal lobe epilepsy (TLE) is a common neurological disorder marked by spontaneous and recurrent seizures and hippocampal circuit dysfunction. Dentate gyrus granule cells (DG GCs) act as a key regulatory gate for excitatory input to the hippocampus, and pathological changes in these neurons (e.g., mossy fiber sprouting, dispersion, and ectopic migration) are implicated in seizure propagation. Prox1, a transcription factor essential for DG GC differentiation, is selectively expressed in these cells, making it a promising candidate for cell type-specific recombinant adeno-associated viral (AAV) vectors targeting.
We constructed AAV vectors using full-length (3kb) and truncated (2 kb) mouse and human Prox1 promoters to drive Cre expression. AAVs (packaged in the PHP.eB serotype) were delivered systemically (via tail vein, intranasal, or intracerebroventricular (ICV) injection) or directly into the hippocampus of tdTomato reporter (Ai9) mice. Adult wildtype C57BL6/J mice also received a Prox1 vector with AAV2.hSyn.DIO.hM4D(Gi).mCherry to test inhibitory DREADD expression. AAVs were stereotactically injected (AP: -1.91 mm, ML: -1.5 mm from the bregma, DV: -1.9 mm from the dura) at titers ranging from 4.2×10^{13} to 1.5×10^{15} viral genomes in 50-150 nL volumes at varying ratios. To assess spatial expression patterns and cell-type specificity, brains were perfused, sectioned, and imaged via confocal microscopy, and fluorescent expression (tdTomato or mCherry) was quantified using ImageJ.
Tail vein injection yielded sparse neuronal expression and widespread epithelial expression. Intranasal injection showed no detectable expression. Neonatal ICV injection drove strong, widespread neuronal and glial expression throughout cortical and subcortical regions. Glial expression was stronger with the human full-length Prox1 promoter. All promoters led to expression in the striatonigral pathway. Quantification showed high expression in cortex,

striatum, and thalamus; moderate levels in hippocampus; and some in cerebellar Purkinje cells. Direct intrahippocampal injection was better at targeting DG GCs, with minimal off-target labeling in CA1, CA3, and the hilus.
ICV results suggest that the Prox1 promoters used in our studies are active in various cell types during development. It is possible that our constructs lack elements that restrict expression to the DG GCs. While promoter length had limited impact on specificity, the human Prox1 promoter consistently outperformed the mouse version in targeting DG GCs. Direct dual virus intrahippocampal injection is a more viable strategy that can be tested in larger animals for translational studies in TLE.

Disclosures: V. Sun: None. **V. Flegeance:** None. **E. Acerbo:** None. **K. Berglund:** None. **R.E. Gross:** None. **C.N. Gutekunst:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.25/C22

Topic: B.08. Epilepsy

Support: NIH Grant R21 NS112948
NIH Grant R01 NS129984
NIH Grant R21 NS132071
NIH Grant R01 NS138733
NIH Grant S10 OD021773

Title: Bioluminescence-optogenetics in astrocytes as a seizure treatment

Authors: *K. BERGLUND[1], S. KOTHAGUNDLA[1], S. IQBAL[1], U. THAKAR[1], H. SKELTON[1], R. E. GROSS[2], C.-A. N. GUTEKUNST[1];
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Abstract: One percent of the general population suffers from at least one episode of epileptic seizures in their lifetime, and one in 3 patients (>1 million people in the U.S.) experience unmanageable seizures despite otherwise quite effective conventional pharmacotherapies. Among these drug-resistant epilepsy patients, only a fraction receives surgical interventions, such as resective surgeries and implantation of deep brain stimulation devices which do not guarantee seizure freedom, leaving a large patient population to undermanaged seizures. This tremendous treatment gap calls for novel approaches for drug-resistant epilepsy.
As an alternative treatment, we targeted astrocytes with systemically administered bioluminescence-optogenetics (BL-OG). Astrocytes sequester and clear extracellular potassium, a predominant determinant of neuronal excitability, through uptake mechanisms, which is linked to intracellular pH in the glia. Thus, altering astrocytic physiology can be an effective strategy to mitigate epilepsy. We tested this indirect neuromodulation in a mouse model. We created a new

BL-OG molecule by incorporating an engineered luciferase that can generate light internally into the light-driven chloride pump, *Natronomonas pharaonis* halorhodopsin (*Np*HR). As a negative control, we introduced triple point mutations that hinder chloride transport function of *Np*HR. The functions of the new molecules were first tested in a heterologous expression system. For astrocytic expression, we developed adeno-associated viral (AAV) vectors with the GFAP promoter and used intracerebroventricular injection in neonates for widespread expression. As for an epilepsy model, we used systemic injection of pilocarpine which causes status epilepticus followed by spontaneous recurrent seizures. We determined pharmacodynamics and developmental profile of AAV-mediated BL-OG using *in vivo* bioluminescence imaging. We then activated the new BL-OG molecules with systemic injection of its substrate. Compared to negative controls, the new BL-OG treatment alleviated epileptic seizures when quantified through behaviors.
While conventional treatments for epilepsy all primarily target and modify neuronal physiology, altering glial physiology can be a novel and effective strategy to treat drug-resistant epilepsy.

Disclosures: K. Berglund: None. **S. Kothagundla:** None. **S. Iqbal:** None. **U. Thakar:** None. **H. Skelton:** None. **R.E. Gross:** None. **C.N. Gutekunst:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.26/C23

Topic: B.08. Epilepsy

Support: NIH Grant K08NS126730

Title: Modulation of mTOR Activity via Parafascicular Nucleus Stimulation in a Mouse Model of Tuberous Sclerosis

Authors: *A. S. BURT[1], M. MARTINOVIC[2], T. J. FOUTZ[2];
[1]Neurosci., Brigham Young Univ., Provo, UT; [2]Neurol., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Tuberous Sclerosis Complex (TSC) is a genetic disorder characterized by the overgrowth of non-cancerous tumors in various organs, including the brain. This condition affects approximately 1 in 6,000 births worldwide and is frequently associated with seizures and epilepsy. Over 50% of individuals with TSC and epilepsy have seizures that are resistant to medications. TSC is primarily linked to mutations in the mammalian target of rapamycin (mTOR) pathway, which plays a crucial role in cell growth and proliferation. Our study aims to investigate the effects of deep brain stimulation (DBS) of the parafascicular nucleus (PF) on the mTOR pathway in mice, to identify potentially therapeutic effects. *Methods:* Over a period of 10-12 days, age-matched control and *Tsc1*^{GFAP}CKO mixed C57Bl/6 and SV129 genetic background mice were randomly assigned to either a no-stimulation control group or an

experimental group that received deep brain stimulation in the PF nucleus (DBS-PF) at a frequency of 150 Hz. Continuous video-electroencephalography was recorded to quantify seizure activity. At the end of the treatment period, brain tissue was harvested from the surviving mice. Two *Tsc1*^{GFAP}CKO mice and four control mice survived. A Western blot analysis was performed to assess the activity of the mTOR pathway by evaluating levels of phosphorylated S6 (pS6) and total S6 ribosomal proteins in the collected tissue. The ratio of pS6 to S6 was used to determine the activity level of the mTOR pathway. *Results:* In the control mice, the pS6/S6 ratio was 0.15 for the stimulated animal, compared to 0.44, 95% CI [.2352, .638] in the non-stimulated control animals. This suggests that stimulation resulted in a reduced ratio of pS6/S6 in the cortex, indicating reduced mTOR pathway activity. Initial results for the stimulated *Tsc1*^{GFAP}CKO mice were inconclusive. *Conclusions:* These data suggest that high-frequency neurostimulation of the PF nucleus has potential as a target for modulating the mTOR pathway. This modulation may have significant clinical implications, warranting further investigation.

Disclosures: A.S. Burt: None. **M. Martinovic:** None. **T.J. Foutz:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.27/C24

Topic: B.08. Epilepsy

Support: NIH Grant K08NS126730

Title: Frequency-dependent effects of parafascicular nucleus stimulation in a mouse model of temporal lobe epilepsy

Authors: *M. MARTINOVIC[1], T. J. FOUTZ[1,2];
[1]Neurol., [2]Neurosci., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Temporal lobe epilepsy (TLE) affects about 50 million individuals worldwide and remains a significant clinical challenge due to the high prevalence of drug-resistant epilepsy (DRE) and hippocampal sclerosis (HS). Deep brain stimulation (DBS) has emerged as a minimally invasive alternative to resective surgery for DRE. However, direct stimulation of the hippocampus can have cognitive side effects such as memory impairment. The centromedian-parafascicular complex (CM/PF) is a promising DBS target for DRE, though its anti-seizure mechanisms are not fully understood. *Methods:* We evaluated the efficacy of PF-targeted DBS (PF-DBS) in a kainic acid (KA)-induced mouse model of TLE using the C57BL/6J strain. Mice received intrahippocampal KA injections to induce spontaneous recurrent seizures. Five groups were treated: control (no stimulation) and PF-DBS at 1, 75, 150, or 300 Hz. Bilateral PF stimulation (1 min on, 4 min off) began 14 days post-KA injection for 28 days, followed by a 14-day post-stimulation observation period. Seizure frequency was determined from continuous video-EEG, and hippocampal morphology was analyzed post-mortem. *Results:* During the early

treatment phase (days 14-28), the 75, 150, and 300 Hz stimulation groups showed significant reductions in seizure frequency compared to baseline. In the late treatment phase (days 29-42), no group exhibited a significant reduction in seizures relative to baseline. During the post-stimulation period, the 75 and 150 Hz groups showed significantly reduced seizure frequency compared to their late treatment phase levels. The 75 Hz group continued to show a significant reduction from baseline during this phase, as did the 300 Hz group, indicating potential delayed therapeutic effects. Survival outcomes also varied across groups. Histological examination revealed the most severe CA1 atrophy in the 1 Hz group. In comparison, the 75, 150, and 300 Hz groups showed milder structural alterations, with the 150 and 300 Hz groups exhibiting slight swelling of the CA1 region, indicating frequency-dependent effects on hippocampal structure. *Conclusions:* Collectively, these findings suggest a frequency-dependent effect of PF-DBS, indicating that mid-frequency PF-DBS may offer an optimal combination of seizure suppression, mitigation of hippocampal sclerosis, and survival benefit. These results support further investigation of PF-targeted neuromodulation as a therapeutic approach for TLE.

Disclosures: M. Martinovic: None. **T.J. Foutz:** None.

Poster

PSTR431: Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR431.28/Web Only

Topic: B.08. Epilepsy

Support: NIH Grant K08NS126730

Title: Using AI for Motion Tracking of Pre-Clinical Mouse Models of Temporal Lobe Epilepsy

Authors: *S. G. HATCHETT[1], M. MARTINOVIC[2], T. J. FOUTZ[2];
[1]Biol. Sci., Univ. of Tennessee at Martin, Martin, TN; [2]Neurol., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Temporal Lobe Epilepsy (TLE) is a neurological condition characterized by abnormal electrical activity and seizures. TLE accounts for 60% of adult epilepsy cases, and approximately one-third of people with TLE continue to have seizures despite appropriate medications, highlighting the need for improved treatments. Animal models of epilepsy provide a pre-clinical platform to test novel therapies and to evaluate underlying mechanisms. However, high-throughput behavioral assessment and seizure classification in these models remain significant obstacles. Advancements in these fields would enhance pre-clinical testing and ultimately contribute to improved treatment options for TLE. In this study, an open-source AI-based software was used to classify the motion of TLE mouse models to better understand the motion patterns associated with seizures. *Methods:* Mouse model animals were generated by a unilateral intrahippocampal kainic acid injection to induce spontaneous recurrent seizures. Electrodes were implanted targeting the bilateral CA1 region of the hippocampus, and low- (1 Hz) or high-

frequency (150 Hz) electrical stimulation was applied periodically (1 minute on, 5 minutes off). EEG activity was recorded from bilateral cortical and hippocampal electrodes, while EMG was recorded for sleep staging. Seizures were identified from epileptiform spectral patterns. Simultaneous video was captured to characterize mouse movements at baseline and during seizures. An open-source, AI-based animal pose estimation tool (DeepLabCut) was used to analyze mouse motion and characterize seizure severity, by extracting video frames and manually labeling eleven anatomical landmarks. A ResNet-50 deep learning model was trained on these labeled frames to detect movement patterns. The trained model was then applied to videos of mice to differentiate between normal behavior and seizure activity. *Results:* Motion analysis identified distinct movement patterns during baseline and seizure activity. The ResNet-50 deep learning model accurately identified epochs of seizure activity. Seizure severity correlated with specific motion patterns, and the duration and frequency of abnormal movements. A comparison of motion analysis and EEG data was done to correlate seizure severity and traditional EEG measures. *Conclusions:* Understanding of the correlation between motion patterns and EEG data can enhance the scope of testing new therapies in temporal lobe epilepsy mouse models. This advancement in pre-clinical assessment may ultimately improve research efforts and lead to more effective treatments for temporal lobe epilepsy.

Disclosures: S.G. Hatchett: None. **M. Martinovic:** None. **T.J. Foutz:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.01/C25

Topic: B.09. Glial Mechanisms

Support: NIH NINDS 1R01NS136434
NIH NINDS 1R01NS137603

Title: A Lack of VRAC: The role of the astrocytic volume regulated anion channel in astrocyte function and neuronal excitability

Authors: *S. SRIRAM[1], P. PHAM[1], M. MIRI[2], K. CARSTENS[3], W. DEWING[1], D. K. BINDER[4], T. A. FIACCO[5];
[1]Univ. of California, Riverside, Riverside, CA; [2]USC, Los Angeles, CA; [3]Univ. of California Riverside, Riverside, CA; [4]Univ. of California Riverside Div. of Biomed. Sci., Riverside, CA; [5]Cell Biol. & Neurosci., UC Riverside, Riverside, CA

Abstract: Astrocyte volume changes feature in a variety of physiological processes but are especially impacted in disease states. Small increases in extracellular potassium concentrations that trigger moderate, astrocyte-specific swelling are sufficient to generate seizure-like activity in intact hippocampal tissue. We have demonstrated that astrocyte swelling constricts the extracellular space, increasing the effective glutamate concentration both within and outside of

the synapse which has a unique effect on neuronal excitability involving slow transmission but not point-to-point synaptic transmission (Walch et al., 2022). While astrocytes rely on several channels and transporters to adapt to changing environments, the volume regulated anion channel (VRAC) is of particular interest due to its potential role in regulatory volume changes, as well as in the release of glutamate during astrocyte swelling. Using a conditional knockout to ablate VRAC selectively in astrocytes (VRAC cKO), we set out to measure the impact of VRAC loss in long-term astrocyte volume regulation under different mechanisms of cell swelling in intact tissue. We then sought to determine the consequences of astrocyte VRAC cKO on acute volume-driven increases in neuronal activity in the form of both rapid and slow excitatory currents that are characteristic of epileptiform activity. We show that the effects of VRAC cKO are highly context dependent, based on both the time course and method of evoking astrocyte swelling. Surprisingly, we observed that, while VRAC cKO has little effect on astrocyte volume responses in elevated extracellular potassium, it does significantly modulate astrocyte swelling in hypoosmolar conditions without an obvious RVD. Future experiments will examine VRAC's role in astrocyte shrinking and neuronal and network excitability, as well as potential interactions between VRAC and other volume-related channels and transporters expressed by astrocytes.

Disclosures: S. Sriram: None. **P. Pham:** None. **M. Miri:** None. **K. Carstens:** None. **W. Dewing:** None. **D.K. Binder:** None. **T.A. Fiacco:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.02/C26

Topic: B.09. Glial Mechanisms

Support: NSF Grant 2117045
NSF Grant 2011220

Title: Exploring biomechanical determinants of glial phenotypic plasticity

Authors: E. J. CISNEROS, S. CHENG, *E. E. SERRANO;
Biol., New Mexico State Univ., Las Cruces, NM

Abstract: This exploratory study investigates the biomechanical properties of two cell lines of glial origin derived from *Rattus norvegicus*: CTX-TNA astrocyte (ATCC CRL-2006; RRID:CVCL_3670) and F98 glioma (ATCC CRL-2397; RRID:CVCL_3510). Here we present preliminary efforts to establish a cell culture model to examine how environment (stiffness) can affect cell fate as assessed by structure (morphology) and mechanical properties (Young's modulus; YM). Experiments are prompted by a body of evidence suggesting that properties of the tumor microenvironment, such as stiffness and extracellular matrix composition, can influence tumor growth and genetics. By comparing results from astrocyte and glioma cell lines grown in controlled environments, we hope to better understand the progression from ordinary

astrocyte to glioma, an aggressive cancer state. Cell lines were cultured in three conditions: 35 mm tissue culture dishes (TCD); CytoSoft® Rigidity 6-well plates with defined elastic moduli (0.2 kPa, 2.0 kPa, 16.0 kPa); and hydrogel (Geltrex™). Cell growth and morphology were assessed with light microscopy every 24 hours after seeding cells. In conventional TCD both lines grew as flat, monolayer cultures. CTX-TNA2 cells grown on CytoSoft® displayed changes in morphology that differed from TCD, such as cluster formation at all kPa, with larger cluster size on higher stiffness. In Cytosoft, F98 morphology differed from TCD. F98 cells formed loose aggregates, but did not show morphological differences at different kPa. In Geltrex™, CTX-TNA2 cells formed clusters that were smaller than those in CytoSoft® and with pronounced intercluster connections. In hydrogel, F98 formed clusters larger than those seen in CTX-TNA2. In all conditions CTX-TNA2 cells proliferated more slowly than F98 cells. In parallel, we also established an experimental framework to measure YM in live cells using the Bruker NanoWizard® 4 XP BioScience biological atomic force microscope (Bio-AFM). Preliminary force maps have been acquired from 2.5 μm x 2.5 μm areas of F98 cells cultured in TCD. Bruker JPK software was used to compute YM from force maps (8 X 8; n= 64). Values acquired from cell centers ranged from 0.05 - 1.7 kPa, while those from the lateral cell body ranged from 0.1 - 1.7 kPa. Future experiments will use BioAFM to determine cell biomechanical properties (YM) from both lines in the experimental environments. Results confirm that our conditions can direct the cells to alter structure in a line-specific manner. It is hoped that comparing the mechanical properties of cell lines in different environments may uncover mechanosensitive pathways that underlie astrocyte transition to a cancer state.

Disclosures: E.J. Cisneros: None. **S. Cheng:** None. **E.E. Serrano:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.03/C27

Topic: B.09. Glial Mechanisms

Support: United States Department of Defense Grant HT9425-23-1-0579
NIH Grant 3-R01-DK103808

Title: Comparing Glial Fibrillary Acidic Protein v. S100 Calcium Binding Protein Beta on identifying astrocytes impacted by sex and diet

Authors: *A. ZHAO[1], B. LEE[1,2], C. SCHULTZ[1], P. MENON[1], G. M. LEINNINGER[1,3]; [2]Physiol., [1]Michigan State Univ., East Lansing, MI; [3]Physiol., Neurosci. Program, East Lansing, MI

Abstract: The incomplete understanding of how the brain regulates energy balance prevents us from finding effective weight loss solutions. Astrocytes are a type of glial cell that have a critical role in feeding behaviors and energy balance. However, much is unknown about them. Previous

studies have shown that in male mice fed a high fat diet (HFD), the astrocytes in the arcuate nucleus (ARC) experienced reactive astrogliosis, potentially leading to obesity. Glial fibrillary acidic protein (GFAP) expression increases in reactive astrocytes, so GFAP is commonly used as an astrocyte marker. However, few GFAP-immunolabeled cells are detected in the brains of chow-fed mice, even though they still have many resident astrocytes. We hypothesize that there may be a better marker to visualize astrocytes during normal physiology (e.g. in chow fed mice) as well as in HFD-fed mice that develop diet-induced obesity. To test this, we immunolabeled GFAP and another protein that is expressed in astrocytes, S100 calcium binding protein beta (S100B), in brains of male and female mice fed chow diet or HFD. Specifically, we assessed expression in areas of the brain that contribute to ingestive behaviors, such as the arcuate nucleus (ARC), lateral hypothalamic area (LHA), lateral preoptic area (LPO), the paraventricular hypothalamic region (PVN), and the ventrolateral periaqueductal gray (vlPAG). Throughout all brain sections that we investigated, we found more S100B-immunolabeled astrocytes than GFAP-immunolabeled astrocytes. Additionally, all GFAP-labeled cells co-expressed S100B. These data suggest that S100B is preferable to GFAP to label astrocytes in mice fed chow or HFD.

Disclosures: A. Zhao: None. **B. Lee:** None. **P. Menon:** None. **G.M. Leinninger:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.04/C28

Topic: B.09. Glial Mechanisms

Support: R21 DA055781

Title: Akt2 regulates astrocytic nicotine responses

Authors: *A. LOMBARDI[1], M. GRIFFIOEN[2], C. BORSKI[1], M. BOWER[2], K. KASTENGREN[1], R. A. MILSTEAD[5], M. A. EHRINGER[6], J. A. STITZEL[3], C. HOEFFER, Jr.[4]; [2]Inst. for Behavioral Genet., [3]Inst. Behav Genet., [1]Univ. of Colorado Boulder, Boulder, CO; [4]Integrated Physiol., Univ. of Colorado Boulder, Lousiville, CO; [5]Linda Crnic Inst. for Down Syndrome, Univ. of Colorado, Boulder, Boulder, CO; [6]Inst. for Behavioral Genetics, Dept. of Integrative Physiol., Univ. of Colorado, Boulder, CO

Abstract: An improved understanding of nicotine neurobiology is needed to reduce or prevent chronic addiction, alleviate the detrimental effects of nicotine withdrawal, and increase successful cessation of use. Nicotine use genome-wide association studies (GWAS) suggest an astrocytic role for nicotine responses. In these studies, astrocyte activation was characterized in LPS and nicotine exposure paradigms using Sholl analysis. We found LPS and nicotine differences in astrocyte activation. We used primary mouse cortical astrocytes for our in vitro studies. We found that live imaging as a basis for astrocyte models is useful for studying the

dynamic nature of astrocytic activation. We used an Adeno-Associated Virus (AAV) to transfect astrocytes with mCherry for visualization. We found differences in instantaneous and average speed of astrocytes, suggesting that nicotine affects astrocytic motility. Previously, we found that AKT2 expression is restricted to astrocytes in mice and humans and may play a role in the nicotinic responses of astrocytes. Behavioral assessments of astrocyte-specific *Akt2* deficient mice were conducted, revealing the impacts of AKT2 loss on behaviors relevant to nicotine use and proving principle results for our ongoing GOI studies. Nicotine binds and activates two astrocytically expressed nicotinic acetylcholine receptors (NAChRs), α4β2 and α7. We found that both NAChRs play a role in astrocytic morphological changes induced by nicotine. Finally, we performed RNASeq experiments comparing nicotine- and LPS-mediated gene expression identifying robust differences between these two astrocytic stimuli. These results will allow for the identification of potential novel drug targets and will improve the current understanding of the astrocytic response to nicotine.

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Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.05/C29

Topic: B.09. Glial Mechanisms

Support: NSF Grant 2011220
NMSU Foundation

Title: Comparative Lipidomic Analysis of Glia Cell Lines

Authors: *G. V. OLAGUNJU[1], E. E. SERRANO[2];
[1]Grad. Program in Mol. Biol. and Interdisciplinary Life Sci., [2]Biol., New Mexico State Univ., Las Cruces, NM

Abstract: Healthy astrocytes are essential for the maintenance of normal brain function. Astrocytes that transition to a cancerous state can give rise to Glioblastoma multiforme (GBM), an aggressive and lethal brain cancer that is characterized by rapid proliferation and resistance to therapy. Understanding the metabolic processes that underlie this cellular transition is vital for improving GBM detection and treatment. In the body, brain lipid content is second to that of adipose tissue, highlighting the role of these organic compounds in membrane integrity, cognitive processing, memory formation, energy production, and inflammatory responses. Growing evidence suggests that dysregulation of lipid metabolism is a feature of glioma progression that supports increased proliferation and survival of malignant cells. This exploratory study aimed to develop a cell culture model for studies of astrocytes and gliomas

with cell lines derived from Rattus norvegicus: CTX-TNA astrocyte (ATCC CRL-2006; RRID:CVCL_3670; sex unknown) and F98 glioma (ATCC CRL-2397; RRID:CVCL_3510; male). F98 and CTX-TNA cells were cultured according to the manufacturer's protocols, then six replicates for each cell line were harvested at passage 3 and stored at -80oC. Samples were sent to the UC Davis West Coast Metabolomics Center for lipid extraction (MTBE method) and analysis with reverse-phase ultra-performance liquid chromatography (Waters Acquity UPLC CSH) coupled with mass spectrometry (Agilent 6530B QTOF; positive and negative-mode). Data files were curated for quality control with internal standards, and to impart functional significance prior to analysis with EXCEL, LipidMaps, and JMP Genomics software. Results showed that although both cell lines comprised the same number and type of lipids (5277), ~83% of lipid spectra were unidentifiable, underscoring a challenge of lipidomic analysis. Both lines comprised 891 identifiable lipids (e.g. phosphatidylcholines, triglycerides, sphingomyelins, fatty acids), and the same number and type of lipid were found within each class. Most spectra fell within fatty acid and glycerophospholipid classes in both lines. Closer scrutiny suggests potential differences in the abundance of a few lipids between the cell lines, an observation to be interpreted with caution due to technical limitations in quantitative lipidomics. Results support the notion that the cell lines share a common lipidome that may reflect their glial and species origin and that can be manipulated in future studies. Ongoing experiments will integrate transcriptomics and establish imaging protocols for lipid droplets using fluorescent probe.

Disclosures: G.V. Olagunju: None. **E.E. Serrano:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.06/C30

Topic: B.09. Glial Mechanisms

Support: NIH Grant DA057776
UNC Cowan Research Excellence Award

Title: Adolescent social isolation stress induces microglial phagocytosis and astrocyte atrophy in the nucleus accumbens and adult social behavior dysfunction in rats

Authors: *J. W. VANRYZIN[1], K. J. REISSNER[2];
[2]Dept. of Psychology and Neurosci., [1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Early life adversity during adolescence increases the risk of psychiatric disorders later in life. Although the underlying mechanisms remain unclear, stress can dysregulate microglia and astrocytes—glial cells essential for neural circuit development and function—which may contribute to long-term behavioral consequences. Here, we used adolescent social isolation as a rodent model of early life adversity, and hypothesized that social isolation stress affects later-life behavior by impairing glial function in the nucleus accumbens (NAc), a brain region responsible

for integrating social, reward, and stress information. Male and female Long Evans rats were isolated or group-housed from weaning until adulthood (P21-P56), after which, rats underwent social behavior testing and brains were collected for histological analysis of astrocytes and microglia. We found that isolated rats spent more time interacting with a novel conspecific compared to group-housed controls in a social interaction test. Moreover, social isolation decreased structural complexity of GFAP+ astrocytes within the NAc, and correspondingly increased in the percentage of phagocytic Iba1+/CD68+ microglia. These phagocytic microglia had significantly more inclusions that co-labeled with the astrocyte marker GLT-1, suggesting that phagocytic microglia may be "pruning" astrocyte processes, leading to astrocyte atrophy. To determine whether these behavior and cellular changes were due to the actions of stress hormones during social isolation, we isolated rats from P21-P56 and administered the glucocorticoid receptor antagonist, RU486 (or vehicle control) once daily throughout the isolation period. RU486 treatment prevented the isolation-induced increase in social interaction time, and rescued GFAP+ astrocyte structural complexity. Ongoing studies will determine the effects of RU486 on microglial phagocytosis. Together, these findings suggest that adolescent social isolation induces aberrant phagocytosis of astrocytes within the NAc, as a novel putative mechanism by which isolation-induced glucocorticoid signaling drives astrocyte atrophy and impairs social behavior.

Disclosures: J.W. Vanryzin: None. **K.J. Reissner:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.07/C31

Topic: B.09. Glial Mechanisms

Support: NRF Grant 2024-00348893
NRF Grant 2025-00553878

Title: Bergmann glia suppress Purkinje cell firing via interneurons

Authors: *J. LEE[1,2], S. KIM[1,4], M. JANG[1,3], Y.-S. LEE[1,2,3], S. KIM[1,2,3];
[1]Dept. of Physiol., [2]Neurosci. Res. Inst., [3]Biomed. Sci., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [4]Psychiatry, Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Bergmann glia (BG) are radial glial cells in the cerebellar cortex that have multiple functions. They have been shown to interact with Purkinje cells in several ways: they modulate synaptic inputs to Purkinje cells, regulate excitability through external potassium concentration, and directly affect Purkinje cells through neurotransmitter release. In this study, we genetically expressed hM3Dq in BG through GFAP-promoter-contained AAV virus. We showed that this BG-PC regulation is mediated by the NMDA receptor and GABAA receptor. Furthermore, using calcium imaging, we confirmed that BG activation induces MLI activation. Taken together, we

concluded that glutamate released from BG induces GABA release from MLI, which in turn inhibits PC activity. Our findings provide a cellular mechanism for understanding the role of BG in the modulation of neuronal activity in the cerebellum.

Disclosures: J. Lee: None. **S. Kim:** None. **M. Jang:** None. **Y. Lee:** None. **S. Kim:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

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Topic: B.09. Glial Mechanisms

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MOST110-2811-B-A49A-039(from Ministry of Science and Technology,Taiwan
AA031(from Ministry of Education (MOE) ,Taiwan)

Title: Specialized pro-resolving mediators regulate aryl hydrocarbon receptor activation in astrocytes

Authors: *S. CHANG, C.-C. HUNG, Y.-H. Y. LEE;
Physiol., Natl. Yang Ming Chiao Tung Univ., Taiwan/Taipei, Taiwan

Abstract: Specialized pro-resolving mediators (SPMs) are a family of bioactive lipids that promote inflammation resolution and maintain tissue homeostasis. SPMs are known to mitigate inflammation in peripheral tissues of chronic kidney disease (CKD) animal models. Our previous study showed that aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor, mediates CKD-associated astrocytic dysfunction and mental disorders via pathological ligand accumulation, which is ameliorated by AhR antagonist. Using molecular docking analysis, we identified that Resolvin E2 (RvE2), an eicosapentaenoic acid (EPA)-derived SPM, docks onto the AhR ligand-binding domain. This study investigated how RvE2 regulates AhR activation and modulates CKD-induced astrocytic dysfunction. First, in human astrocyte cultures, we found that RvE2 attenuated AhR activation induced by the endogenous uremic toxins kynurenic acid (KYNA) and indoxyl sulfate (I3S), but not by exogenous ligand TCDD, as measured by a dioxin-response element (DRE) luciferase reporter system. RvE2 also attenuated KYNA-induced AhR nuclear translocation and the expression of AhR target genes, including CYP1B1 (canonical pathway) and p21 (non-canonical pathway). Furthermore, knockdown of ChemR23, the membrane receptor of RvE2, did not affect the inhibitory effect of RvE2 on KYNA-induced AhR activation, suggesting that RvE2 may regulate AhR activity through a ChemR23-independent mechanism. We used a 5/6 surgical nephrectomy-induced CKD mouse model with intranasal RvE2 administration for 4 weeks. We found RvE2 attenuated CKD-induced expression of AhR target genes, while increasing AhR expression and reducing the expression of

its suppressor gene Ahrr in the mouse anterior cortex. RvE2 also reduced CKD-induced astrogliosis marker GFAP and proinflammatory cytokine TNF-α expression while preserving anti-oxidant protein HO-1 and alleviating CKD-induced anxiety. These results suggest that RvE2 modulates ligand-activated AhR in astrocytes and reduces astrogliosis and neuroinflammation caused by CKD. This conclusion highlights the therapeutic potential of RvE2 to improve brain function and may offer new insights for treating mental disorders in CKD patients.

Disclosures: S. Chang: None. **C. Hung:** None. **Y.Y. Lee:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.09/C33

Topic: B.09. Glial Mechanisms

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Title: Experience-dependent emergence of astrocyte-mediated dopamine regulation shapes prefrontal cognitive maturation

Authors: *J. ROYER[1], X. LI[1], W. NIU[1], M. GALANTE[1], P. BEZZI[2], G. DALLERAC[1]; [1]NeuroPSI, Saclay, France; [2]Univ. Lausanne, Lausanne, Switzerland

Abstract: The prefrontal cortex is essential for higher cognitive functions such as decision making, working memory, and social interaction, and these are tightly regulated by dopamine. Adolescence represents a critical period for the maturation of prefrontal circuits, and proper development of the prefrontal dopaminergic system is known to be essential for this process. However, the cellular mechanisms supporting tonic dopamine signaling during this window remain unclear. Recent evidence shows that the vesicular monoamine transporter VMAT2 is expressed in prefrontal astrocytes and contributes to dopaminergic homeostasis. We hypothesized that astrocytes regulate tonic dopamine levels through astroglial release, thereby shaping the development of prefrontal cognition. Given that prefrontal astrocytic dopamine function also develops during adolescence, we further postulated that this astroglial maturation process contributes to the critical-period refinement of prefrontal circuits. Using *ex vivo* two-photon imaging of GRAB-DA in acute prefrontal slices, we found that astrocytes release dopamine in a calcium-dependent spontaneous manner. This tonic dopamine release was strongly reduced in mice lacking VMAT2 selectively in astrocytes (aVMAT2cKO), confirming the key role of astrocytes in prefrontal dopamine dynamics. We then interfered with the prefrontal critical period by subjecting mice to post-weaning social isolation (PWSI), a model of neurodevelopmental vulnerability. PWSI significantly decreased astroglial VMAT2 expression and led to a ~30% reduction in spontaneous dopamine release. Behaviorally, PWSI mice

exhibited hallmark deficits including hyperactivity, impaired pre-pulse inhibition, and decreased social interaction. *In vivo* miniscope GRAB-DA imaging during social interaction tasks revealed a blunted dopamine signal in the prefrontal cortex of PWSI animals. Strikingly, virally inducing tyrosine hydroxylase expression in prefrontal astrocytes to enable de novo dopamine synthesis partially restored social behavior and sensorimotor gating. Similarly, chemogenetic activation of astrocytes partially rescued aspects of social and cognitive function in these mice. Together, these findings reveal that astrocyte-derived dopamine is a key regulator of prefrontal circuit maturation during adolescence, and suggest that impaired astroglial dopamine function may contribute to neurodevelopmental disorders such as schizophrenia.

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Poster

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Topic: B.09. Glial Mechanisms

Support: Fondecyt 1221508

Title: Lactate receptor activation in hypothalamic astrocytes leads to gliotransmission for surrounding neurons

Authors: *S. LOPEZ[1], V. AZÓCAR[2], R. C. ARANEDA[4], R. ELIZONDO[3], M. GARCIA ROBLES[5];
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Abstract: The hypothalamus is the primary local and peripheral signal integrator in the brain and home to a diverse population of cells in the arcuate nucleus (ARC), including orexigenic and anorexigenic neurons and glial cells, such as astrocytes and tanycytes. The bodys energy level is primarily determined by the metabolic interaction between glia and neurons through nutrient sensing; however, the underlying metabolic and molecular mechanisms have not been elucidated. Recently, we showed that activating the lactate receptor (HCAR1) by L-lactate, increases the electrical activity of anorexigenic pro-opiomelanocortin (POMC) neurons. Nevertheless, we discovered that HCAR1 is not expressed in POMC neurons or tanycytes, although it is expressed in hypothalamic astrocytes. However, the presence of slow inward currents (SICs) derived from gliotransmitters such as glutamate has not yet been evaluated in POMC neurons. Here, we investigated how HCAR1 activation in astrocytes by tanycyte-derived L-lactate induces the activation of POMC neurons. Hypothalamic astrocyte cultures expressing lactate receptor were transfected with specific siRNA-HCAR1 or siRNA-control and were

incubated with HCAR1-pharmacological agonist (3Cl-HBA) or L-lactate to quantify glutamate release. Next, we generated knock-down (KD) HCAR1 astrocytes, injecting adenovirus-associated in ARC to evaluate the calcium increase in astrocytes that also co-expressing GCaMP, as a response to perfusing a single tanycyte with glucose and subsequent lactate release. Additionally, we used transgenic POMC-Cre mice to analyze changes in the electrical activity of neurons close to KD-HCAR1 astrocytes by patch-clamp to identify SICs, in slices incubated with HCAR1 agonists. Interestingly, we found that L-lactate and 3Cl-HBA induce an increase in glutamate release from control astrocytes, compared to cultures transfected with siRNA-HCAR1. Tanycyte-derived L-Lactate also led to calcium increase in control astrocytes, unlike KD-HCAR1 astrocytes, in slice recordings. Finally, we successfully identified a decrease in the frequency of SICs in POMC neurons adjacent to KD-HCAR1 astrocytes, compared to control astrocytes in hypothalamic slices. Together, these results suggest that Lactate released by tanycytes as a glycolytic product acts on its receptor localized in hypothalamic astrocytes, increasing the electrical activity of surrounding POMC neurons.

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Poster

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Title: Deciphering the Nonlinear Astroglial and Neuronal Dynamics of Dopamine Release in the Prefrontal Cortex

Authors: *W. NIU[1], X. LI[1], S. MACH[1], J. ROYER[1], M. GALANTE[1], M. LERASLE[2], S. JACQUIR[1], G. DALLERAC[1];
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Abstract: The prefrontal cortex (PFC) is a critical cognitive center that plays an essential role in information integration, online processing and executive functions. It is well known that these prefrontal functions are strongly modulated by dopamine (DA). The release of this neuromodulator can be classified into two types: phasic and tonic release. Phasic DA release is triggered by the activation of neurons in the ventral tegmental area (VTA), leading to burst firing of neurons and the release of a large amount of DA. Tonic DA release on the other hand, is thought to result from the slow and continuous spontaneous firing of dopamine neurons.

Importantly, previous studies from our laboratory have shown that, in addition to neurons, astrocytes contribute substantially to tonic release of DA in PFC. Phasic release is characterized by a sharp increase in DA concentration within a short time, which can be detected using techniques such as voltammetry and amperometry. In contrast, the lower DA concentrations involved in tonic release make this process more difficult to study. Recently, a high-resolution dopamine-sensitive fluorescent probe, known as the GPCR-activation-based DA sensor (GRAB-DA), has been developed, enabling the observation of both types of DA release. Indeed, we found that GRAB-DA high-resolution two-photon microscopy imaging of living ex vivo brain slices, allows detection of spontaneous tonic DA release events. However, these discrete fluorescent signals appear randomly in time and space, and are accompanied by high levels of noise. Due to variability in signal magnitude, shape, frequency, location, and potential displacement or spread, these signals are extremely complex for spatiotemporal dynamics analysis. Existing detection algorithms still have significant limitations, especially when dealing with complex backgrounds or weak signals. To address this challenge, we designed a pipeline named DETECT (Dynamic Extraction and Tracking of Emitted Cellular Transients) to efficiently identify and analyze these signals and extract spatiotemporal features. Building on this, using the extracted fluorescent signals, in the present study we further developed a mathematical modeling of the nonlinear diffusion dynamics of DA within the prefrontal cortex to elucidate the contributions of neurons and astrocytes to DA diffusion. By using VMAT2 knockout mice (a transgenic line incapable of releasing dopamine from astrocytes), and combining chemogenetic and pharmacological approaches, we aim to separate DA release signals originating from neurons and astrocytes to investigate their respective contribution to DA dynamics in the PFC.

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Poster

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Title: Astrocytes in the Medial Prefrontal Cortex Regulate Social Approach Behavior

Authors: *E. KIM[1,2], H. DU[1,2], X. YU[2];
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Abstract: ABSTRACT Social behavior is a complex and essential function, often disrupted in neuropsychiatric disorders such as autism spectrum disorder (ASD), schizophrenia, and social anxiety. While neuronal mechanisms underlying social recognition have been extensively studied, the role of non-neuronal components, particularly astrocytes, remains underexplored. Astrocytes are known to modulate neuronal activity and synaptic function through calcium-dependent signaling and neurotransmitter homeostasis. In the medial prefrontal cortex (mPFC), a region critically involved in social decision-making and emotional regulation, astrocytes have been shown to influence excitatory/inhibitory balance and circuit output. To investigate the role of astrocytic calcium activity in social behavior, we used *in vivo* fiber photometry to monitor astrocyte Ca^{2+} dynamics during social interaction tasks. To assess the causal contribution of astrocytic activity, we employed genetic (CalEx) and chemogenetic (hM3Dq) strategies to suppress or enhance astrocyte Ca^{2+} signaling. These approaches allow us to explore how modulating astrocyte activity impacts distinct aspects of social interaction. Our ongoing work aims to further elucidate how astrocytes contribute to the processing of social cues and regulate circuit-level mechanisms. **KEYWORDS** Astrocytes, medial prefrontal cortex, social behavior, fiber photometry, Ca^{2+} imaging

Disclosures: E. Kim: None. **H. Du:** None. **X. Yu:** None.

Poster

PSTR432: Astrocytes: Biology II

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Topic: B.09. Glial Mechanisms

Title: Astrocytes in the Dentate Gyrus Differentially Modulate Pattern Separation, Pattern Completion and Fear Extinction

Authors: *M. WANG[1,2], M. KAMBALI[2], R. NAGARAJAN[2], J. LYU[2,1], X. YU[1,3], U. RUDOLPH[2,1,4];
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Abstract: Astrocytes play crucial roles in regulating neuronal circuits, but the behavioral consequences of manipulating astrocytes in the dentate gyrus (DG) are not well understood. To investigate the role of astrocytes in the DG, we inhibited the activity of DG astrocytes in adult C57BL/6J mice by expressing the calcium extrusion pump hPMCA2w/b (CalEx) from the astrocyte-specific GfaABC1D promoter, or chronically activated DG astrocytes by expression of

G_i- or G_q-coupled DREADDs from the same promoter. CalEx disrupts calcium-dependent astrocytic functions by removing calcium from astrocytes, while DREADDs typically activate astrocytes by stimulating G_i or G_q-coupled GPCR pathways. A vector expressing tdTomato was used as control. Viral constructs were stereotaxically injected into the DG hilus. After a three-week recovery and, for the DREADD experiments, deschloroclozapine (DCZ) administration, mice underwent behavioral testing, including the Morris water maze (MWM), latent inhibition to conditioned freezing, pre-pulse inhibition/startle habituation, pattern separation and completion tasks, fear extinction and various anxiety-related and social interaction tests. Mice with CalEx expression showed improved performance in the learning phases of the MWM compared to controls, enhanced performance in a contextual pattern separation task, and a deficit in pattern completion in the MWM. Mice with chronic G_i DREADD activation displayed a deficit in pattern separation and a fear extinction deficit specifically for between-session fear extinction, whereas mice with chronic G_q DREADD activation displayed an improvement in pattern separation and a minor deficit in within-session fear extinction. Our results indicate that inhibition or activation of astrocytic calcium signaling represent valuable tools for studying the role of DG astrocytes in behavioral tasks previously linked to DG principal neurons. We propose that astrocytes in the DG are essential components of DG neural circuits and are required for hippocampus-dependent cognitive functions.

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Poster

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Title: Investigating the role of MeA astrocytes in prosocial behavior

Authors: *K. SAMUEL[1], H. DU[2], X. YU[3];
[1]UIUC, Champaign, IL; [2]UIUC, Urbana, IL; [3]Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Prosocial interactions, defined as voluntary behaviors intended to benefit others, are essential for maintaining social cohesion across various species. One prominent example of

prosocial behavior is allogrooming, an affiliative touch often directed toward stressed conspecifics. Allogrooming plays a critical role in reinforcing social bonds, and its dysregulation is a hallmark of various neuropsychiatric disorders. One of the key brain regions responsible for this comforting behavior is the medial amygdala (MeA), which regulates prosocial behaviors including allogrooming. While most research has focused on the roles of GABAergic and glutamatergic neurons, much less is known about the contribution of non-neuronal cells, particularly astrocytes, to MeA-mediated allogrooming. Astrocytes tile the entire central nervous system, dynamically interacting with neurons and blood vessels, and actively regulate synaptic transmission, neural plasticity, and behavior through intracellular calcium (Ca^{2+}) signaling. In this study, used *in vivo* fiber photometry to monitor astrocytic Ca^{2+} signals in the MeA of freely behaving animals. We demonstrate that astrocytic Ca^{2+} activity in the MeA was selectively and temporally correlated with allogrooming, but not with other social behaviors, suggesting a specific role for astrocytes in modulating prosocial allogrooming interactions. To further understand underlying mechanisms, we analyzed gene expression profiles of MeA astrocytes, which revealed enriched expression of adrenergic receptors, indicating that norepinephrine (NE) may be a key neuromodulator in this region. We also observed a similar temporal correlation between astrocytic NE signaling and allogrooming behavior. Together these findings suggest a novel role for NE-astrocyte signaling in modulating allogrooming behavior and highlight astrocytic Ca^{2+} dynamics as a key component of MeA circuit function. Overall, this work provides new insight into the cellular mechanisms underlying prosocial behavior and expands our understanding of how astrocyte-neuronal interactions shape social brain function.

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Poster

PSTR432: Astrocytes: Biology II

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Title: Astrocytes encode complex behaviorally relevant information

Authors: *K. MERTEN[1], R. W. FOLK[1], D. DUARTE[1], C. PENG[2], A. NIMMERJAHN[1];
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Abstract: While neurons are generally accepted to underlie behavior and brain computation, the contribution of non-neuronal cells remains poorly understood. Among these, astrocytes—glial cells of the central nervous system—exhibit complex calcium-based signaling, yet the functional significance of this activity remains unclear. Here, we identify mechanistic links between astrocytes' spatiotemporally complex activity patterns, neuronal signaling, and behavior. Using in vivo calcium imaging during a visual detection task, combined with statistical and mechanistic modeling, and machine learning, we show that cortical astrocytes encode information about trial type, trial outcome, reward, performance level, and sensory features. Behavioral context strongly shapes astrocytic dynamics, as demonstrated by distinct response characteristics and context-dependent modulations in naïve versus trained conditions. Performance level influences response onset timing, while reward delivery also impacts amplitude and response offset, suggesting cell-intrinsic reward-related mechanisms that constrain astrocytic activity. Moreover, astrocyte responses are modulated by motor parameters such as run onset, duration, and proximity to the previous run. Our model indicates that astrocytes integrate signals related to locomotion, reward, and local neuronal activity to shape the timing and magnitude of their responses. These findings highlight astrocytes as active participants in behaviorally relevant neural processing, extending their role beyond homeostasis and metabolism.

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Poster

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Brain Research Foundation grant to X.Y.

Title: The role of astrocyte Ca^{2+} signaling in attention modulation

Authors: *H. DU[1,2], E. KIM[3,2], X. YU[4];
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Abstract: Attention is a fundamental cognitive process that enables selective focus on relevant stimuli while filtering out irrelevant information. This ability is essential for effective interaction with the environment, as it allows prioritization of sensory inputs aligned with current goals.

Understanding the mechanisms that govern both forms of attention is critical to decoding cognitive flexibility and control. The medial prefrontal cortex (mPFC) is a key integrative hub within attention networks, responsible for coordinating input from diverse brain regions and relaying information to downstream structures. Previous studies have demonstrated that mPFC plays a vital role in attention modulation. For example, parvalbumin-expressing interneurons in the mPFC coordinate local circuit activity during goal-directed attention. Furthermore, research has shown that altered mPFC function, such as in post-traumatic stress disorder (PTSD), disrupts top-down control and enhances bottom-up responses to threat, highlighting the importance of mPFC in mediating the attention process. While most studies have focused on neuronal activity, recent findings emphasize the contribution of non-neuronal elements—particularly astrocytes—to attentional regulation. As one of the most abundant resident cells tiling the entire central nervous system, astrocytes form intimate associations with neurons. Astrocytes express numerous transporters, channels and receptors that are essential to monitor, integrate and maintain neuronal activity. A key mechanism of such interactions is astrocyte Ca^{2+} signaling. Prior work has shown that activating striatal astrocytic Ca^{2+} signaling via Gi-GPCRs leads to hyperactivity and disrupted attention. However, the contribution of astrocytes to attention modulation in mPFC remains poorly understood. To address this question, we employed a chemogenetic strategy using designer receptors exclusively activated by designer drugs (DREADDs) to selectively activate Ca^{2+} signaling in mPFC astrocytes to investigate the role of mPFC astrocyte in the modulation of attention associated behavior.

Disclosures: H. Du: None. **E. Kim:** None. **X. Yu:** None.

Poster

PSTR432: Astrocytes: Biology II

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Title: Optogenetic cAMP production in mouse barrel cortex astrocytes induces PKA dependent long term potentiation

Authors: N. NGUM[1], L. SITJA ROQUETA[2], F. DELICATA[4], D. DALKARA[5], A. MOGLICH[6], M. MASANA[3], ***R. PARRI**[4];
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Abstract: Astrocytes are known to be involved in several from of synaptic plasticity with calcium dependent release of glutamate or D-Serine. Our previous work showed that LTP in

response to Theta burst stimulation in barrel cortex L4 to L2/3 synapse was blocked by BAPTA chelation of astrocyte calcium. In this study, using a genetically encoded photoactivated adenylyl cyclase (DdPAC) we investigated the possible role of increased astrocyte cAMP in synaptic plasticity at this synapse. Acute slices containing somatosensory cortex (350 μm) were cut in the coronal plane, and placed in MEA probe (MED 64, Alphamed). Stimulation was applied to electrodes underlying L4 and fEPSPs recorded at electrodes underlying L2/3. LTP . AAV-GFAP-DdPAC was activated by stimulation with 660nm LED. For comparison between LTP and baseline, Wilcoxon's test was used. Differences between two groups were determined by Mann-Whitney *U* test. For multiple comparisons to the same control, the one-way ANOVA non-parametric Kruskal-Wallis followed by Dunn's post hoc test was used. Light activation of DdPAC resulted in LTP of 187.90 ± 6.92% (n = 4), similar to theta based stimulated LTP of : 214.80 ± 5.56%, n = 4, p=0.057). DdPAC induced LTP induction was blocked by PKA inhibition. DdPAC-LTP and TBS-LTP induction were both blocked in the presence of MK801, an open channel blocker, and 5,7 DCK, an antagonist of the NMDAR Glycine/Serine site. DdPAC induced LTP was also seen in DdPAC expressing slices from $IP_3R2^{-/-}$ mice. We conclude that astrocyte cAMP elevation can induce somatosensory cortex LTP in an astrocyte calcium independent manner, but utilising the same neuronal LTP induction mechanisms as synaptic theta burst stimulation.

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Poster

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Title: Astrocytes phagocytose adult dendritic spines via calcium-dependent scramblase TMEM16F to regulate neuronal excitability and memory formation

Authors: *W.-J. KIM, W.-S. CHUNG;
KAIST, Daejeon, Korea, Republic of

Abstract: Astrocytes phagocytose excessive synapses to support proper circuit refinement, learning, and memory formation. In Alzheimer's disease (AD), microglia have been suggested to preferentially engulf hyperactive spines with elevated calcium levels, potentially by recognizing enhanced phosphatidylserine (PS) exposure on the synaptic surface. However, the neuronal mechanisms underlying this process, and the potential roles of astrocytes, remain elusive. Here, by generating conditional knockout mice lacking TMEM16F, a calcium-activated phospholipid scramblase, we found that neuronal TMEM16F mediates dendritic spine phagocytosis by

astrocytes. TMEM16F is localized to dendritic spines, and calcium influx promotes PS externalization on these spines in hippocampal neurons *in vitro* in a TMEM16F-dependent manner. Neuron-specific deletion of TMEM16F in excitatory neurons led to reduced astrocytic engulfment of spines and increased spine density in the adult hippocampus. Notably, only the numbers of mushroom and branched spines, morphologically mature spine types, were significantly elevated. As a result, excitatory neurons in TMEM16F knockout mice exhibited hyperactivation and significantly enhanced fear memory. Together, our work sheds light on how neuronal calcium signaling and TMEM16F-mediated PS exposure regulate spine phagocytosis by astrocytes to control neuronal excitability and shape behavior.

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Poster

PSTR432: Astrocytes: Biology II

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Title: Adenosine A2B receptors modulate the respiratory rhythm and lactate release during hypoxia

Authors: *K. RODRIGUES[1,2], A. BRAGA[2], B. H. MACHADO[3], A. G. TESCHEMACHER[4], S. KASPAROV[5], A. KIBE[6], N. E. DALE[7], A. V. GOURINE[2];
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Abstract: Astrocytes provide neurons with essential metabolic support under physiological conditions and also during metabolic challenges. Hypoxia, a major stressor, is sensed by astrocytes facilitating glycolysis and increasing lactate release. Release of adenosine is also strongly enhanced during hypoxia. Adenosine has been recently shown to modulate astrocyte metabolism via A2B adenosine receptors expressed by these glial cells, however, the significance of this signaling mechanism in the response to hypoxia and the control of breathing is not known. This study investigated whether adenosine acting at A2B receptors on brainstem astrocytes promotes lactate production under hypoxic conditions and modulates the respiratory activity. Adult C57Bl/6J (WT), Adora2b$^{flox/flox}$ (WT CTLR) and astrocytic A2B knockdown (KD) mice were used in this study. Brainstems were extracted under terminal anesthesia and sectioned into 250 μm coronal slices. Amperometric lactate biosensors were placed on the ventral brainstem slice to record lactate release. Hypoxia was induced by saturating aCSF with

nitrogen. Primary astrocytic cultures were transfected with the genetically encoded ATP GRAB sensor ($GRAB_{ATP}$) to record ATP/adenosine release in response to hypoxia. It was found that (i) in astrocyte cultures hypoxia induced significant release of ATP (by 82±28 nM, n=90 cells/9 biological samples, P=0.03); (ii) hypoxia-induced release of lactate was significantly reduced in brainstem slice preparations of A2B KD mice (n=6) compared to $Adora2b^{flox/flox}$ (n=8) and WT (n=3) animals (25.3±14.4 vs 68.7±56.0 vs 63.6±12.1, P=0.02). Application of A2 adenosine receptor antagonist ZM241385 (10 μM) led to a significant reduction of lactate release in all experimental groups and further decreased the amount of lactate release during hypoxia (2.4±11.9 vs 52.9±43.1 vs 34.8±5.97, P=0.003); and (iii) A2B KD (n=10) mice showed an increase in the respiratory rate when compared with the WT (n=13) animals at baseline conditions (231±49 vs 158±16 breaths per minute, P=0.0008). These results suggest that in the brainstem regions which generate the respiratory command, signalling via astrocyte A2B receptors modulate respiratory frequency at normoxic conditions and mediate hypoxia-induced release of lactate. These data highlight the complexity of metabolic signalling in the brainstem involving astroglial release of purines and lactate, which are hypothesized to provide metabolic support of neuronal function and maintain respiratory activity.

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Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.20/C44

Topic: B.09. Glial Mechanisms

Support: NIH-NIMH R01MH119355
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W911NF2110328

Title: Dopamine effects on hippocampal synaptic plasticity and learning through activation of astrocytes

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Abstract: Activity-dependent synaptic modifications, such as long-term potentiation (LTP) and long-term depression (LTD), are fundamental mechanisms that underlie learning and memory. While the molecular and cellular underpinnings of LTP have been extensively characterized at hippocampal glutamatergic synapses, growing evidence highlights the essential modulatory role of neuromodulators, particularly dopamine (DA), in shaping synaptic plasticity. Dopamine, a

critical neurotransmitter involved in motor control, reward processing, and higher-order cognitive functions, exerts its effects in the hippocampus primarily through D1-like and D2-like receptor families. Although DA's influence on neuronal circuits is well documented, its interaction with non-neuronal elements, such as astrocytes, is less well understood. Once considered merely supportive glial cells, astrocytes are now recognized as active participants in synaptic function, capable of bidirectional communication with neurons. Through dynamic changes in intracellular calcium signaling and the release of gliotransmitters, astrocytes can modulate synaptic strength and plasticity. In this study, we investigated the role of astrocytes in DA-mediated modulation of hippocampal synaptic plasticity and behavior. Using a combination of genetic and optogenetic approaches, we selectively manipulated astrocytic function in a cell type- and region-specific manner. Our results demonstrate that dopamine robustly enhances astrocytic Ca^{2+} signaling in the hippocampus, which in turn facilitates the induction of LTP and supports improved performance in memory tasks. These findings highlight a previously underappreciated mechanism by which dopamine engages astrocytic signaling pathways to regulate synaptic plasticity and behavior. By elucidating the astrocyte-specific contributions to DA-dependent neuromodulation, this work provides new insights into the cellular basis of learning and memory and opens potential avenues for targeting glial cells in cognitive and neuropsychiatric disorders.

Disclosures: R. Falcon Moya: None. **A. Araque:** None. **P. Kofuji:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.21/C45

Topic: B.09. Glial Mechanisms

Title: Relationship between astrocyte calcium and cerebral blood flow changes during awake-sleep cycles

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Abstract: Changes to free astrocyte calcium regulates local cerebral blood flow. Astrocyte calcium activity also changes during awake-to-sleep transitions, yet whether astrocytes help regulate the changes to cerebral blood flow that are observed when mice switch between awake, NREM and REM sleep states, remains unclear. Using in vivo two-photon fluorescence imaging in head-fixed, unanesthetized mice (10-12 weeks old), we monitored astrocyte calcium activity and diameter changes of penetrating arterioles in the retrosplenial or the barrel cortex to better understand how astrocyte calcium signals correlate with cerebral blood flow during awake-sleep cycles. We used a chronic cranial window approach with bone removal and brain nano-injection

of AAV2/5 to express jGCaMP8m to astrocytes (GfaABC1D promoter, 4 weeks recovery). To determine the physiological state, we continuously measured the size of the pupil and the movement of whisker during two-photon imaging, which, when assessed in combination, are a reliable indicator of the awake state (dilated pupil with active whiskers) and sleep (small pupil with less active whiskers). We commenced imaging when sleep pressure was highest (7-8am). Under this condition, each mouse regularly fell asleep after approximately 1-1.5 hours under the microscope, followed by periods of alternating wakefulness and sleep occurrences every few minutes. We found in the quiet awake mouse, the magnitude of penetrating arteriole diameter and endfoot Ca^{2+} changes were weakly correlated. However, vessel diameter and astrocytes calcium activity concomitantly increased when each mouse woke up, revealing a strong correlation, with no sex difference. Cross-correlation analysis of diameter versus endfoot Ca^{2+} revealed the strongest correlation was positive X=0 (no time delay). However, we failed to see the enhanced hemodynamic changes when the mouse falls asleep previously reported. Specific IP3R2 knockdown in astrocyte reduce the increase of the endfoot Ca^{2+} level and the magnitude of arteriole diameter from sleep to awake transitions partially. Together, our data demonstrate cerebral blood flow regulation during sleep to awake cycle is functionally linked with IP3R2 signaling in astrocyte.

Disclosures: F. Wang: None. **G. Hoang:** None. **G. Peringod:** None. **J. Sun:** None. **G.R. Gordon:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

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Program #/Poster #: PSTR432.22/C46

Topic: B.09. Glial Mechanisms

Support: FAPESP Grant 2021/12832-7
FAPESP Grant 2013/07699-0
CNPq Grant 303359/2022-6

Title: Context-dependent modulation of astrcytic calcium dynamics by mitochondria: a computational study

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Abstract: Mitochondria play a pivotal role in shaping intracellular Ca^{2+} dynamics in astrocytes and have been implicated in modulating synaptic plasticity. However, their precise influence on astrocytic Ca^{2+} signaling under varying input conditions remains poorly understood. Here, we present a biophysically detailed compartmental model of an astrocyte that incorporates mitochondrial Ca^{2+} handling mechanisms to investigate how mitochondrial dynamics shape the

astrocytic response to glutamatergic and dopaminergic inputs. In the model, mitochondria sequester cytosolic Ca^{2+} via the mitochondrial Ca^{2+} uniporter (MCU) and release it through the mitochondrial permeability transition pore (mPTP). Glutamate, modeled as a local Poisson input to distal compartments, and dopamine, a global Poisson input, stimulate IP_3 synthesis via PLC activation, triggering ER Ca^{2+} release. Glutamate also elevates intracellular Ca^{2+} through Na^{+}/Ca^{2+} exchange. We simulated two morphologies: a unipolar structure with 20 compartments and a bifurcated terminal morphology with 24 compartments. Mitochondria were included in every other compartment starting from the soma, excluding distal terminals. Our simulations show that concurrent glutamatergic and dopaminergic inputs increase intramitochondrial Ca^{2+}, generating oscillation amplitudes consistent with experimental observations. While mitochondrial compartments exhibit lower Ca^{2+} oscillation amplitudes, mitochondria enhance the global oscillation frequency (fCa^{2+}) by preventing Ca^{2+}-dependent IP_3 degradation. In the unipolar model, mitochondria suppress Ca^{2+} propagation and fCa^{2+} under low-frequency glutamatergic input without dopamine but enhance both metrics under high-frequency input or dopaminergic co-stimulation. In the bifurcated morphology, mitochondria located at the bifurcation inhibit Ca^{2+} signal propagation from terminal compartments and reduce fCa^{2+} in a dopamine-dependent fashion. These results highlight a context-dependent role for mitochondria in regulating astrocytic Ca^{2+} signaling, acting as a dynamic gate that suppresses responses to weak synaptic input in the absence of neuromodulators while amplifying responses to stronger or neuromodulator-enhanced inputs.

Disclosures: T. Ohno Bezerra: None. **A.C. Roque:** None.

Poster

PSTR432: Astrocytes: Biology II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR432.23/C47

Topic: B.09. Glial Mechanisms

Support: NIH Grant DA054449

Title: Scalable and adaptive features of astrocyte architecture

Authors: *P. CANTU[1], S. SRINIVASAN[3], Y. GODA[4], H. NEDELESCU[2];
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Abstract: Synapses are central to brain function, underpinning learning and memory. Astrocytes, glial cells that regulate synaptic transmission and plasticity, are integral to this process. Recent studies show that astrocyte morphology and function vary across regions, species, and in disorders like addiction that induce lasting changes. Understanding how astrocyte morphology influences synaptic function requires first examining their organization in terms of morphology and density, and how these adapt to local environments. We identified two features

of astrocyte organization. Using light microscopy and snRNA-seq in mammals, including humans and primates, we found that astrocyte densities are region-specific yet conserved across species. Second, tracings of GFP-filled mouse astrocytes and literature data revealed astrocytes to have a fractal, self-similar architecture, with branch lengths shortening from the soma following a Gaussian distribution. This conserved feature suggests a common adaptive algorithm across astrocytes that enables them to tune their branching (dense or sparse) via a single parameter to adapt to the local environment. Such an organization can optimize coverage versus cost across morphologies while remaining adaptable. Importantly, disruption of the principle in disorders like addiction underscores the functional significance of astrocyte morphology.

Disclosures: P. Cantu: None. **S. Srinivasan:** None. **Y. Goda:** None. **H. Nedelescu:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.01/C48

Topic: B.10. Neuro-Oncology

Support: Grant-DOI: 10.55776/P28909

Title: Sprouty2 is involved in chemoresistance of glioblastoma cells

Authors: *L. P. KLIMASCHEWSKI, B. HAUSOTT;
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Abstract: The Sprouty (SPRY) proteins are evolutionary conserved modulators of growth factor signaling. The four mammalian SPRY isoforms (SPRY1-4) are tumor suppressors or oncogenes depending on the cellular context. Among the four SPRY isoforms, SPRY2 is an oncogene in glioblastoma (GBM), and high SPRY2 expression correlates with reduced survival of GBM patients. In this study, we analyzed the effects of SPRY2 on chemoresistance of GBM cells in response to temozolomide, the standard cytotoxic chemotherapy for GBM, and compared it to the clinically less frequently used cisplatin in SPRY2-regulated GBM cells. In U251 cells with low endogenous SPRY2 levels, SPRY2 overexpression increased the cell viability, and this effect was further enhanced by overexpression of fibroblast growth factor receptor 1 (FGFR1). Temozolomide at 1 mM had a weaker cytotoxic effect on U251 cells than cisplatin at 30 µM. After treatment with temozolomide or cisplatin the cell viability of U251 cells overexpressing SPRY2 was still higher than of U251 cells with low endogenous SPRY2 levels. Together, our data demonstrate that SPRY2 overexpression not only increases the cell viability but it also enhances chemoresistance of GBM cells against temozolomide and cisplatin. Funding: Austrian Science Fund (FWF), Grant-DOI: 10.55776/P28909

Disclosures: L.P. Klimaschewski: None. **B. Hausott:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.02/C49

Topic: B.10. Neuro-Oncology

Support: PRIN-Next Generation EU P2022EZ9LN to FB and FC
Ricerca Corrente and 5x1000 grants to FB and EC

Title: Pharmacological and genetic approaches toward new therapies for glioblastoma

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Abstract: Glioblastoma (GBM) is a type of brain tumor with very high genetic, epigenetic, and molecular heterogeneity, which represents the principal cause of malignancy and diagnosis/cure failure. GBM cells alter the physiology of the tissue that surrounds the tumor mass, resulting in brain tumor-related epilepsy (BTRE). Due to the high resistance of GBM cells to conventional therapies, this study explores novel therapeutic strategies. One approach focuses on direct membrane disruption, leading to rapid and irreversible cell death, bypassing intracellular resistance mechanisms. We developed a pharmacological approach focused on membrane poration based on BV-1, a novel membrane-targeted photoswitchable conjugated compound that integrates into cell membranes and, upon light activation, induces controlled optoporation and cell death, showing efficacy *in vitro* in GBM cells and *in vivo* in a GBM mouse model. The study also investigates gene therapy approaches targeting GBM-induced neuronal hyperexcitability associated with glioma-related epilepsy. We propose a novel onco-epileptic treatment using a modified closed-loop chemo-optogenetic probe, a pH-sensitive inhibitory luminopsin (pHIL). The first prototype of this tool demonstrated the ability to selectively counteract the hyperexcitability of epileptic neurons and reduce seizure activity in preclinical in vivo models of epilepsy, owing to its closed-loop pH responsiveness. We engineered an optimized version to enhance its BRET/FRET efficacy, while concurrently validating a glioblastoma-associated epilepsy mouse model to study tumor-related seizures.

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Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

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Program #/Poster #: PSTR433.03/C50

Topic: B.10. Neuro-Oncology

Support: ATENEA-Bogotá
Universidad Nacional de Colombia-Bogotá

Title: Targeting GPR55 and PINK1 in glioblastoma models using Cannabis sativa and Piper nigrum derivates

Authors: A. TURIZO SMITH[1,2], K. L. VELASQUEZ MENDEZ[3], L. GARCIA RAIRAN[1], J. ARIAS[1], J. MARIN LOAIZA[1], *G. ARBOLEDA[4];
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Abstract: Glioblastoma multiforme (GBM) is a highly aggressive brain tumor with poor prognosis and limited treatment options. Given the growing interest in the endocannabinoid system and mitochondrial quality control as therapeutic targets, we investigated the antitumor potential of phytochemicals from *Cannabis sativa* and *Piper nigrum*, focusing on GPR55 and PINK1 modulation. Using a combined *in silico and in vitro approach*, we performed molecular docking with AlphaFold models of human PINK1 and GPR55, revealing high binding affinities for cannabichromene (CBC), cannabigerol (CBG), cannabidiol (CBD), and piperine. *In vitro* assays were conducted in GBM cell lines (U87MG, T98G, CCF-STTG1) and primary patient-derived cultures to assess cytotoxicity, apoptosis, and mitochondrial function. Cell viability (MTT, WST, LDH), apoptosis (V/EB-AO), and mitochondrial membrane potential (TMRE/MitoTracker) assays showed that cannabinoids and *Piper nigrum* derivates induce dose-dependent cytotoxicity and mitochondrial depolarization. Pharmacological inhibition altered these effects, supporting a mechanistic link. Gene and protein expression analyses confirmed changes in PINK1 and other markers. Notably, *Piper nigrum* derivates modulated cannabinoid-induced cytotoxicity in a cell-line dependent manner, suggesting complex interactions within mitochondrial and cannabinoid signaling. These findings indicate that phytochemicals targeting GPR55 and PINK1 disrupt GBM cell survival through mitochondrial dysfunction and highlighting their translational potential. Further studies are warranted to validate these interactions and explore combinatorial therapies exploiting these natural compounds.

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Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

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Topic: B.10. Neuro-Oncology

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RF1NS100440
P50DC019900
R21DC021557

Title: Glioma-induced reorganization of somatosensory representations

Authors: D. L. DAVIS[1], L. B. HINKLEY[2], V. JAYABAL[3], A. M. FINDLAY[1], *C. L. DALE[5], S. HERVEY-JUMPER[4], S. S. NAGARAJAN[1];
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Abstract: The functional integration between glioma cells and neural circuitry has shifted the perception from passive to active when it comes to glioma activity. Their coupling allows for induced changes such as modification of dendritic spikes and inhibitory synapses, which can contribute to disruption in typical activity and function, Disruption within these regions can lead to hyperexcitability in the surrounding tissue, specifically in low frequency evoked responses. To evaluate the hyperexcitability and representational changes, we apply a neural decoding and encoding approach to somatosensory evoked field (SEF) representations of the hand and lip regions of primary somatosensory cortex.
Somatosensory responses to pneumatically driven stimuli (~256 pulses of 140ms duration @ 2Hz) delivered to the lip and second (D2) digit of the hand were recorded in 174 presurgical tumor patients using a 275-channel whole-head MEG system (CTF MEG; Coquitlam, BC). Tumors included astrocytomas (n=74), oligodendrogliomas (n=65), and glioblastomas (n=35). Of these cases, n=65 were designated as infiltrating somatosensory cortex based on the presence of tumor voxels extending along the Rolandic cortex (via T2-FLAIR MRI and MEG dipole localization). The remaining 109 cases were classified as non-infiltrating. MEG sensor data was epoched, filtered (0.5-50 Hz) and SEF decoding between the hand and lip stimulation was performed using a sliding window classifier with 5-fold cross-validation and bootstrapping. Encoding strength was quantified via the first principal component (PCA) of SEFs observed on the sensor array, z-scored to pre-stimulus baseline for each subject.
Decoding accuracy between hand and lip was high across all tumor types, peaking at 87% for infiltrating and 85% for non-infiltrating tumors. However, tumor infiltration significantly reduced decoding accuracy between hemispheres, for all tumor patients and for all tumor subtypes regardless of histopathology. In contrast, neural encoding of the amplitude and timing of the evoked responses did not differ by infiltration or stimulus location, but did show slight hemispheric differences across Astrocytoma and GBM for Lip and Hand SEF respectively. These results demonstrate that glioma-infiltrated cortex causes reorganization of somatosensory

representations. However, these neural representation changes cannot be accounted for non-specific hyperexcitable responses in tumor-infiltrated cortex.

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Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.05/C52

Topic: B.10. Neuro-Oncology

Title: Identifying small molecule modulators of TREM2 for glioblastoma treatment

Authors: *E. HUIE[1], G. KIZEEV[2], K. BHAT[2];
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Abstract: Background: Glioblastoma (GBM) is an aggressive and incurable malignant tumor of the central nervous system, characterized by resistance to treatment and poor prognosis. Therefore, there is a critical need to develop novel therapeutics for GBM. Increased infiltration of myeloid cells is frequently observed in GBM. Expression of Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) in myeloid cells has been found to mediate phagocytosis of gliomas, suggesting a potential tumor-inhibitory role in GBM. Moreover, TREM2-based therapeutics may serve as a promising immunotherapeutic target for GBM. **Methods:** We developed 105 TREM2 modulators via *in silico* drug design. Generative Adversarial Networks (GANs), trained on docking, absorption-distribution-metabolism-excretion-toxicity (ADMET), and molecular dynamics data were used to generate novel small molecule compounds targeting TREM2. These compounds were screened using an HMC3 TREM2-overexpressing cell line. Lead candidates were further evaluated using phagocytosis assays. **Results:** Utilizing mTOR activation as a surrogate for TREM2 activity, we found numerous activators and inhibitors of this pathway. Phagocytosis assays are ongoing, which will uncover novel regulators of TREM2. **Conclusion:** This study has successfully identified novel TREM2-targeting small molecule compounds for GBM using GAN-based *in silico* design and *in vitro* validation. Future studies will focus on evaluating the efficacy of these lead compounds in a TREM2-expressing mouse model.

Disclosures: E. Huie: None. **G. Kizeev:** None. **K. Bhat:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

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Program #/Poster #: PSTR433.06/C53

Topic: B.10. Neuro-Oncology

Title: Nkcc1 mediated chloride regulation is necessary for glioma progression

Authors: *C. NAVA GONZALES, S. KRISHNA, S. HERVEY-JUMPER;
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Abstract: Glioblastoma's incurability is primarily attributed to the migratory behavior of glioma cells, which complicates surgical interventions. Neuron-glioma interactions have been shown to influence tumor cell migration, with enhanced functional connectivity in these networks correlating with poorer prognoses. We hypothesize that knocking down NKCC1 can restore physiological chloride regulation, thereby reducing glioma cell migration and network connectivity. To investigate the role of NKCC1-mediated chloride regulation in glioma migration and network connectivity, we conducted chloride imaging on glioma cells with either intact or shRNA-mediated knocked-down NKCC1 in both monoculture and glioma-neuron co-culture systems. This approach allowed us to assess how neuron-glioma interactions influence chloride regulation. Additionally, we injected GBM cells with either intact or knocked-down NKCC1 into organotypic human and mouse brain slices, using live cell imaging to monitor tumor cell migration and connectivity. Our findings revealed that in monoculture, glioma cells with NKCC1 knocked down exhibited a significant reduction in intracellular chloride concentration. In co-culture, neurons paired with NKCC1-deficient glioma cells also showed significantly lower chloride concentrations compared to those paired with NKCC1-intact glioma cells. Furthermore, NKCC1-deficient tumor cells demonstrated decreased migration and fewer intertumoral connections. These results indicate that NKCC1 is crucial for glioma-induced chloride dysregulation and tumor cell invasion. Knocking down NKCC1 presents a potential therapeutic target for inhibiting glioma progression by diminishing tumor cell migration and network connectivity. This study uncovers a promising therapeutic vulnerability in glioma treatment, suggesting that targeting NKCC1 could be a viable strategy to impede glioma progression and improve clinical outcomes.

Disclosures: C. Nava Gonzales: None. **S. Krishna:** None. **S. Hervey-Jumper:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

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Program #/Poster #: PSTR433.07/C54

Topic: B.10. Neuro-Oncology

Support: CBF2023-2024-1982

Title: Study of ROS production by TiO_2-Folic Acid-ZnPc nanoparticles for PDT applications in glioblastoma cells

Authors: *E. ORTIZ[1], M.-R. MANRIQUEZ[3], S. RODRIGUEZ[4], C. RODRÍGUEZ-PÉREZ[2], J. GUSTAVO[5];
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Abstract: One option for finding a different therapeutic treatment for glioma cancer is photodynamic therapy, which uses a photosensitizer as a key component to produce reactive oxygen species (ROS) that kill cancer cells. Semiconducting titanium dioxide (TiO_2) is a prominent photosensitizing agent for PDT because it produces a large amount of ROS under UV light irradiation, and it is inert and highly biocompatible. In the present work, an in vitro study was carried out on the production of ROS by irradiating a nano-photosensitizer-based TiO_2-folic acid-ZnPc with UV light. The nanoparticles were obtained by combining TiO_2 with folic acid (as a targeted ligand) and then loading ZnPc molecules. The resulting nanoparticles were characterized using microscopy, spectroscopy and thermogravimetric techniques. The in vitro study involved irradiating the TiO_2-FA-ZnPc nano-photosensitizer with UV light over time to produce singlet oxygen ($^1O_2$), which reacted with the colored 1,3-diphenylisobenzofuran (DPBF) reagent to form a colorless product. LN18 and C6 cells were incubated with TiO_2-FA-ZnPc for 24 h, then irradiated with UV light, and next, the cell viability was determined using the MTT assay. Characterization probes showed that the obtained nanoparticles were between 10 and 100 nm in size and had an anatase-amorphous mixed structure with thermal stability. Indirect measurement of singlet oxygen indicates color disappearance over time, forming a colorless solution into 16 min. After the irradiation, cell viability decreased in a dose-dependent manner.

Disclosures: E. Ortiz: None. **M. Manriquez:** None. **S. Rodriguez:** None. **C. Rodríguez-Pérez:** None. **J. Gustavo:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

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Program #/Poster #: PSTR433.08/C55

Topic: B.10. Neuro-Oncology

Title: Synthetic Biology-Based Activation of ROS-Sensitive dTRPA1 Channel for Apoptosis Induction in Glioblastoma

Authors: *N. DANG;
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Abstract: Glioblastoma (GBM) is the most aggressive primary brain tumor, marked by poor prognosis and resistance to conventional therapies. Elevated reactive oxygen species (ROS) levels in GBM contribute to tumor progression but also create a therapeutic vulnerability. We

propose a novel synthetic biology approach using the ROS-sensitive *Drosophila* TRPA1(A)10b (dTRPA1) ion channel to convert elevated ROS from a pro-survival to a pro-death signal by triggering sustained intracellular calcium influx and apoptosis in GBM cells. To explore the apoptotic potential of dTRPA1 in response to ROS, we first assessed basal ROS levels in six established GBM cell lines (D54, LN18, LN229, U251, U373, and U87) using DCFDA and HyPer-3 assays. U251 exhibited the lowest ROS levels, comparable to normal fibroblasts, while D54 showed the highest. Based on these profiles, we generated Tet-on inducible dTRPA1(A)10b-expressing cell lines in both D54 (ROS-high) and U251 (ROS-low) to evaluate calcium influx, apoptosis, and cell viability. *In vivo*, dTRPA1 will be introduced into orthotopic xenografts, and expression will be induced via doxycycline. Tumor growth and survival along with apoptotic markers will be monitored over time. Given the innate heterogeneity of cancer cell populations at the genetic, transcriptional, and protein expression levels, as well as the ability of cancer cells to evolve over time, we anticipate that subpopulations of glioblastoma will exhibit both intrinsic as well as acquired low levels of ROS, and therefore, be treatment resistant. To target ROS-low and resistant subpopulations, we will combine dTRPA1 expression with ROS-inducing agents such as temozolomide (TMZ) or ionizing radiation (IR). This strategy will be tested in standard cell lines, orthotopic xenografts and patient-derived xenograft (PDX) models. This project proposes a novel approach to targeted cancer therapy that uses a recombinant ROS-sensitive, calcium-permeable channel, to initiate apoptosis in diverse glioblastoma cell populations, potentially overcoming resistance and improving treatment efficacy.

Disclosures: N. Dang: None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.09/C56

Topic: B.10. Neuro-Oncology

Support: NIH grant 5R01NS122163-04

Title: Characterization of human olfactory ensheathing cells as delivery vehicles for cancer gene therapy in an hiPSC-derived brain-glioma organoid model

Authors: J. HAN[1], E. ROUMIEH[1,2], N. BRAVO-VASQUEZ[1], H. MNATSAKANYAN MOVSESYAN[1,2], T. XIAO[1], P. REPITON[1], H.-D. TRAN[1], E. NORENBERG[1], C. VAINE[1], C. BADR[1,2], K. BREYNE[1,2], G. SCANGAS[2,3], X. O. BREAKEFIELD[1,2], ***C. BRAGG**[1,2];
[1]Massachusetts Gen. Hosp., Charlestown, MA; [2]Harvard Med. Sch., Boston, MA;
[3]Massachusetts Eye and Ear Infirmary, Boston, MA

Abstract: Olfactory ensheathing cells (OECs) are hybrid glial cells enriched in the olfactory bulb and nasal mucosa. Previous studies have reported that OECs traffic through the brain and

accumulate at sites of tumorigenesis, suggesting their potential to serve as vehicles for delivering therapeutic transgenes to CNS neoplasms. Here we further characterized these properties in mucosal OECs, which can be obtained from patients and engineered for personalized cell-based therapies. Nasal biopsies were obtained from de-identified tissue from human subject volunteers and dissociated to generate mixed cultures of mucosal cells. The isolation protocol was validated in parallel by culturing olfactory bulbs dissected from mice. Immunostaining of the human mucosal (hM) cultures revealed cells expressing established markers of OECs, including p75NGFR, S100beta, N-Cadherin, and k-Cadherin. To further evaluate the composition of the mixed cultures, RT-PCR was performed on RNA isolated from hM and mouse olfactory bulb cells using species-specific primers which confirmed the expected expression patterns of OEC marker genes. We then evaluated the migratory capacity of hM cells in a cortical organoid (CO)-based bioassay. COs were seeded with MGG8 glioblastoma stem cells labeled with mCherry to create assembloids. After 7 days, the assembloids were co-cultured with GFP(+) hM cells for an additional 7, 14, or 21 days. Sections of the assembloids were imaged at these timepoints to track migration of the two cell types in the biomass. By 7 days, mCherry(+) MGG8 cells had invaded the assembloid with sparse cells still visible at the periphery, and by 28 days showed significant expansion within the tissue core. GFP(+) hM cells also migrated into the assembloids, and after 21 days approximately 62% of the population showed strong co-localization with the MGG8 cells. To test the ability of these cells to deliver a therapeutic transgene, hM cells were transduced with a lentiviral vector encoding CD-UPRT and GFP and injected into brains of nude mice implanted with CT-2A glioma cells. After 7 days, mice received daily injections of 5-fluorouracil (5-FC) which is converted by CD-UPRT to toxic metabolites. Survival curves demonstrated that untreated mice exhibited decreased viability compared to hM-implanted mice treated with 5-FC. Taken together, these results establish a pipeline for assaying the capacity of hM cells to deliver investigational therapeutics to human cancer cells of interest within a human brain tissue model, prior to performing larger studies *in vivo*.

Disclosures: J. Han: None. **E. Roumieh:** None. **N. Bravo-Vasquez:** None. **H. Mnatsakanyan Movsesyan:** None. **T. Xiao:** None. **P. Repiton:** None. **H. Tran:** None. **E. Norenberg:** None. **C. Vaine:** None. **C. Badr:** None. **K. Breyne:** None. **G. Scangas:** None. **X.O. Breakefield:** None. **C. Bragg:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.10/C57

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

Support: NIH R37CA275954
NIH K08NS118138

Title: Cd19-directed car t cells preferentially infiltrates the meninges and brain parenchyma

Authors: *Y.-T. TSAI[1], H.-K. LIM[1], L. PARK[1], M. BOSE[1], J. GUST[1,2];
[1]Norcliffe Fndn. Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA;
[2]Neurol., Univ. of Washington, Seattle, WA

Abstract: Neurotoxicity is a common complication of CD19-directed chimeric antigen receptor (CAR) T cell therapy for leukemia and lymphoma. About 40% of patients experience acute cognitive disturbances, seizures, and/or cerebral edema. The mechanism of neurotoxicity may include cytokine-mediated injury and brain capillary plugging by circulating leukocytes, as we have previously shown, but there is also concern that CAR T cells specifically attack nontumor targets in the brain. Our goal was to determine whether CAR T cells infiltrate the brain in a targeted way, or whether they are simply surveilling the brain like normal T cells. To answer this question, we used non-tumor bearing immunocompetent balb/c mice treated with 10 million CAR T cells and 10 million mock transduced T cells that don't express CAR, exposing both to the same cytokines. The CAR T cells target normal CD19+ B cells, which is sufficient to induce toxicity even in non-tumor bearing mice. We assessed T cell infiltration on day 6, during peak of toxicity. Immunolabeled brain sections showed significantly more CAR T cells infiltrating the parenchyma than mock T cells (n=3 mice). As CAR T cells encounter their targets, they proliferate more than mock T cells. To determine whether CAR T to mock ratio in the brain only reflects their relative abundance, or if CAR T cells are preferentially infiltrating the brain, we conducted flow cytometry on whole blood, spleen, brain with leptomeninges, and dura, and compared the ratios. We found that CAR to mock T cell ratios in the brain and leptomeninges are 6 fold higher than in spleen (n=6 mice, p=0.0001) and 3.48 fold higher than in the blood (p=0.0011). To longitudinally track the behavior of T cells in the brain and meninges, we used in vivo two photon imaging. We found the majority of extravasated and actively migrating CAR T cells in the dura and leptomeninges, with far fewer deeper in the parenchyma. No mock T cells were seen in parenchyma (n=3 mice). At all time points, there were significantly more extravasated CAR T cells than mock T cells. Interestingly, B cells were completely depleted 3 days post cell administration (n=2 mice), but CAR T cells remain in the meninges past 56 days. Taken together, these results show that CD19-directed CAR T cells are more likely to infiltrate the brain parenchyma and meninges than mock T cells, even though both are exposed to the same cytokine milieu. CAR T cells remain in the meninges long after target depletion. Further work will explore potential cues and consequences of CAR T cells migrating into the parenchyma and meninges, as well as therapeutic implications for treating CNS autoimmunity and malignancy.

Disclosures: Y. Tsai: None. **H. Lim:** None. **L. Park:** None. **M. Bose:** None. **J. Gust:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.11/C58

Topic: B.10. Neuro-Oncology

Support: AACR-Novocure (20-60-62-WILL)
AACR-Novocure (24-60-62-HUEL)
UO1 CA223976
DRSN Revision (3UO1CA223976-03S1)
T32NS121721

Title: Investigating the therapeutic potential of tumor treating fields efficacy and molecular mechanisms in radiation-resistant glioblastoma

Authors: *T. SCHANEL[1], R. PANDIT[1], J. ANDERSON[1], A. JONES[2], P. HICKS[1], A. HJELMELAND[1], C. WILLEY[1];
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]St. Jude, Memphis, TN

Abstract: Glioblastoma (GBM) remains the most common and lethal malignant primary brain tumor in adults, with a 3-year survival rate of less than 5% despite aggressive treatment strategies involving maximal surgical resection, radiation, temozolomide (TMZ), and Tumor Treating Fields (TTFields). Resistance to therapy, particularly radiation, is driven in part by brain tumor-initiating cells (BTICs), contributing to treatment failure. Although TTFields—a noninvasive modality delivering low-intensity, intermediate-frequency alternating electric fields—has shown clinical benefit, its mechanisms of action, particularly in radiation-resistant GBM, are poorly understood. Most GBM survival and multi-omic studies focus on the pretreatment *de novo* tumor. Therefore, we aimed to understand the effects and mechanisms of action of TTFields to identify actionable targets in more clinically relevant models for TTFields treatment by specifically using our radiation therapy selected PDX. To address this, we employed patient-derived xenograft (PDX) models, and their acquired radiation-resistant derivatives generated via serial *in vivo* radiation exposure in immunodeficient (nu/nu) mice. PDX-derived BTICs were cultured on 22mm coverslips under serum-free, geltrex-adherent conditions and treated with TTFields using the Novocure inovitro™ system. TTFields were administered at 200kHz in a cooling incubator (18ºC) to maintain 37ºC sample temperature in the ceramic well plates of the device. Growth was assessed at 72 hours using a 25% glutaraldehyde 5% crystal violet staining solution and absorbance quantification. Additionally, we performed kinomic profiling (PamChip peptide arrays) 4 hours post TTFields administration to characterize molecular alterations associated with treatment. TTFields significantly reduced cell growth in radiation-resistant PDX-derived BTICs (Jx14P-RT and X1465P-RT), indicating significant efficacy despite radiation-resistance. Through kinomic analysis we identified altered signaling in both parental and radioresistant PDX indicating possible TTFields mechanisms of action, as well as biomarkers for sensitivity or resistance. We plan to use the Novocure inovivo™ system to further assess TTFields efficacy of radioresistant GBM PDXs in *in vivo* models, and leverage FDA-approved, blood-brain barrier-penetrant kinase inhibitors to enhance the efficacy of TTFields therapy.

Disclosures: T. Schanel: None. **R. Pandit:** None. **J. Anderson:** None. **A. Jones:** None. **P. Hicks:** None. **A. Hjelmeland:** 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.; Institution receives research funding from AACR-Novocure (to A.B.H and C.D.W). **C. Willey:** 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.; Institution receives research funding from AACR-Novocure (to A.B.H and C.D.W).

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.12/C59

Topic: B.10. Neuro-Oncology

Title: The oncogenic potential of psychedelics

Authors: *T. RUNEBERG[1], A. VIRENQUE[3], M. BAROK[1], V. LE JONCOUR[2], E. CASTREN[4];
[2]Neurosci. Ctr., [1]Univ. of Helsinki, Helsinki, Finland; [3]HiLIFE/ Neurosci. center, [4]Neurosci. Ctr., Helsinki Univ., Helsinki, Finland

Abstract: Background: Beyond their recreational use, psychedelic compounds such as LSD and psilocybin are gaining increasing attention for their potential to treat psychiatric disorders and alleviate depressive symptoms in cancer patients. Recent findings from our lab show that psychedelics bind with high affinity to TrkB, enhancing brain-derived neurotrophic factor (BDNF) signaling by acting as positive allosteric modulators and promoting neuroplasticity in the adult brain. However, TrkB is a well-established oncogene, and is expressed in tumors outside the central nervous system (CNS), questioning the unsupervised use of highly potent compounds targeting TrkB. This exploratory project focuses on assessing if TrkB activation by psychedelics might accelerate cancer progression. **Methods**: For human metadata analyses, the iCAN Discovery Platform (Finland, N= 3209) and The Cancer Genome Atlas Program (TCGA, U.S.A., N=5415) were used to assess TrkB expression level in all cancers. Mechanistic studies of upregulation and activation of TrkB and other receptor tyrosine kinases were performed in human cancer cell lines. Protein activation by phosphorylation was determined in immunoprecipitated samples, with LC-MS/MS employed for protein ID confirmation. Biological activity of TrkB activation by psychedelics was verified using cell viability (MTT assay) and cell morphology measurements. **Preliminary results**: *In silico* profiling confirmed that brain, breast and lung cancers upregulate TrkB compared to other cancers and non-neoplastic control tissue. Next, we analyzed the JIMT-1 HER2+ human breast cancer cell line and identified robust TrkB expression. High levels of BDNF release in cell culture medium (~60 pg/mL) suggested autocrine/paracrine TrkB activity. In line with this, high BDNF (100 ng/mL) supplementation enhanced JIMT-1 proliferation, while TrkB receptor antagonist ANA-12 (5 μM) reduced cell viability. LSD (100 nM) did not affect cell proliferation or viability but induced notable morphological changes. Specifically, cell phenotypes shifted from a rounded shape to highly branched and elongated forms, suggestive of enhanced cell adhesion and motility. **Conclusions**: Our data indicate that psychedelics might evoke an oncogenic response in breast cancers. We are currently assessing whether the phenotypic cell shift is associated with increased malignancy and/or metastatic potential *in vivo*. These preliminary findings raise concerns about psychedelic

exposure in patients with TrkB-positive tumors and underscore the need for caution and risk-benefit assessment when considering psychedelic use in oncology patients.

Disclosures: T. Runeberg: None. **A. Virenque:** None. **M. Barok:** None. **V. Le Joncour:** None. **E. Castren:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.13/C60

Topic: B.10. Neuro-Oncology

Support: FRB680064/0240 (NSRF)

Title: Bioactive Fractions of Phyllanthus taxodiifolius Beille Inhibit Glioma Cell Invasiveness via Disruption of Cytoskeletal and Adhesion Pathways.

Authors: *J. KWANTHONGDEE, T. VICHAYAPRASERTKUL;
Princess Srisavangavadhana Fac. of Medicine, Chulabhorn Royal Acad., Bangkok, Thailand

Abstract: Gliomas are the most prevalent and aggressive malignant primary brain tumors, characterized by their capacity to infiltrate surrounding brain tissue. Cellular processes such as migration and adhesion are key drivers of glioma progression and recurrence, largely mediated by cytoskeletal remodeling and upregulation of adhesion proteins including vimentin and N-cadherin. In our previous study, a crude extract from *Phyllanthus taxodilfolius*, a medicinal plant native to Southeast Asia, was shown to inhibit glioblastoma progression; however, the specific bioactive constituents responsible remained unidentified. This study aimed to isolate the active compounds from the methanolic extract and elucidate their mechanisms of action in glioma cell invasiveness. Sequential fractionation of the extract was performed using flash column chromatography, followed by eight rounds of purification with silica gel and Sephadex LH-20. At each round, biological activity was systematically screened using a transwell migration assay in C6 rat glioma cells to identify and prioritize the most active subfraction for further purification. The final active subfraction was evaluated for its impact on cytoskeletal dynamics and adhesion-related proteins. Microtubule structure and dynamics were analyzed via live-cell imaging and immunofluorescence. Expression levels of N-cadherin, vimentin, were assessed by Western blot and functionally confirmed by immunofluorescence. Focal adhesions and actin cytoskeleton organization were visualized using confocal microscopy. The active subfraction significantly suppressed glioma cell migration, disrupted microtubule integrity, and downregulated N-cadherin and vimentin without inducing cytotoxicity. These results support the therapeutic potential of *P. taxodiifolius*-derived bioactive compounds as promising candidates for anti-cancer therapy.

Disclosures: J. Kwanthongdee: None. **T. Vichayaprasertkul:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.14/Web Only

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Enhanced sensitivity of grade IV glioblastoma multiforme from the U-87 cell line to temozolomide by inhibiting sigma-1 receptor overexpression with high-dose haloperidol encapsulated in nanoparticles

Authors: *J. G. DE LA CRUZ GARCÍA[1], R. ECHAVARRIA[2], Y. K. GUTIERREZ-MERCADO[3];
[1]Clin. department, Univ. of Guadalajara, Tepatitlan de Morelos, Mexico; [2]Guadalajara, ; [3]Univ. de Guadalajara - Ctr. Universitario Los Altos, Guadalajara.

Abstract: Glioblastoma multiforme grade IV is the most common and most aggressive malignant brain tumor of all primary tumors of the central nervous system in adults. This tumor is characterized by very accelerated cell proliferation, a very high capacity to infiltrate underlying tissues and resistance to currently available therapies such as temozolomide (Fang, 2015). The treatment of this neoplasia combines 3 approaches such as neurosurgical resection , radiotherapy and chemotherapy. It has an incidence of 3.2 cases per 100,000 inhabitants worldwide per year, and of every 100 cases, 39 are alive after one year and only 5 are alive after 3 years, with resistance to temozolomide (first-line chemotherapy) being one of the main problems in the treatment of these patients (Louis, 2021). Overexpression of the sigma-1 receptor has been observed in glioblastoma cells and has been identified as a highly relevant tumor pathophysiological factor, since this receptor is related to the regulation of the endoplasmic reticulum, calcium homeostasis, tumor proliferation, and poor apoptosis function. The sigma-1 receptor acts primarily as a chaperone, so its inhibition could significantly decrease the proliferation mechanisms of glioblastoma multiforme and thus increase the efficacy of temozolomide (Fang, 2015). Haloperidol is an anticonvulsant drug that is an antagonist of the sigma-1 receptor, but at high concentrations it is toxic to neurons (Shi, 2023). It is thought that, when administered at high doses in a controlled-release system using nanoparticles that serve as capsules, they would react directly on the sigma-1 receptor, improving the sensitivity of U-87 cells to temozolomide, but without becoming neurotoxic (Orza, 2013). These findings are expected to reinforce the hypothesis that inhibiting the sigma-1 receptor will help reduce glioblastoma cell resistance by disrupting their cell death resistance mechanisms. Furthermore, it will be seen whether encapsulating haloperidol in nanoparticles will help find an innovative way to deliver neurotoxic drugs (Papadopoulos, 2020).

Disclosures: J.G. de la Cruz García: None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.15/C61

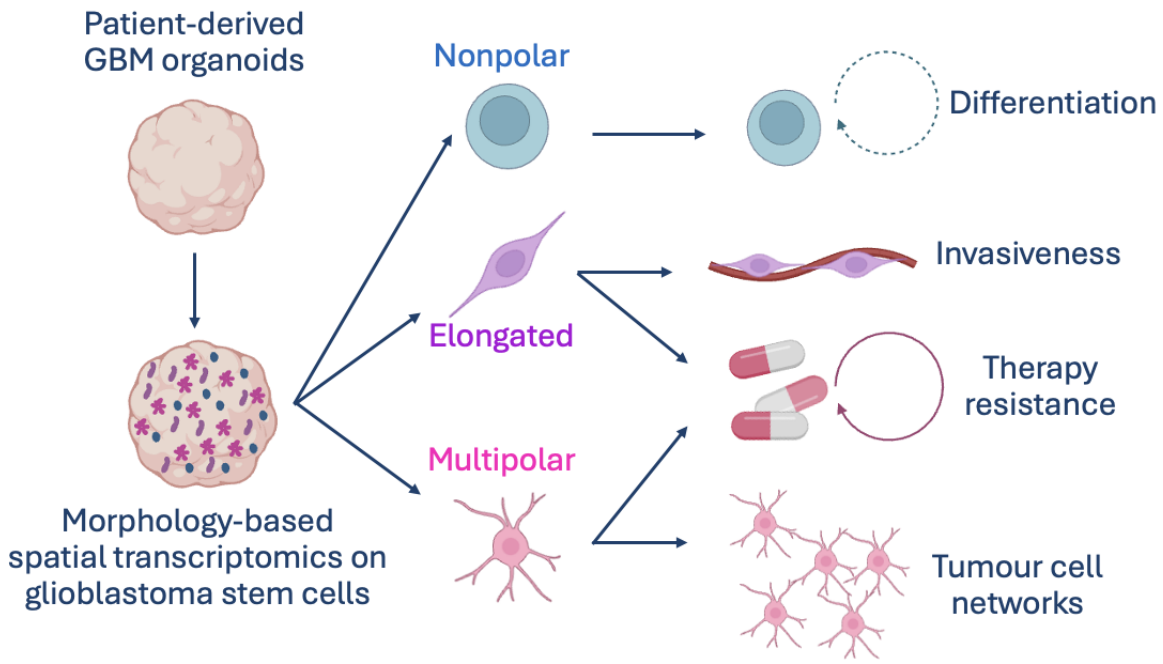
Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: AIRC Grant MFAG 2022 ID 27157 (NK)
Gilbert Family Foundation Award #: 923004 (NK)
Funds of the Human Technopole (NK)

Title: Glioblastoma stem cell morphology is linked to clinically relevant functions

Authors: *C. BARELLI, N. KALEBIC;
Human Technopole, Milan, Italy

Abstract: Glioblastoma (GBM) is an aggressive primary brain tumor characterized by cellular heterogeneity, invasiveness, therapy resistance and recurrence. These features are driven by a population of glioblastoma stem cells (GSCs) which reactivate neurodevelopmental pathways. Specifically, GSCs resemble a type of neural progenitor cells called basal radial glia, where morphology is key to mediate their proliferative and migratory functions. Leveraging on this similarity, we investigated the morphological heterogeneity of GSCs and its link with GBM invasiveness and chemoresistance. Using primary tissue samples and patient-derived organoids, we identified three GSC morphoclasses - nonpolar, elongated, multipolar - and developed a custom spatial transcriptomics approach to profile individual morphoclasses. While nonpolar cells showed signatures of differentiation and lower proliferation, elongated and multipolar cells displayed features of the GBM progenitor-like cell state and chemoresistance. Functional studies in patient-derived organoids and primary samples showed that multipolar cells form functional resistant networks with mitochondrial interplay, while elongated GSCs are associated to the vasculature and are invasive. Importantly, the genes underlying resistance in elongated GSCs are tightly linked to invasiveness and angiogenesis, suggesting a common molecular mechanism. Our data show a direct link between GSC morphology and clinically relevant functions, opening the path to morphology-informed therapies in GBM.



Disclosures: C. Barelli: None. **N. Kalebic:** None.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.16/C62

Topic: B.10. Neuro-Oncology

Title: Rapid discovery of neutralizing nanobodies against an emerging immune checkpoint receptor CD200R1

Authors: N. POLEWACZYK[1], D. LUO[1], K. ZOU[1], H. YANG[1], M. L. SMITH[1], Y. YU[1], S. MAHAPATRA[1], K. HUANG[1], V. PAI[3], S. S. HINMAN[3], J. PERREAU[3], M. HO[1], B. A. ZABEL[1], ***C. L. HSIEH**[1,2];
[2]Antibody Discovery, Engin. & Characterization, [1]Curia Biologics, Hayward, CA; [3]Bruker Cell. Analysis, Emeryville, CA

Abstract: Nanobodies are a growing modality in antibody therapeutics with FDA-approved treatments driving demand for VHH (variable heavy domain of heavy chain) discovery. Nanobodies, or VHH, are single-domain antigen recognition fragments derived from heavy-chain-only camelid antibodies with favorable features to overcome limitations of larger antibodies. Their small size (~15 kDa) facilitates tissue penetration; typically, longer CDR3

enables targeting challenging epitopes; and their single, thermostable domain simplifies engineering and production. Using a robust single B cell antibody discovery and characterization platform, we rapidly identified a diverse set of 31 potent and high-affinity llama antibodies against huCD200R1, an emerging therapeutic immune checkpoint target (nanobody EC_{50}= 390 pM to 4.4 nM against huCD200R1; K_D= 1.9 nM to 850 nM against huCD200R1). CD200R1 is an inhibitory cell surface receptor highly expressed on microglia, macrophages, and dendritic cells. CD200R1 and its ligand, CD200, regulate microglia activation in the CNS. Importantly, epitope-binning experiments and IC_{50} assays demonstrated that most of the discovered nanobodies (17) neutralized ligand binding to CD200R1 (IC_{50}= 200 pM - 108 nM). These small, human and cyno cross-reactive CD200R1 neutralizing nanobodies possess ideal properties for preclinical testing to promote CNS tumor clearance via reversal of tumor-resident myeloid-derived suppressor cell activity.

Disclosures: **N. Polewaczyk:** A. Employment/Salary (full or part-time): Curia Biologics. **D. Luo:** A. Employment/Salary (full or part-time): Curia Biologics. **K. Zou:** A. Employment/Salary (full or part-time): Curia Biologics. **H. Yang:** A. Employment/Salary (full or part-time): Curia Biologics. **M.L. Smith:** A. Employment/Salary (full or part-time): Curia Biologics. **Y. Yu:** A. Employment/Salary (full or part-time): Curia Biologics. **S. Mahapatra:** A. Employment/Salary (full or part-time): Curia Biologics. **K. Huang:** A. Employment/Salary (full or part-time): Curia Biologics. **V. Pai:** A. Employment/Salary (full or part-time): Bruker Cellular Analysis. **S.S. Hinman:** A. Employment/Salary (full or part-time): Bruker Cellular Analysis. **J. Perreau:** A. Employment/Salary (full or part-time): Bruker Cellular Analysis. **M. Ho:** A. Employment/Salary (full or part-time): Curia Biologics. **B.A. Zabel:** A. Employment/Salary (full or part-time): Curia Biologics. **C.L. Hsieh:** A. Employment/Salary (full or part-time): Curia Biologics.

Poster

PSTR433: Neuro-oncology, Therapeutics and Innovation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.17/C63

Topic: G.04. Neuroimmunology and Neurovirology

Title: Spatial proteomics investigation of biomarker dynamics in astrocytoma and glioblastoma using COMET^{TM} platform

Authors: *A. E. KALYUZHNY[1], K. TRUEMAN[2], J. HAGEN[3], A. OLIVER[3], E. THRASH[2]; [1]Bio-Techne, Minneapolis, MN; [2]; [3]Minneapolis, MN.

Abstract: Biomarkerdynamics are important when analyzing different grades of astrocytoma.Different grades exhibit variations in biomarker expression levels, which canprovide insights into disease progression and patient outcomes. Understandingthe dynamics of biomarkers within different grades of astrocytoma can help intailoring personalized treatment strategies for patients based on theirmolecular profiles. Biomarker dynamics can reveal the underlying mechanisms ofthis heterogeneity and aid in identifying specific molecular subtypes

thatrespond differently to treatments. We have conducted a multi-omics study usingLunaphore COMET platform and analyzed the spatial distribution of differentbiomarkers in normal human brain, in astrocytoma (grade 1-3) and in glioblastoma(grade 4) using Lunaphore HORIZON image analysis software. The tissuebiomarkers were detected using primary antibodies against these targets:Gelsolin, FAP, MAP2, CD8, TIM3, Ki67, Col4A1, Fibronectin, CD11c, SMA andHLA-DR. We have discovered co-localization of CD8 with TIM3, profoundupregulation of Gelsolin in astrocytoma grade III in which HLA-DR and Ki67 weredownregulated. We observed strong upregulation of FAP in glioblastoma grade IVbut not in grade III. The expression levels of Fibronectin, Col4A1, SMA, CD11cwere moderate and comparable throughout different grades of glioblastoma. MAP2expression appeared the weakest in every grade of glioblastoma. Our studyprovides valuable information that can be used for comprehensive disease characterization,predicting patient outcomes, devising personalized treatment approaches, andadvancing research efforts towards improving the management of this aggressivebrain cancer.

Disclosures: A.E. Kalyuzhny: None.

Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.01/C64

Topic: C.01. Brain Wellness and Aging

Support: 5R01AG076835-04

Title: Investigating the interface between epigenetics and metabolism underlying memory formation in the adult and aging brain

Authors: J. A. PICONE[1], M. WOOD[2], T. L. FETTERLY[4], J. E. CHILDS[1], A. RODRIGUEZ[5], V. ALIZO VERA[3];
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Abstract: Emerging evidence indicates that there are chromatin modifications that decrease accessibility of memory-associated genes, resulting in dysfunction of synaptic plasticity that occur as we age and is exacerbated in the context of Alzheimer's disease (AD). The dysregulation of the epigenome may occur due to transcriptional regulators and enzymes becoming uncoordinated in the aging brain. In unpublished work, the Wood lab has recently identified the transcriptional regulator, Calcium Responsive Transactivator (CREST) as a potential keystone coordinator of epigenetic and metabolic mechanisms necessary for memory processes, making it a point of vulnerability in age-associated epigenetic malfunction. Genomic analyses revealed *Crest* expression decreases in human AD affected brain tissue, and altered

Crest expression correlates with longitudinal changes in AD pathology. CREST levels also correlate with age-associated memory deficits, showing declines across the mouse lifespan in the hippocampus and in AD model mice. Our preliminary data show that manipulating CREST bidirectionally affects synaptic plasticity and long-term memory. Pilot experiments investigating CREST function have used the object location memory (OLM) task to examine just long-term memory formation, but not the relatively new Objects Updating Location (OUL) task to examine memory updating. The OUL task builds on the OLM by further examining memory updating, which is a memory process that specifically becomes impaired with aging. Aging (18 mo) C57Bl/6 mice exhibit a severe impairment in memory updating in this task, even when they have normal long-term memory formation. To assess the transcriptional profile of this memory deficit, dHPC tissue was collected from adult (2mo) and aged (18mo) mice, that went through the OUL task during memory consolidation (Day 9) and memory updating (Day 10) (plus homecage controls) and then processed through snRNAseq. Further, manipulation of CREST function via Y397 point mutations induces bi-directional effects of hippocampal long-term potentiation (LTP) and long-term memory (LTM) in the OLM task. Additionally, our data shows that CREST may orchestrate the regulation of acetyl-CoA levels, via binding to the competing acetyl-CoA regulatory enzymes *Acss2* (increases acetyl-CoA) and *Acc1* (decreases). Acetyl-CoA is a necessary component in histone acetylation, which itself is reduced in the aging brain. Therefore, CREST appears as a potential key point of vulnerability in the dyscoordination of epigenetic mechanisms that are implicated in age-associated cognitive decline and memory deficits.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.02/D1

Topic: C.01. Brain Wellness and Aging

Support: VA R&D Grant B3123-I / I01RX003123
VA R&D Grant B78071 / 1I01RX000502-01A

Title: Repetitive TMS as a Therapeutic for a Rodent Model of Natural Cognitive Aging

Authors: *N. M. WESTON[1,2], K. S. KLIPPEL[2,1], D. PLANT[1], G. HWANG[2,1], J. MURPHREE[2], S. HEJAZI[2], C. E. DOWNIE[2,1], J. HOU[1,2], A. KUMAR[3,1], P. K. BOSE[1,2,4]; [1]Brain Rehabil. Res. Ctr., North Florida/South Georgia Veterans Hlth. Syst., Gainesville, FL; [2]Anesthesiol., [3]Neurosci., [4]Neurol., Univ. of Florida, Gainesville, FL

Abstract: Age related cognitive decline is a natural process that can occur independently from any neurological disease or disorder. Despite cognitive aging becoming an increasingly prevalent occurrence with longer lifespans, there are still limited advancements in development of

treatments. Repetitive transcranial magnetic stimulation (rTMS) is a form of non-invasive neuromodulation that can induce cellular depolarization within the brain and lead to an upregulation of plasticity mechanisms. In this study, we administered rTMS in aged female Fischer rats with various degrees of cognitive decline. Animals were either considered early aged (17 mo. old; n = 9) or late aged (24 mo. old; n = 15), and were randomly divided into rTMS treatment or control. All animals performed a baseline Morris Water Maze (MWM) memory task and received MRI scans prior to any treatment intervention. Following the baseline measurements, the rTMS treatment group received rTMS therapy once a day every other weekday for the duration of three weeks. The targeted region for rTMS therapy was the hippocampus due to its essential involvement in learning and memory, with the hypothesis that treated rats would have a preservation or enhancement in cognitive abilities compared to controls and this would be supported by enhanced hippocampal activity. At the conclusion of all rTMS therapy, the animals repeated the MWM memory task and MRI scans, in addition to positron emission tomography (PET) imaging to characterize differences in metabolic activity and hippocampal electrophysiology to determine neuroplasticity contributed from the rTMS therapy. This study found that animals that received rTMS therapy showed a significant increase in their performance on learning and memory tasks compared to the controls. Interestingly, when taking multiple parameters into consideration for the MWM task, the late aged (24 mo. old) animals showed worse performance overall compared to early aged (17 mo. old); however, they showed the largest improvement on memory performance after treatment. On the PET scans conducted after rTMS treatment was completed, both rTMS groups showed significantly higher metabolic activity in the hippocampus and fMRI data showed enhanced hippocampal connectivity. The findings from this study serve as an establishment for using the translationally feasible approach of noninvasive brain stimulation techniques to aid in function in an aging brain.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.03/D2

Topic: C.01. Brain Wellness and Aging

Support: PAPPIT IN220120

Title: Effect of repetitive transcranial magnetic stimulation on working memory in aged rats under a chronic unpredictable mild stress model

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Abstract: Currently, the therapeutic effect of repetitive transcranial magnetic stimulation (rTMS) has been observed in the cognitive improvement of patients diagnosed with depression, who exhibit deficits in attention and memory processes similar to those observed in aging individuals. Moreover, memory impairment represents one of the main concerns in older adults due to its impact on quality of life and social functioning, since memory is a malleable system influenced by aging and certain diseases, including stress exposure. In this study, our aim was to assess the impact of rTMS on either the slowing or enhancement of working memory. We used male Wistar rats (n = 8) that were subjected to two periods of the Chronic Unpredictable Mild Stress (CUMS) model at 6 and 11 months of age. Following the stress procedures, the animals underwent the elevated T-maze test to evaluate behavioral performance before and after rTMS. Half of the subjects received real rTMS stimulation for 15 days (1 Hz) while the other half received sham stimulation (sham rTMS). After the final stimulation period, coronal brain sections were collected from the hippocampus (HPC) and stained with cresyl violet to assess cytoarchitectural changes. All statistical analyses were conducted using R Studio 4.3.2, with significance thresholds set at *$p < 0.05$. The effect of the induced stress was associated with a significant decrease in body weight in group Control with respect to group CUMS + rTMS and CUMS + sham rTMS ($p = 0.004$). A one-way ANOVA revealed no significant difference in latency to the goal arm between groups (rTMS vs. sham). Additionally, the Wilcoxon rank-sum test showed the same result between the pre-rTMS and post-rTMS phases in exploration time. Also, the exact McNemar test indicated no significant difference in the proportion of correct responses between pre- and post-test in the sham group, nor in the rTMS group. The CUMS induced disorganization in the hippocampus. The rTMS seemed to prevent the disorganization caused by stress. The results suggest that neither real rTMS nor sham treatment significantly modified the performance evaluated by the elevated T-maze test of old rats compared with data obtained when they were adult (6 months). We observed a trend in the CUMS+rTMS group toward a reduction in error frequency from the first behavioral assessment to the last, indicating an improvement in working memory that could be attributed to brain plasticity effects. The absence of significant effects may be related to sample size limitations. Therefore, it is possible that rTMS exerts a modulatory effect on cognitive processes such as working memory under conditions of prolonged stress.

Disclosures: V.R. Pille-Gutiérrez: None. **J. Vargas:** None. **M. Gómez-Chavarín:** None. **L. Verdugo-Diaz:** None.

Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.04/D3

Topic: C.01. Brain Wellness and Aging

Title: Neural Efficiency in Action: Participants with the Most Cortical Volume Reduction Show the Largest Behavioral Gains After 10 Weeks Task Switching Practice

Authors: *Y. SHUAI[1], W. ZHAO[1], M. DAHL[2], H. YOO[1], K. NASHIRO[1], C. CHO[1], A. J. KIM[1], P. NASSERI[1], J. MIN[1], P. CHOI[1], H. LEE[1], K. ALEMU[1], N. NG[3], J. THAYER[4], M. MATHER[1];
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Abstract: Cognitive training is often assumed to increase brain volume to support behavioral improvements. However, emerging evidence suggests that practice-related cognitive gains may also coincide with selective cortical reduction during the training process.We investigated whether 10 weeks of a cued rule-task switching practice was associated with structural brain changes in older adults using the Lumosity game Ebb and Flow. Ebb and Flow is a computerized cognitive training task that requires switching between responding to the direction of movement or the orientation of a stimulus, depending on its color, thereby measuring cognitive flexibility and task-switching ability. Participants (N = 55, age range = 50-70) completed daily practice and underwent structural MRI scans before and after the 10-week training period. Task performance improvement (game score) was quantified, and cortical volume change in 34 bilateral regions was extracted via FreeSurfer. Partial correlations were computed between post-training cortical volumes and post-task performance, controlling for baseline cortical volume and baseline task performance. After controlling for multiple comparisons using False Discovery Rate (FDR) correction, significant negative associations were observed in two right hemisphere regions: the lingual gyrus ($r = -0.42$, $p = 0.034$) and the lateral occipital cortex ($r = -0.429$, $p = 0.034$). Both regions are critically involved in visual attention, object recognition, and task cue processing—cognitive processes essential to the Ebb and Flow task, which requires rapid cued task-switching in response to changing visual features. Additional regions, including the right superior parietal lobule, right rostral anterior cingulate cortex and left supramarginal gyrus, showed similar negative associations at uncorrected thresholds. These findings reveal a counterintuitive but consistent pattern: participants who showed the greatest behavioral gains also exhibited the most pronounced cortical volume reductions in task-relevant areas. This negative correlation between behavioral improvements and cortical volume change may indicate a phase of synaptic refinement and circuit-level reconfiguration, aligned with structural efficiency and use-dependent plasticity models. Rather than indicating structural preservation or global growth, these findings support a model of training-dependent optimization—where performance improvements emerge through selective structural streamlining for greater efficiency.

Disclosures: Y. Shuai: None. **W. Zhao:** A. Employment/Salary (full or part-time): Full Time. **M. dahl:** A. Employment/Salary (full or part-time): full-time. **H. Yoo:** A. Employment/Salary (full or part-time): full-time. **K. Nashiro:** A. Employment/Salary (full or part-time): full-time. **C. Cho:** A. Employment/Salary (full or part-time): full-time. **A.J. Kim:** A. Employment/Salary (full or part-time): full-time. **P. Nasseri:** A. Employment/Salary (full or part-time): full-time. **J. Min:** A. Employment/Salary (full or part-time): full-time. **P. Choi:** A. Employment/Salary (full or part-time): full-time. **H. Lee:** A. Employment/Salary (full or part-time): full-time. **K. Alemu:** A. Employment/Salary (full or part-time): full-time. **N. Ng:** A. Employment/Salary (full or part-

time): full-time. **J. Thayer:** A. Employment/Salary (full or part-time): full-time. **M. Mather:** A. Employment/Salary (full or part-time): full-time.

Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.05/D4

Topic: C.01. Brain Wellness and Aging

Support: R01AG047972
R01AG029523
R01NS106711
R01NS106702

Title: Age-related carotid and vertebral blood flow lateralization differences in relation to working memory

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Abstract: Neurocognitive aging studies aim to identify the neural mechanisms underlying cognitive decline in aging. Previous studies have demonstrated that cerebral blood flow (CBF) is integral for effective processing speed (PS) in both younger and older adults. CBF can be estimated as the summation of flow through the left and right internal carotid arteries (ICAs) and the left and right vertebral arteries (VAs). We have previously shown that age-related decreases in total flux through the four arteries has similarly been associated with PS decline. However, it has yet to be investigated (1) whether age-related decreases in blood flow metrics are associated with working memory decline, (2) whether there are hemispheric distinctions in these contributions, and (3) whether distinctive arterial contributions are different between age groups. During scanning, 51 younger adults (18-34 yr, M_{age} = 23.88 yr) and 50 older adults (54-72 yr, M_{age} = 62.34 yr) completed a Sternberg-type Working Memory task with set sizes (SS) 2 (sub-capacity), 4 (at-capacity), and 6 (supra-capacity). During the task, participants completed a pseudo-continuous dual-echo arterial spin labeling sequence (22 transverse slices; flip angle = 90°, TR = 4,000 ms, TE_1 = 13 ms, TE_2 = 30 ms, voxel size = 3.44 x 3.44 x 6 mm^3, scan duration = 408 sec). Additionally, while at rest, participants completed four 3T phase contrast (PC) MRI scans. Each scan was localized at the level of the neck to left or right VAs and left or right ICAs (single slice, flip angle = 15°, TR = 20 ms, TE = 6.9 ms, voxel size = 0.45 × 0.45 × 5 mm, maximum velocity encoding (V_{ENC}) = 80 cm/s, 4 signal averages, scan duration = 0.5 min). PC MRI utilizes phase information to encode the flux, cross-sectional area, and velocity of the

venous blood. Item-by-item RT and accuracy costs for the SWM task were calculated for each subject as the slope of the best-fit line across the three set sizes. Older adults experienced a higher cost across set sizes in both RT and accuracy. For younger but not older adults, left ICA flux, area, and mean velocity were associated with higher RT costs. For older but not younger adults, right ICA flux, area, and mean velocity were associated with higher RT cost. Results are indicative of age-related changes in the anatomical locus of reduced neural efficiency during working memory task performance.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR434.06/D5

Topic: C.01. Brain Wellness and Aging

Support: R01 AG066430/AG/NIA NIH HHS/United States

Title: Cardiorespiratory adaptability and cognitive flexibility in aging

Authors: *J. M. JOHNSON[1], E. RILEY[2], A. K. ANDERSON[2], E. D. DE ROSA[2];
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Abstract: To navigate the challenges of everyday life, the mind and body must adapt - and do so together. The coordination of mind and body adaptability, which shifts with age, depends on clear brain-body communication. This is fundamental for staying resilient in the face of challenges. However, it is unclear how age-related changes in the mind and body influence each other. Therefore, we ask whether cognitive flexibility is linked to physiological adaptability and whether the relationship changes with age. To investigate this, we had young adults (n=24, Mean age=34, (n) females=17) and older adults (n=17, Mean age=71, (n) females=16) complete a proactive interference paradigm during an fMRI session. Our task examined the phenomenon of proactive interference, in which previous learning hinders the learning of new material. The task had three conditions: baseline, proactive interference (PI; target stimulus from baseline becomes a distractor; high interference), and new learning (NL; new stimuli; low interference). The more interference, the more cognitive flexibility is required. Cardio (GE Healthcare Plethysmograph Finger Probe) and respiratory (GE Respiratory Belt) measures were also collected. To measure physiological adaptability, we calculated two indices of brain-body interactions. Heart rate variability (HRV) refers to the variation in time between consecutive heartbeats, and respiratory sinus arrhythmia (RSA) is the natural variation in heart rate that occurs during respiration. Higher HRV (higher adaptability) has been shown to decrease with age. We found through a linear mixed effects model that older adults were significantly less accurate across all conditions ($F(1,\infty)=21.998$, $p<.001$) but post hoc emmeans showed the largest deficit emerged at the

beginning of the proactive interference condition ($z=5.84$, $p<.001$). This suggests that cognitive flexibility, rather than new learning in general, is decreased with age. HRV showed slight decreases with age and slight increases during the most challenging task condition, especially at the beginning of the PI condition, however, none of the main effects or interactions of the linear mixed model reached significance. RSA showed slight increases with age and slight decreases during the most challenging conditions; however, none of the variables within the linear model reached significance. The opposite effects of HRV and RSA were unexpected, and although inconclusive, more research on heart/brain coupling could lead to a biomarker of brain/body functioning that is crucial to understanding how aging impacts mind and body adaptability.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

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Program #/Poster #: PSTR434.07/D6

Topic: C.01. Brain Wellness and Aging

Title: Age-related changes in decision-making by Columba livia in a simultaneous discrimination operant task.

Authors: *T. M. BURNS[1], V. P. BINGMAN[1], V. J. COPPOLA[2];
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Abstract: While well-studied in humans and mammals, the effects of aging on the cognition and behavior of birds remain poorly understood. Emerging evidence suggests that aging birds, specifically pigeons, may also experience cognitive decline, particularly with respect to the nidopallium caudolaterale (NCL), an avian brain structure analogous to the prefrontal cortex. This study examines how age influences risk-based decision-making by comparing the choices of young and old homing pigeons across two NCL-dependent tasks. Ten (10) unsexed homing pigeons (Columbia livia) were divided into two experimental groups based on age: young (N = 6, mean age = 6.67 years) and old (N =4, mean age = 15.25 years). Subjects from both groups were tested on a repeated-measures design using a simultaneous discrimination paradigm. In the first task, pigeons were presented with S1 and S2 on a computerized touchscreen inside an operant chamber. Pecking S1 (the “safe” option) resulted in a small (2 s), constant food reward, while pecking S2 (the “risky” option) resulted in a large (4 s), variable food reward on 50% of trials. Across 80 trials per session, the long-term outcomes for pecking either stimulus were equal (160 s total). Pigeons participated in one session per day for five consecutive days. In the second task, the same pigeons were subjected to a new pair of stimuli and trained on a new contingency. In this task, pecking the “risky” option had the same outcome as in the first task, while pecking the “safe” option resulted in a 1 s reward per trial, making the long-term outcomes between the two

choices unequal (Risky = 160 s, Safe = 80 s). Subjects completed the second task one session per day for five consecutive days. First order results suggest a significant difference in choices made ($F(1, 8) = 8.64$, $p = .02$) as well as a significant interaction between choice and age ($F(1, 8) = 5.22$, $p = .05$). Further analysis revealed that older pigeons were more likely than younger pigeons to choose the safe choice regardless of equal or unequal outcome conditions ($p < .05$), and they were significantly more likely to choose the safe choice over the risky choice in both conditions ($p = .01$). These results suggest that aging may be associated with increased risk aversion in decision-making. More research will be necessary to determine if this aversion represents age-related changes in how risks and rewards are evaluated, or if older pigeons are suffering from a deficit in learning, memory, or executive function.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.08/D7

Topic: C.01. Brain Wellness and Aging

Support: Oregon Raspberry & Blackberry Commission

Title: Long-term consumption of Oregon blackberries improved cognition in healthy older humans but did not generally alter the microbiome

Authors: *K. R. MAGNUSSON[1], D. CHIU[2], L. LEWIS[2], M. HOSSEINIKIA[2], K. J. KIM[3], C. HOROWITZ[2], S. UESUGI[2], C. WONG[2], E. HO[4], A. GOMBART[3], A. MICHELS[2];
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Abstract: Preclinical and clinical trials have shown flavonoid-rich fruits can improve markers of cognitive function. Many berries are rich in phenolic compounds that have the potential to modulate inflammatory processes in the brain and throughout the body. Daily supplementation of many berries in healthy older humans improves memory and executive function. Cognitive studies on raspberries and blackberries, however, have been limited to animals, so human studies are needed. A potential mechanism by which compounds from Oregon blackberries may influence health is through alteration of the gut microbiome. There is growing evidence the gut microbiota modulates brain function through production of microbial metabolites of dietary components. We hypothesize the health benefits from Oregon blackberry consumption could come from a wide range of bioactive compounds present in the fruit or produced by structural and functional changes to the microbiota. In the current study, our goal is to determine if short- or long-term consumption of Oregon blackberries can influence markers of cognitive function in older people and if these are influenced by changes in the resident gut microbiota. Adults (55 or older) were prescreened for age-related cognitive deficits, but not dementia. Nineteen

participants underwent cognitive testing (testers were blinded to the treatment), with the use of NIH Toolbox Cognitive Battery and our virtual version of the Morris water maze, at baseline and following an acute dose (20 g) and then 20 g twice daily freeze-dried blackberry powder mixed in water for 12 weeks. Control group consumed only water. Fecal samples collected at baseline and end of study were examined for microbial DNA by Microbiome Insights. Long-term consumption of blackberries resulted in a greater improvement from baseline in the NIH Toolbox Composite Fluid Cognition score ($p = .015$) and the List Sorting Working Memory task ($p = .045$), as compared to control participants ($N = 9$-10). There were also trends for improvement after a single dose of blackberry powder in the Composite Fluid Cognition score ($p = .11$) and the Flanker Inhibition test of cognitive flexibility ($p = .16$). Principal Components Analysis showed no noticeable clustering of treatment groups or time point of sampling. The samples from long-term blackberry consumption did show associations between relative abundance of species and gene functions involved in respiration (ATP functions) and DNA repair. These results suggest that long-term consumption of blackberry powder has positive effects on cognition in older humans and has a relationship to some genes, but does not have a significant effect overall on the microbiome.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.09/D8

Topic: C.01. Brain Wellness and Aging

Support: Prebys Foundation

Title: Both age and sex affect the performance of rats on a multidestination spatial task

Authors: *C. TORRES, R. BLASER, I. PAGANINI;
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Abstract: The Traveling Salesman Problem (TSP) is a multidestination route finding problem that is useful for the translational study of spatial cognition. While the cognitive mechanisms used in this task are still being explored, multiple processes including decision-making, attention, spatial orientation, spatial memory, and planning may be involved. Humans are able to complete even complex TSPs with a high degree of efficiency, and distance minimization in TSP analogues has been observed in a variety of non-human species as well. Previously, we demonstrated that lesions of the hippocampus or the medial entorhinal cortex in rats affected performance on spatial configurations that required a global strategy for efficient navigation, with little impairment on configurations for which a local strategy produced efficient

performance. We have also found that humans with memory disorders (e.g. Alzheimer's Disease) produce less efficient routes on the TSP, suggesting that this task may be a useful tool to study changes in spatial cognition during healthy aging or as a result of neurodegenerative disorders. The current study was designed to examine the effects of aging on route selection by rats in the TSP. Cohorts of rats began pre-training at 4, 8, or 12 months of age, and were then tested on each of several target configurations. We examined the routes for evidence of two local strategies (nearest neighbor and crossing avoidance), and one global strategy (tracing the convex hull). Our results indicate that in general, performance on the TSP is impaired with age, although this effect interacted with sex. Impairment was greater on performance measures related to memory than those related to route choice.

Disclosures: C. Torres: None. **R. Blaser:** None. **I. Paganini:** None.

Poster

PSTR434: Age-Related Alterations in Learning and Memory

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Program #/Poster #: PSTR434.10/D9

Topic: C.01. Brain Wellness and Aging

Support: CONACYT Grant 252808, for Gonzalo Flores

Title: Comparative effects of Cerebrolysin and Erythropoietin in dendritic spines and memory in an animal model of aging

Authors: *L. AGUILAR HERNÁNDEZ[1], J. MORALES-MEDINA[2], G. FLORES[1]; [1]Inst. de fisiología, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico; [2]Ctr. de Investigación y Estudios Avanzados, Tlaxcala, Mexico

Abstract: Cognitive processes such as memory and learning are critically dependent on neuronal plasticity, supported by the connectivity between corticolimbic regions, including the prefrontal cortex (PFC), hippocampus, and amygdala. These connections are primarily established between synaptic boutons and dendritic spines, whose morphology determines the efficacy of synaptic transmission. Dendritic spines are highly plastic structures, responding dynamically to synaptic stimuli, and their structural integrity is modulated by inflammation, oxidative stress, mitochondrial function, neurotrophic factors, and overall cellular milieu. During brain aging, increased inflammation and oxidative stress are observed, along with impaired antioxidant capacity, mitochondrial dysfunction, and decreased release of neurotrophic factors. These alterations contribute to a progressive loss of dendritic spines and altering their morphology, which correlate with age-associated cognitive decline. Several studies demonstrate the neuroprotective potential of agents with anti-inflammatory, antioxidant, and neuroprotective properties. Cerebrolysin (CBL) has been shown to improve cognitive function and induce the expression of neurotrophic factors and antioxidant defenses. Erythropoietin (EPO) has demonstrated neuroprotective and restorative effects in the central nervous system through its

interaction with its receptors on neurons and glia. In the present study, we evaluated the effects of chronic treatment with CBL and EPO in 3-, 6-, and 12-month-old mice. Memory was analyzed using the Novel Object Recognition Test, and dendritic spine density and morphology were assessed using Golgi-Cox staining. Our results reveal that both treatments significantly improved short-term recognition memory across all age groups, with no statistically significant differences between them. Age-related declines in dendritic spine density were observed, particularly in 12-month-old mice. However, both CBL and EPO were able to attenuate this alteration and even induce significant increases in synaptic density in the PFC, CA1, and BLA compared to age-matched controls. Furthermore, aging was associated with a reduction in mushroom spines and an increase in stubby spines, changes that were reversed by both treatments. In these groups, a recovery in the proportion of mushroom spines and a decrease in stubby spines were observed, suggesting maintenance of functional synaptic properties. These findings support the therapeutic potential of CBL and EPO in the prevention and treatment of structural and functional alterations associated with brain aging.

Disclosures: L. Aguilar Hernández: None. **J. Morales-Medina:** None. **G. Flores:** None.

Poster

PSTR434: Age-Related Alterations in Learning and Memory

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.11/D10

Topic: C.01. Brain Wellness and Aging

Support: R01AG047972
R01AG029523
R01NS106711
R01NS106702

Title: Age-differential relationships between control networks, default-mode networks and working memory set size

Authors: *M. CROSBY[1], G. SHERARD[2], Y. ZHAO[3], D. H. ABDELKARIM[4], A. CAMPOS[5], B. P. RYPMA[6];
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Abstract: Neurocognitive aging studies aim to identify the neural mechanisms underlying cognitive decline in aging. Previous studies have shown associations between BOLD signal in frontal regions (e.g., the prefrontal cortex) and age-differences in item-by-item response time (RT) and accuracy costs during working memory tasks. The current study aimed to examine these relationships for brain regions in established functional networks (e.g., the Control

Network and Default-Mode Networks; CN and DMN). During fMRI scanning, 46 younger adults (18-34 yr, M_{age} = 23.83 yr; SD_{age} = 4.07 yr; 23 female) and 39 healthy older adults (54-74 yr, M_{age} = 61.41 yr; SD_{age} = 4.94 yr; 23 female) completed a Sternberg-type Working Memory task with set sizes (SS) 2 (sub-capacity), 4 (at-capacity), and 6 (supra-capacity). During the task, participants completed a pseudo-continuous dual-echo arterial spin labeling sequence (22 transverse slices; flip angle = 90°, TR = 4,000 ms, TE_1 = 13 ms, TE_2 = 30 ms, voxel size = 3.44 x 3.44 x 6 mm^3, scan duration = 408 sec). BOLD signal was taken from brain regions as defined in the Schaefer 2018 200 parcellation atlas across rest and all set sizes. Across 131 of the 200 regions, younger adults had higher BOLD signal than older adults during rest. Almost no age differences were significant at SS2, but 88 regions (during SS4) and 112 regions (during SS6) showed higher BOLD signal in older adults. None of the 200 regions showed higher BOLD signal in younger than older adults during SS4 and 6. Item-by-item RT and accuracy costs were calculated for each subject as the slope of the best-fit line across the three set sizes. Older adults experienced a higher cost across set sizes in both RT and accuracy. In the left and right CN, in older but not younger participants, higher BOLD signal at rest was associated with lower item-by-item costs in accuracy; however, higher BOLD signal during SS4 was associated with higher item-by-item accuracy costs. This result indicates the importance of suppressing CN regions for preservation of accuracy at-capacity. In the left and right DMN, in younger but not older adults, higher BOLD signal at rest was associated with higher RT costs but with lower RT costs during SS4. This result indicates that the recruitment of DMN regions at-capacity preserves response speed. Additional network results, and relationships between network connectivity and item-by-item RT and accuracy costs, are also presented.

Disclosures: M. Crosby: None. **G. Sherard:** None. **Y. Zhao:** None. **D.H. Abdelkarim:** None. **A. Campos:** None. **B.P. Rypma:** None.

Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.12/D11

Topic: C.01. Brain Wellness and Aging

Title: Age-related changes in oscillatory power and connectivity in the prefrontal cortex and hippocampus during associative episodic memory

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Abstract: Memory decline is a hallmark of normal aging, yet its underlying physiological mechanisms remain poorly understood. The associative deficit hypothesis posits that older adults have increased difficulty forming and retrieving associations between items, contributing to poorer performance on tasks that require distinguishing intact associations from rearranged

pairings. Successful performance on these tasks requires suppression of individual item-level familiarity in favor of retrieving associated details. This process likely requires post-retrieval monitoring, a process supported by the prefrontal cortex (PFC), to evaluate the accuracy and relevance of retrieved content. A growing body of research indicates that older adults show increased PFC activity and altered PFC network integration during memory tasks, potentially reflecting compensatory mechanisms in response to diminished hippocampal function. To establish direct neurophysiological mechanisms underlying age-related differences in memory retrieval within the PFC and hippocampus, we analyzed intracranial EEG recordings from 32 patients with refractory epilepsy divided into two distinct age groups (16 younger <25 years, 16 older ≥50 years) as they performed a word-pair associative recognition task. Using linear mixed-effects models, we examined interaction effects between age group and memory condition (correct vs. incorrect) on baseline-normalized spectral power and lagged mutual information (MI). We observed increases in PFC power in older adults for correctly recalled items in the theta (2-8 Hz) frequency band compared to younger adults (FDR-corrected $p < 0.05$). In contrast, we did not observe significant age × memory interaction effects for any frequency bands in the hippocampus. In younger adults, MI analysis revealed a significant pattern of bidirectional hippocampus-PFC connectivity during correct retrieval. However, we did not observe significant age × memory interaction effects or age effects on connectivity during correct trials. These findings provide novel electrophysiological evidence that increased PFC oscillatory activity may compensate for reduced hippocampal engagement, supporting successful associative memory retrieval in aging despite stable hippocampus-PFC directional coupling.

Disclosures: S. Arya: None. **B.C. Lega:** None.

Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR434.13/D12

Topic: C.01. Brain Wellness and Aging

Support: National Institute on Aging R01AG082680
National Institute on Aging 1RF1AG039103

Title: Differential associations of fornix fractional anisotropy and free water with memory performance and future memory decline

Authors: *J. M. OLIVIER[1], M. HOU[1], M. BERGAMINO[2], M. A. DE CHASTELAINE[1], M. D. RUGG[1];
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Abstract: Free water correction is a procedure to separate the contributions of white matter and extracellular free water to diffusion tensor imaging (DTI) metrics such as fractional anisotropy

(FA). Prior studies employing diffusion MRI have reported associations between free water in white matter tracts of the medial temporal lobe and cognitive measures in various domains, including episodic memory and executive function, in cognitively healthy older adults as well as patients with mild cognitive impairment. Using single-shell diffusion acquisition, we recently reported that in older adults, free water corrected FA of the fornix predicted longitudinal memory decline but not memory performance at baseline. Here, we extend those observations by examining associations between amount of free water in the fornix, water-corrected fornix FA, and memory performance in two datasets: a cross-sectional "lifespan" dataset of healthy adults comprising young (ages 18-30, N= 41, 18 female), middle-aged (ages 43-55, N= 38, 20 female), and older (ages 63-76, N= 67, 37 female) age groups, and a 3-year longitudinal dataset from a subset of the healthy older adults employed in that lifespan sample (ages 63-76 at baseline, N = 55, 28 female). We administered a neuropsychological test battery to all participants. Older adults in the longitudinal group received the same battery on two occasions, separated by a month, and then again 3 years later. Using a series of multiple regression models, we found that fornix free water, but not fornix FA, was associated with recall scores on the California Verbal Learning Test (CVLT) independently of age group in the lifespan sample. In addition, in the longitudinal sample, fornix free water, but not fornix FA, was associated with baseline CVLT recall and a memory component score derived from a principal components analysis of the neuropsychological test scores. We did not, however, find a reliable association between fornix free water and longitudinal memory change in these participants. Instead, fornix FA remained a significant predictor of memory change after controlling for free water. Together, these findings suggest that fornix free water and fornix FA reflect neurobiologically distinct metrics of cognitive performance and vulnerability to future memory decline.

Disclosures: J.M. Olivier: None. **M. Hou:** None. **M. Bergamino:** None. **M.A. De Chastelaine:** None. **M.D. Rugg:** None.

Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.14/D13

Topic: C.01. Brain Wellness and Aging

Support: NIA R01 AG058574

Title: Age-related degradation in structural connectivity associated with memory retrieval and decision-making performance

Authors: *J. Y. KANG, C. M. HOWARD, J. CHAN, K. BLACK, S. YU, E. J. JUAREZ, R. E. CABEZA, G. R. SAMANEZ LARKIN;
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Abstract: As the aging population continues to grow, understanding the effects of healthy aging on memory and decision-making becomes increasingly important for maintaining quality of life and autonomy in older adults. In the present study, 82 adults aged 25-80 completed a consumer-choice task that varied in memory and task demand. Participants chose between pairs of consumer products with ratings shown using one or two rows of stars on a five-star scale. Product ratings were displayed either simultaneously (no-memory decision) or sequentially with a delay (memory decision). Behavioral results showed age-related decline in memory-dependent decision trials, such that older adults chose more suboptimal products when they maintained product information over a delay before making a choice. In a simultaneous choice condition that did not require memory, older adults were disproportionately affected by increased demand (two-rows of ratings), suggesting that increased perceptual processing demands also contributed to age-related suboptimal decisions. Diffusion tensor imaging was used to construct individual structural connectomes based on the average fractional anisotropy along streamlines connecting gray matter regions. The task demand-related reduction in decision quality in the no-memory simultaneous choice condition was correlated with connectivity between prefrontal regions (ventromedial and dorsolateral cortex), medial temporal lobe (MTL), inferior frontal gyrus, orbital gyrus, and inferior parietal lobe while controlling for age. In contrast to the no-memory condition, which applied to all age groups, the associations between brain structure and memory-related decision task performance were strongest in older adults. In older participants (N = 33, ages 60-80), there was a significant interaction between age and the integrity of MTL to early visual cortex (EVC) connections on memory-related reduction in choice quality. This suggests that MTL-EVC degradation may hinder integration of perceptual information into the memory network especially during older adulthood. These findings point to a potential age-related vulnerability in neural networks supporting perception, value integration, and executive control, in the presence or absence of memory demands. Together, these results highlight that memory and decision-making are not isolated processes but dynamically interact through shared and distinct neural systems. By identifying specific structural pathways that both support memory-related decision making and are vulnerable to age-related disconnection, this study provides a potential target for early detection and intervention.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.15/D14

Topic: C.01. Brain Wellness and Aging

Title: Comparative Analysis of Verbal Learning in Older Adults With and Without Cognitive Impairment

Authors: *A. VEGA FERNANDEZ[1], R. BONILLA[1], J. CONTRERAS SORIA[1], G. RIVERA-URBINA[2];
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Abstract: Aging is often accompained by various cognitive, social, physical, and emotional changes, some of which may involve gradual losses. Given the complexity of this life stage, it is essential to study its specific characteristics in depth. One cognitive function that is frequently impacted in the early stages of cognitive decline and neurodegenerative diseases, such as Alzheimer´s, is verbal memory-defined as the ability to recall words, words list, or narratives. The objective of this study was to examine verbal memory function in older adults. A total of 114 participants were recruited, all of whom scored 27 or higher on the Mini-Mental State Examination (MMSE), indicating cognitive performance within the normal range. Participants were categorized into three age-based groups: Group 1: 60 to 69 years, Group 2: 70 to 79 years and Group 3: 80 years and older.
Additionally, a fourth group (Group 4) was formed, consisting of participants who scored 26 or below on the MMSE, a range that may indicate the presence of mild cognitive impairment. Verbal memory was assessed using TAVEC verbal learning test. The results indicated that Groups 1 and 2 showed comparable performance in word learning and recall tasks. In contrast, Group 3 performed significantly worse, reflecting a diminished verbal learning capacity. Notably, Groups 3 and 4 exhibited similar learning curves, suggesting a comparable pattern of impairment-even though participants in Group 3 had obtained scores within the normal range on the MMSE.
These findings highlight the sensitivity of verbal memory assessment in detecting subtle cognitive changes that may not be captured by general cognitive screening tools such as the MMSE. This underscores the importance of incorporating specific neuropsychological tests in the assessment of older adults to facilitate early identification of cognitive decline.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR434.16/D15

Topic: C.01. Brain Wellness and Aging

Support: R01AG088306

Title: Naturalistic task framing improves older adults' ability to infer and navigate complex associative networks

Authors: *R. A. PALSULE, J. GUO, S. M. NOH, A. M. BORNSTEIN;
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Abstract: Humans are able to infer complex associative networks from individual experiences, even when specific elements across events were not directly experienced together. However, the ability to extract and infer these indirect associations has been shown to decline with age (Noh et al., 2023). Previous work has suggested that framing tasks to be more real-world relevant can improve performance in older adults (Desrichard & Kopetz, 2005). In the present study, we examined whether framing a graph-structured associative learning task using a naturalistic narrative would improve older adults' ability to infer and navigate complex associative structures. In the original version of the task (Noh et al., 2023), participants are told to learn a series of arbitrary object pairs (edges) drawn from an underlying graph structure. In this naturalistic variant, participants are asked to learn a series of flight paths between two cities. For both versions of the task, participants are tested on their ability to infer the underlying associative network (graph structure) through a shortest path judgment task, which consists of determining which of two options (nodes) seen during learning is "closer" to a target based on the learned associations. We hypothesized that the more realistic framing would attenuate age-related deficits previously seen in shortest-path judgments. We recruited 28 younger (ages 25-40) and 30 older participants (65+) through Prolific. Participants were randomly assigned to take either the original (arbitrary objects) or naturalistic (flight paths) version of the task. We found that there was a significant interaction between age group and task framing ($p=0.031$), such that older adults' ability to infer and judge relative distances was better in the naturalistic variant of the task, whereas this framing benefit was not seen in younger adults. These results could not be attributed to a ceiling effect in young adult performance as individual participants were not consistently achieving near-perfect accuracy in any condition, suggesting that the older adult improvements observed are likely due to their ability to draw on greater crystalized knowledge. These findings demonstrate that older adults show improvements in multi-step inference judgments when tasks are framed to be more realistic, emphasizing the importance of framing tasks appropriately to maximize performance.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR434.17/D16

Topic: C.01. Brain Wellness and Aging

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Title: Investigation of sex-dependent cognitive decline and neural complexity in mice from juvenile to middle age

Authors: *K. CHRISTIANSEN[1], V. TRUONG[1], C. QUINTERO[1], J. L. VERPEUT[2];
[2]Psychology Dept., [1]Arizona State Univ., Tempe, AZ

Abstract: Typical aging results in reduced neural complexity and brain atrophy that can impact processing speed during learning. While many studies track cognitive decline, there has been little research on sex-dependent rates of decline. We utilized a translational method, the visual discrimination (VD) task, to determine if performance could predict neural changes. We hypothesized that juvenile female mice would exhibit equal cognitive performance compared to males, but would undergo more drastic cognitive decline into middle age. We further predicted that juveniles would have increased neural complexity compared to middle-aged mice. Cognitive changes across the lifespan were examined in male (n=21) and female (n=24) C57BL/6J juvenile (P21) and middle-aged (10 month old) mice using a pairwise VD task. In this task, animals learn to associate the correct image with a sweetened condensed milk (15%) reward. Learning (acquisition) was assessed across 10 days, then the correct shape was switched to test flexible cognition (reversal learning) for ~10 days or until reaching criteria (70%). Trial initiation, response, and reward collection latencies were analyzed. Following behavior testing, brain tissue was analyzed using Golgi-Cox staining for dendritic complexity in the somatomotor layers 2/3 and hippocampus (CA1). We found that amongst female mice, juveniles completed more trials during early ($F(1,22)=13.1$, $p=0.002$) and mid-learning stages ($F(1,22)=11.9$, $p=0.002$) of acquisition. Also, juvenile females responded faster during acquisition ($U=9540$, $p<0.001$) and were faster to collect the reward during acquisition ($U=7838$, $p=0.043$) and reversal ($U=14518$, $p<0.001$). Interestingly, aged females were faster to initiate trials during acquisition ($U=3716$, $p<0.001$). Amongst males, juveniles completed more trials during acquisition ($U=4361$, $p=0.008$) and were faster to respond ($U=7709$, $p<0.001$) and collect their reward ($U=7709$, $p<0.001$) compared to middle-aged males. In reversal, juvenile males were faster to initiate trials ($U=11694$, $p<0.001$) and collect their reward ($U=11498$, $p<0.001$). We found region- and sex-specific changes in neural complexity. Middle-aged females had more distal dendritic intersections compared to middle-aged males in the CA1 ($p=0.001$), while juvenile males had greater total ($p<0.001$) and proximal ($p<0.001$) intersections in layer 2/3 of the somatomotor region. Therefore, performance did predict changes in neural structure. This study demonstrates that the VD is effective at predicting sex and age-related changes in cognition and neural complexity and may be useful for better individualized treatments.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.18/D17

Topic: C.01. Brain Wellness and Aging

Support: NINDS R56NS128177
NIA R01 AG76845

Title: Aging alters cue and place encoding in the mouse dentate gyrus

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Abstract: Background: Age-related memory decline has been associated with dysfunction in the hippocampus and associated temporal lobe regions which aid in episodic memory storage. The dentate gyrus (DG) is the initial stage of the hippocampal "trisynaptic circuit" and has been suggested to perform the computational role of pattern separation, or the disambiguation of similar input patterns to increase memory precision. Such functions may decline during aging and can be significantly impaired in individuals with age-related cognitive disorders.
It has been proposed that disruptions in the entorhinal cortex inputs to the DG play a particularly important role in the cognitive alterations observed in aging. The DG receives its primary input from the lateral and medial entorhinal cortex, which have been suggested to encode egocentric information about sensory cues and allocentric spatial information respectively. While examining the activity of large populations of DG neurons, we have recently discovered that the DG exists as largely distinct populations of "cue cells" and "place cells". Here we examine the properties of cue cells and place cells in the DG in mouse models of aging in order to see the effects of these manipulations on systems-level representations of specific environmental features in the DG.
Methods: We performed in vivo 2P calcium imaging in the dorsal DG granule cells of wild-type (WT) (n=10) and aged (18mo+) (n=10) mice. The mice ran on a 2-m-long linear treadmill while head-fixed, and a 2s odor cue was given in the middle of the track, which was then shifted or omitted on a subset of laps in order to determine the properties of DG cue cells or place cells. The activity of single neurons was subsequently followed over the course of one month to assess the stability of these representations. Responses to two different similar odors were also measured to assess stimulus selectivity.
Results: We found that aged mice showed a significantly higher population spatial information content as well as a trend for increased ensemble stability compared to WT mice. They also exhibit lower cue cell activity over time. The results suggest that DG networks become hyper-stable with age.
Conclusion: This provides insight into novel circuit defects underlying hippocampal dysfunction during aging, providing an avenue to potentially aid in treating associated cognitive deficits. Specifically, hyperstability in DG cue encoding may underlie defects in cognitive flexibility of aged individuals, and may contribute to aged-related memory decline.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.19/D18

Topic: C.01. Brain Wellness and Aging

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Central Michigan University Neuroscience Program
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John G. Kulhavi Professorship in Neuroscience
E. Malcolm Field and Gary Leo Dunbar Endowed Chair in Neuroscience at CMU

Title: Progesterone Differentially Affects Cognitive Function in Young vs. Aged Male and Female C57 Mice

Authors: *G. BORGMAN[1,2], O. SMITH[1], D. DOYLE[3], L. GARMO[4], K. REED[5], A. UPRETY[6], K. A. JENROW[7], J. ROSSIGNOL[8], G. L. DUNBAR, Sr.[9];
[2]Neurosci., [1]Central Michigan Univ., Mount Pleasant, MI; [3]Central Michigan Univ., Mt Pleasant, MI; [4]Central Michigan Univ., Farmington Hills, MI; [5]Central Michigan Univ., Auburn, MI; [6]Central Michigan Univ., Kathmandu, Nepal; [7]Psychology, [8]Col. of Med., Central Michigan Univ., Mount Pleasant, MI; [9]Psychology/Program in Neurosci., CENTRAL MICHIGAN UNIVERSITY, MOUNT PLEASANT, MI

Abstract: Background: Progesterone, a neurosteroid and sex hormone, has demonstrated neuroprotective properties in models of brain injury. However, little is known about whether these effects are modulated by biological sex or age. Given the sex-specific expression of progesterone receptors and the hormone's interaction with other neuroendocrine pathways, it is plausible that progesterone may differentially influence cognitive performance in males and females. Aging adds another layer of complexity, as age-related changes in steroid hormone levels and receptor sensitivity may alter the brain's responsiveness to exogenous progesterone. The objective of this study aimed to evaluate the influence of progesterone on cognition in both young and aged male and female C57 mice. Methods: Animals in the young cohort were between 4 and 9 months old, while those in the aged cohort ranged from 20 to 25 months. Mice received daily subcutaneous injections of either progesterone (5 mg/kg) or a vehicle control (30% 2-hydroxy beta-cyclodextrin) for 56 consecutive days. Cognitive performance was assessed using the water T-maze and passive avoidance behavioral paradigms. Western blotting was performed on both brain and liver tissue homogenates to assess the expression levels of key proteins involved in neuroprotection, inflammation, and oxidative stress, including mTOR, TNF-α, SOD1, progesterone receptors A and B (PR-A/B), and brain-derived neurotrophic factor (BDNF). Results and Conclusion: Our findings revealed that progesterone-treated young males completed the water T-maze task more efficiently than their female counterparts who received the same treatment. In contrast, no significant effects of progesterone were observed in either aged males or aged females across both cognitive tasks. Notably, young females treated with progesterone exhibited a reduction in successful task completions in the water T-maze compared to vehicle-treated young females. These results suggest that while progesterone may enhance

cognitive performance in young male mice, it may impair learning in young females. One potential explanation is that exogenous progesterone disrupted the balance of endogenous hormone levels in young females, thereby interfering with optimal cognitive functioning.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

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Topic: C.01. Brain Wellness and Aging

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Title: Aging deteriorates Aplysia escape network activity and abolishes network components of non-associative learning

Authors: *V. K. MISTRY, W. N. FROST;
Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: The mollusk *Aplysia californica* has provided major advances to our understanding of the cellular and network basis of behavior and learning. As *Aplysia* can be sourced from a rearing facility, recent work has also utilized this species to investigate how aging impacts behavior and learning, as well as underlying synaptic function. One challenging problem has been deciphering how aging-related synaptic-level changes impact network function to degrade behavior and cognitive function. Our laboratory has previously used large-scale voltage-sensitive dye (VSD) imaging to study fictive locomotion network activity in young *Aplysia*, and has also identified behavioral and cognitive deficits in intact aged *Aplysia*. Here, we used VSD imaging to record from the pedal ganglia of young adult (5-7mo) and old adult (12-13mo) *Aplysia* to identify network activity deficits in aged *Aplysia* during fictive locomotion. Aged *Aplysia* network activity (average # of spikes/cell) was lower than that in young *Aplysia,* both at rest and after an initial nerve-evoked fictive motor program. When a nerve stimulus was used to repeatedly evoke the locomotion motor program, brains from aged *Aplysia* demonstrated a progressive decrease in network activity, longer motor program onset latencies, and fewer locomotion cycles than brains from young animals. Interestingly, the deficits observed in elderly deafferented brains were greater than those observed in elderly intact animals. While these results demonstrate that age-related deficits in *Aplysia* escape behavior are driven by deficits within the CNS, the fact that the locomotion networks of elderly animals perform better in intact animals than in the isolated brain preparation suggests a potential role for the periphery in mitigating age-related behavioral and cognitive decline.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

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Topic: C.01. Brain Wellness and Aging

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Title: Age-related social memory dysfunction is associated with diminished perineuronal nets in the hippocampal CA2 region

Authors: *J. M. MOATS, K. M. SPONAUGLE, J. M. KILMER, E. C. COPE;
Neurosci., Univ. of Virginia, Charlottesville, VA

Abstract: Aging is accompanied by several non-pathological brain changes that, even in the absence of disease, significantly and deleteriously influence cognitive capacities. One of the lesser-known cognitive deficits associated with aging is impairments in social memory, or the inability to recognize and remember previously encountered individuals. To investigate this, we compared social memory abilities of young (3-month-old) and aged (18-month-old) mice by assessing their interactions with novel versus familiar conspecifics. While young mice displayed intact social memory, aged mice did not show the characteristic reduction in interaction time when exposed to a recently encountered conspecific. We then examined whether aged mice could detect social novelty by comparing their interactions with a highly familiar cagemate versus a novel conspecific. Like young mice, aged mice had greater investigation times for the novel conspecific. Taken together, these findings suggest that aging impairs social memory for recently encountered conspecifics, without affecting the ability to distinguish between novel and well-known conspecifics. The CA2 region of the hippocampus, an area critical for social memory processing, contains a high abundance of condensed extracellular matrices known as perineuronal nets (PNNs). Previous work has shown that disruption of CA2 PNNs impairs social memory in mice. PNNs consists of many components, including chondroitin sulfate proteoglycans (CSPGs). To examine PNNs, we used the plant-based lectin *Wisteria floribunda agglutinin* (WFA), which binds to the glycosaminoglycans attached to CSPGs, and observed a robust age-related reduction in WFA+ PNNs. Since CA2 PNNs surround both PCP4+ excitatory pyramidal cells and PV+ inhibitory interneurons, we next analyzed these cell populations separately. We found a decrease in WFA+ PNNs in both populations, with a more pronounced decrease in PCP4+ cells. However, no differences were observed in aggrecan, the most abundant CSPG in PNNs, between age groups in the CA2. These findings indicate that CA2 PNNs are disrupted with healthy aging and raise the possibility that this may contribute to age-related social memory impairments.

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Poster

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Program #/Poster #: PSTR434.22/D21

Topic: C.01. Brain Wellness and Aging

Support: R01AG088306

Title: The impact of learning sequences in encouraging distinct memory representations to support associative inference in older-adults

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Abstract: Prior research has demonstrated that associative inference (the ability to infer A-C after exposure to A-B and B-C) can be supported by distinct neural representations: upon encountering B-C after learning A-B, one may integrate the two memories into an overlapping A-B-C representation or differentiate them and infer A-C using retrieval and recombination strategies. Prior work has also shown that manipulating how information is presented can bias whether associations become integrated or differentiated: blocked learning sequences (where A-B pairs are learned before B-C pairs) encourage differentiated memory representations, whereas intermixed sequences (where A-B and B-C pairs are randomly interleaved) encourage integrated representations (Zhou et al., 2023). In the present study, we examined whether older adults may particularly benefit from blocking, given their susceptibility to interference and age-related declines in memory discrimination. By separating overlapping information in time, we predicted that blocking might reduce interference and promote distinct A-B and B-C memories. We recruited 71 older adults (aged 65+) online and randomly assigned them to blocked (N = 34) or intermixed (N = 37) training. We found that blocking improved memory for directly studied pairs (A-B and B-C). When examining A-C inference conditionalized on correct A-B and B-C recall, there was no accuracy difference across training conditions. However, participants were slower to make inference judgments in the blocked condition, suggesting that blocking supports distinct A-B and B-C memories that must be retrieved and recombined, whereas faster responses in the intermixed condition may suggest inference via integrated representations. These findings contrast with prior work in younger adults, where blocked learning promoted integration (Schlichting et al., 2015), suggesting individual differences in memory capacity may influence how learning sequences shape memory. Given age-related discrimination deficits (Stark et al., 2019), blocking may help older adults differentiate similar memories through temporal separation. These results suggest that presentation order can bias memory toward integration or discrimination, informing individualized learning strategies.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.23/D22

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Title: Toward a translational model of cognitive aging: spatial working memory in marmosets and humans

Authors: *S. R. DUNN[1], C. R. VANDERLIP[2,1], P. A. ASCH[1], J. H. REYNOLDS[1], C. E. L. STARK[2], C. GLAVIS-BLOOM[1];
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Abstract: Working memory is among the earliest and most consistently affected cognitive domains in both normal healthy aging and Alzheimer's disease, yet its underlying neural mechanisms and patterns of decline remain poorly understood. Translationally relevant animal models are essential for elucidating these mechanisms and patterns, and ultimately for developing early interventions. The common marmoset (Callithrix jacchus), with its short lifespan (~12 years) and strong neuroanatomical and behavioral homology to humans, offers a powerful model for aging research. However, despite growing interest in marmoset models for aging and neurodegenerative disease, comprehensive cognitive characterization remains limited. To address this gap, we implemented a Delayed Non-Match to Position (DNMP) task to assess spatial working memory and probe interference resolution, functions supported by the prefrontal cortex and hippocampus. In this task, subjects view a sample location and, after a variable delay (1, 5, 10s), must select the novel position from two choices. In addition to delay, spatial proximity between choices was manipulated to increase interference and cognitive load. A large cohort of marmosets ranging from young adult to geriatric (4-16 years of age) completed the 1s delay condition, with a subset tested at longer delays. Cross-sectional analyses showed that performance declined with both increasing delay and reduced spatial separation, demonstrating sensitivity to both memory load and spatial interference. Longitudinal data showed stable performance over time on short delays, suggesting that longer delays may be required to detect age-related decline within individuals. Parallel testing in humans revealed strikingly similar

effects of delay and spatial proximity, further validating the task's translational relevance. Together, these findings establish DNMP as a robust, scalable measure of spatial working memory in marmosets. This task provides a critical foundation to define normative aging trajectories, which form the foundation for identifying early impairments and interpreting cognitive outcomes in emerging disease models.

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Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

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Topic: C.01. Brain Wellness and Aging

Support: GACR grant 23-05540S

Title: Knockout of Chst11 enhances cognitive function and alters perineuronal net composition across the lifespan in mice

Authors: *J. SVOBODOVA BURIANOVA[1,2], J. SVOBODA[1,3], J. RUŽICKA[2], K. STEPANKOVA[2], N. MARTINEZ VAREA[2], P. JENDELOVA[2], J. W. FAWCETT[4,2], J. C. KWOK[5,2];
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Abstract: Perineuronal nets (PNNs), specialized extracellular matrix structures, regulate neuronal plasticity, learning, and memory. PNN composition undergoes dynamic remodeling across development and aging, notably in the sulfation pattern of chondroitin sulfate (CS) glycosaminoglycans. Early-life plasticity is supported by 6-sulfated CS (C6S), while aging is associated with a shift toward 4-sulfated CS (C4S), primarily through the down-regulation of C6S production, and has been linked to reduced plasticity and cognitive decline. To investigate the functional impact of this shift, we generated a pan-neuronal knockout of Chst11 (Chst11-nestin KO). Behavioral performance, PNN morphology, and synaptic physiology were assessed at 3, 6, 12, and 20 months of age. Chst11-nestin KOs exhibited improved cognitive function in the novel object recognition test; both short- and long-term memory were significantly enhanced relative to controls. In the Morris water maze, Chst11KO mice showed improved short-term spatial memory retention. Social interaction assays revealed increased sociability and preference for social novelty. Morphological analysis demonstrated reduced PNN density, and electrophysiological recordings revealed enhanced field excitatory postsynaptic potentials (fEPSPs) and altered synaptic inputs onto parvalbumin-positive (PV^+) interneurons in Chst11

KO mice. These findings indicate that reducing C4S via Chst11 deletion promotes cognitive function and plasticity-related network dynamics. Modulation of CS sulfation may represent a novel strategy for mitigating age-related cognitive decline and neurodegenerative disease.

Disclosures: J. Svobodova Burianova: None. **J. Svoboda:** None. **J. Ružicka:** None. **K. Stepankova:** None. **N. Martinez Varea:** None. **P. Jendelova:** None. **J.W. Fawcett:** None. **J.C. Kwok:** None.

Poster

PSTR434: Age-Related Alterations in Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR434.25/D24

Topic: C.01. Brain Wellness and Aging

Support: GACR grant 23-05540S

Title: Excessive plasticity in parvalbumin neurons during development contributes to schizophrenia-like behavior

Authors: *J. SVOBODA[1,2], J. SVOBODOVA BURIANOVA[1,3], J. RUŽICKA[3], K. STEPANKOVA[3], N. MARTINEZ VAREA[3], L. MACHOVA URDZIKOVA[4], P. JENDELOVA[3], J. W. FAWCETT[5,3], J. C. KWOK[6,3];
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Abstract: Perineuronal nets (PNNs) are specialized extracellular matrix structures that enwrap a subset of neurons, particularly parvalbumin-expressing interneurons (PVNs), and contribute to the regulation of synaptic plasticity. The functional properties of PNNs are critically influenced by the sulfation pattern of chondroitin sulfate glycosaminoglycans. During development and aging, there is a down-regulation of chondroitin 6-sulfation production, resulting in a higher C4S/C6S ratio. This shift has been associated with reduced plasticity and stabilization of neuronal circuits. While reducing C4S has been shown to enhance plasticity and improve memory in adult models, persistent hyperplasticity initiated during development may produce maladaptive outcomes. Schizophrenia (SZ), a neurodevelopmental disorder characterized by cognitive deficits, anxiety, impaired social interaction, and behavioral inflexibility, has been linked to altered PNN composition and PVN dysfunction. To investigate whether developmental deletion of Chst11 in PVNs induces SZ-like phenotypes, a constitutive knockout mouse model was generated, targeting Chst11 specifically in PVNs. Our results indicate that PVN-specific Chst11 deletion leads to reduced behavioral flexibility, cognitive control, and increased anxiety-like behavior. While this parallels key features observed in established SZ models, these mice on the other hand showed enhance sociability. Ongoing studies are examining electrophysiological

and molecular correlates of these behavioral changes. These results suggest that proper temporal regulation of C4S in PVNs is critical for maintaining behavioral homeostasis and that dysregulation of chondroitin sulfates in development may contribute to excessive plasticity correlated with the potential SZ-relevant phenotypes.

Disclosures: J. Svoboda: None. **J. Svobodova Burianova:** None. **J. Ružicka:** None. **K. Stepankova:** None. **N. Martinez Varea:** None. **L. Machova Urdzikova:** None. **P. Jendelova:** None. **J.W. Fawcett:** None. **J.C. Kwok:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.01/D25

Topic: C.02. Alzheimer's Disease and Other Dementias

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NIH/NIGMS P20GM113123
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UND SMHS funds

Title: Detection of lung inflammatory changes in the App^{NL-G-F} mouse model of Alzheimer's Disease

Authors: *C. CHENG, J. FUHRER, T. ISHIDA-TAKAKU, C. K. COMBS;
Univ. of North Dakota, Grand Forks, ND

Abstract: Alzheimer's disease (AD) is a progressive age-related dementing neurodegenerative disorder affecting around 7.2 million people in the U.S. in 2025, characterized by the accumulation of amyloid beta (Aβ) peptide-containing plaques, neurofibrillary tangles, neuronal degeneration, and neuroinflammation in the brain. The Aβ peptide is cleaved from the larger cell surface amyloid precursor protein, APP, that is highly expressed in central nervous system neurons, suggesting that these cells may be the source of the accumulating peptide in the brain. Interestingly, APP is expressed in numerous cell types within and outside of the brain, supporting the notion that changes in the biology of the protein outside of the brain may be relevant for health and disease. For example, our previous work demonstrated APP expression in intestinal epithelial cells as well as their ability to secrete and take up the Aβ peptide. In this study, we asked whether an additional organ, the lung, also expresses APP and produces Aβ. 12-month-old C57BL/6 littermate control wild-type and App^{NL-G-F} mice were used to collect broncho-alveolar lavage fluid (BALF) and lungs. We observed significantly increased Aβ1-42 in BALF supernatant from male App^{NL-G-F} mice, with no significant detection difference of Aβ1-40 in either sex. Diffuse APP immunoreactivity was observed in the lungs of both WT and App^{NL-G-F} mice, with no obvious Aβ detected via immunostaining. Increased pulmonary airway thickening, elevated mucus and collagen production, as well as a trend towards increased

immune cells in the lungs, including CD4, CD68, and Ly6B, were found in the *App*$^{NL-G-F}$ mice. We observed a trend toward decreased vimentin immunoreactivity in the female lungs of *App*$^{NL-G-F}$ mice, but no obvious changes in fibronectin staining. These findings demonstrate that a possible disease-related inflammatory alteration exists in the lungs of *App*$^{NL-G-F}$ mice during AD development. Further exploration of inflammatory changes, as well as lung epithelial APP function, may improve our understanding of this unique lung-brain axis in AD development.

Disclosures: C. Cheng: None. **J. Fuhrer:** None. **T. Ishida-Takaku:** None. **C.K. Combs:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Hori Sciences & Arts Foundation

Title: Characterization of CCL3-mediated pathophysiological mechanisms in preclinical Alzheimer's disease models

Authors: *M. HIJIOKA, R. UENISHI, R. KAWATA, T. MANABE, T. SAITO;
Dept. of Neurocognitive Sci., Nagoya City Univ., Nagoya, Japan

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by amyloid β (Aβ) and tau accumulation. Recent evidence emphasizes the role of microglial activation, particularly disease-associated microglia (DAM) or plaque-associated microglia (PAM), in AD pathogenesis. Here, we investigated microglia-derived chemoattractants in *App*$^{NL-G-F}$ knock-in (KI) mice, a preclinical AD model with a humanized Aβ sequence containing the Arctic mutation (E22G), leading to robust Aβ deposition and gliosis. Brain lysates from these mice showed significantly elevated levels of C-C motif chemokine ligand 3 (CCL3), a chemoattractant for lymphocytes. Single-molecule fluorescent *in situ* hybridization revealed *Ccl3* mRNA was selectively expressed in PAM but not in non-PAM. This spatial specificity was further confirmed by photo-isolation chemistry RNA-seq, which demonstrated *Ccl3* enrichment in PAM versus non-PAM and WT microglia. To examine its functional relevance, we generated *Ccl3* knockout *App*$^{NL-G-F}$ KI mice. Immunohistochemistry and ELISA revealed increased Aβ burden in *Ccl3*-deficient mice. Flow cytometry with methoxy-X04 labeling showed reduced Aβ phagocytosis in *Ccl3* knockout microglia, though microglial numbers remained unchanged.

These findings indicate that CCL3 is selectively expressed in plaque-associated microglia and contributes to limiting Aβ pathology in a spatially defined manner. While further studies are needed to elucidate the underlying mechanisms, CCL3 may represent a protective factor in early-stage AD.

Disclosures: M. Hijioka: None. **R. Uenishi:** None. **R. Kawata:** None. **T. Manabe:** None. **T. Saito:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JST Moonshot R&D Program (Grant Numbers JPMJM2024)
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JSPS KAKENHI (Grant Numbers JP22K06865)

Title: Cxcl10 worsens the progression of tau pathology in a sex-dependent manner in a mouse model of tauopathy

Authors: *R. UENISHI, M. HIJIOKA, R. KAWATA, T. MANABE, T. SAITO;
Dept. of Neurocognitive Sci., Nagoya City Univ., Nagoya, Japan

Abstract: Tauopathy is a neurodegenerative disorder characterized by the abnormal accumulation of tau protein, which normally associates with microtubules. The disease is characterized by the accumulation of hyperphosphorylated and misfolded tau that forms neurofibrillary tangles. A key pathological aspect of tauopathy is neuroinflammation, which is driven by inflammatory factors such as cytokines and chemokines produced by glial cells. The inflammatory response of glial cells has been reported to be sex-dependent, with male tauopathy models exhibiting particularly severe disease phenotypes. Additionally, recent studies have suggested that T cells in the brain contribute to the progression of tau pathology. However, the mechanisms behind the increased T cell levels in tauopathy cases and the factors that lead to sex-specific tau pathology remain unclear. We hypothesized that inflammatory factors elevated in the brains of tauopathy model mice might play a role in T cells increase and could influence the sex-dependent progression of the disease. In our study, we identified C-X-C motif chemokine ligand 10 (CXCL10) as an inflammatory factor that is elevated in the brains of tauopathy model mice by comprehensive transcriptomic and biochemical analyses. Moreover, the absence of CXCL10 resulted in a significant reduction in T cell accumulation in the brains of tauopathy model mice,

regardless of sexes. However, only female mice demonstrated a suppression of tau pathology and improved survival upon CXCL10 deletion, indicating a sex-dependent role for CXCL10 in disease progression. These findings identify CXCL10 as a critical factor of neuroimmune interactions in tauopathy and suggest that CXCL10 signaling may contribute to the observed sex-based differences in disease severity. By elucidating previously unrecognized immunopathological mechanisms, our research offers the potential for the development of disease-modifying strategies targeting CXCL10.

Disclosures: R. Uenishi: None. **M. Hijioka:** None. **R. Kawata:** None. **T. Manabe:** None. **T. Saito:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.04/D28

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG043522

Title: Convergent disease-resolving effects in amyloid pathology following myeloid-specific nuclear receptor deletion in a mouse model of Alzheimer’s disease

Authors: *B. T. CASALI[1], A. P.-Y. TSAI[3], K. P. MACPHERSON[4], E. G. REED[2], G. E. LANDRETH[5];
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Abstract: Alzheimer’s disease (AD) is a highly prevalent neurodegenerative disorder typified by extracellular deposition of β-amyloid (Aβ) plaques, neurofibrillary tangles, robust neuroinflammation, and progressive cognitive decline. Nuclear receptor agonists upregulate genes associated with Aβ clearance and phagocytosis and repress inflammatory gene expression to ameliorate these hallmarks in various AD mouse models. In microglia, the brain-resident myeloid cells, these agonists engage liver X receptor (LXR) and peroxisome proliferator-activated receptor (PPAR) which heterodimerize with retinoid X receptor (RXR). While nuclear receptors play a prominent role in peripheral myeloid cells, how they contribute to modification of AD pathology is unknown. Furthermore, given the well-characterized beneficial roles of nuclear receptors in neurodegenerative diseases, whether myeloid-cell selective deletion of RXRs exacerbate AD pathology is unclear. We demonstrate the deletion of the predominant isoform of RXR, RXRα, in either peripheral monocytes or microglia ameliorated aspects of amyloid pathology in the 5xFAD mouse model at both early and late stages of disease, reducing plaque burden, curtailing inflammatory gene transcripts, and abrogating neuritic dystrophy.

Deletion of RXRα in microglia diminished apolipoprotein E expression and suppressed genes associated with microglial neurodegenerative phenotype in young animals. Remarkably, RXRα-deficiency in blood monocytes reduced parenchymal plaque load and brain inflammation in the absence of brain infiltration. Additionally, RXRα gene expression was upregulated in human AD brain samples, pointing to a potential role in neurodegenerative diseases. Our study reveals the importance of further understanding the nuanced actions nuclear receptors exert in various myeloid subsets during AD progression.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Program #/Poster #: PSTR435.05/D29

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF RS-2022-NR068424

Title: Hepatic inflammation drives hippocampal pathology and cognitive decline in amyloid beta-induced rat models

Authors: *G. CHOI, K. HEE-SEOK;
Korea Basic Sci. Inst., Cheongju-si, Korea, Republic of

Abstract: Liver disease affects a significant portion of the global population and is caused by various factors such as alcohol consumption, chronic fatigue, and diet. These factors are also known to increase the risk of Alzheimer’s disease (AD). This study aimed to investigate the impact of liver inflammation on the pathogenesis of AD. Central to AD development is the imbalance between amyloid-beta (Aβ) production and clearance. Recent studies have highlighted the contribution of the liver to Aβ clearance, suggesting that the liver may be a key regulator of the metabolic dysfunction observed in AD. Based on this, we hypothesized that hepatic dysfunction could exacerbate neurodegenerative symptoms in AD. To test this hypothesis, we induced liver inflammation in an AD animal model and assessed whether AD symptoms were aggravated. Our results showed that the group with both AD pathology and liver inflammation (AB+DMN group) exhibited more severe learning and memory impairments than the group with AD pathology alone (AB group). These impairments were accompanied by increased expression of Aβ production-related factors and decreased expression of Aβ clearance-related factors. Taken together, these findings strongly suggest that liver dysfunction contributes to AD-related neurodegeneration. In conclusion, our study demonstrates that hepatic inflammation significantly accelerates the progression of AD neuropathology and cognitive decline, underscoring the importance of liver health in preventing neurodegeneration.

Disclosures: **G. Choi:** A. Employment/Salary (full or part-time): Korean Basic Science Institute. **K. Hee-Seok:** A. Employment/Salary (full or part-time): Korea Basic Science Institute.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF-2022K1A3A1A20015190
RS-2023-00302751
RS-2024-00468036

Title: Fluoxetine, selective serotonin reuptake inhibitor (SSRI), reduced neuroinflammatory responses in the hippocampus and stabilized emotional behaviors in Alzheimer's disease (AD) model mice

Authors: *H. CHOI[1,2,3], C. JEONG[1,2,3], Y. PARK[4], H. SEO[1,2,3];
[2]Sch. of Bio-Pharmaceutical Convergence, [3]Ctr. for Bionano Intelligence Educ. and Research, Inst. for Precision Therapeut., [1]Hanyang Univ., Ansan, Korea, Republic of; [4]McLean Hosp., Belmont, MA

Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by symptoms such as cognitive deficit, memory loss and mood disturbances. The progressive pathology of AD is driven by neuronal degeneration, mitochondrial dysfunction, excessive neuroinflammatory responses, and abnormal protein processing, with selective vulnerability of specific neurons in particular brain regions. In a previous study, we found that selective serotonin reuptake inhibitors (SSRIs) reduced amyloid beta accumulation in an *in vivo* AD mouse model. In this study, we aimed to investigate the effects of SSRI on behavioral recovery and to elucidate its molecular mechanisms in the 5xFAD mouse model. We administered SSRI (Fluoxetine; Flu) to 5xFAD mice (10 mg/kg/day, i.p., 4 weeks) and performed multiple behavior tests including Elevated Plus Maze (EPM), Open Field Test (OF), Morris water maze (MWM), and the Tail Suspension Test (TST). We found that Flu enhanced learning in the MWM and stabilized anxiety-like behaviors in EPM and OF which align with known behavioral deficits in 5xFAD mice including spatial memory impairment and hyperactivity. To understand the underlying mechanism, we investigated transcriptomic changes after Flu treatment with next generation sequencing (NGS) using the bulk RNA sequencing method using hippocampal tissues of 5xFAD mice. In 5xFAD mice, differential expression of 549 genes (454 upregulated, 95 downregulated) highlights pathways associated with neuroinflammation (e.g., microglial activation) and amyloid processing ($\geq$ 2-fold, $p<0.05$). Flu treatment reversed expression of 187 genes (84 upregulated, 103 downregulated), including PSEN1, which was elevated in 5xFAD but normalized post-treatment. PSEN1 overexpression in 5xFAD mice drives amyloidogenic Aβ42 production, suggesting Flu may mitigate Aβ pathology via PSEN1 modulation. Cross-analysis identified genes linked to

neuroinflammation (e.g., Trem2, C1qa) and neurodegeneration (e.g., Bace1), consistent with 5xFAD's robust microgliosis and amyloid-driven synaptic loss. Functional validation using siRNA and agonists in hippocampal neurons supports these targets' roles in AD pathology. These data indicate that the molecular pathway found from NGS data after Flu treatment can be applied for future AD therapeutics.

Disclosures: H. Choi: None. **C. Jeong:** None. **Y. Park:** None. **H. Seo:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Program #/Poster #: PSTR435.07/D31

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS112350
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Brightfocus Foundation

Title: Altered neuroinflammation and reduced cerebral amyloidosis after seizure activity

Authors: *N. H. VARVEL[1], C. ESPINOSA-GARCIA[2];
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative and dementing condition of complex etiology and a major cause of disability and death. The pathological hallmarks of the disease include cerebral and vascular amyloidosis, neurofibrillary tangles, neuronal loss and atrophy, and a neuroinflammatory response. In addition to dementia, a subset of AD patients experiences abnormal epileptiform activity and sub-clinical seizures. Interestingly, epileptiform activity can hasten cognitive decline in this AD subset, and cerebral amyloid deposition is more common in epileptic brain tissue than in non-epileptic controls. However, it is unclear if and how epileptiform activity promotes AD pathology. To examine the role of seizures in AD-related cerebral amyloidosis in an exploratory experiment, we subjected four-month-old male 5xFAD mice and age- and sex-matched non-transgenic littermates to pilocarpine to induce seizure activity and sacrificed the mice four days or one month later. Interestingly, seizures provoked a more florid pro-inflammatory response following seizures in the 5xFAD mice compared to non-transgenic controls four days after seizure activity. One month after seizures, the immunohistological analysis revealed enhanced staining for Iba1 and CD68, a marker of microglial activation and phagocytosis, suggesting an altered neuroinflammatory milieu triggered by seizure activity. Interestingly, 5xFAD mice experiencing seizure activity showed approximately 28% decrease in cerebral amyloidosis across several brain regions, including the cortex, hippocampus, and thalamus. Taken together, these results demonstrate that seizure activity leads to reduced cerebral amyloidosis in an AD mouse model, which is potentially attributed to altered activation and phagocytic capability of microglia.

Disclosures: N.H. Varvel: None. **C. Espinosa-Garcia:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Program #/Poster #: PSTR435.08/D32

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NINDS RF1NS128626
NINDS T32NS131140

Title: Effect of sepsis on survival and tau pathology in the transgenic PS19 mouse model

Authors: *Q. VO[1], D. NACIONALES[2], K. BISWAS[1], A. ITURBE[3], C. GORSKI[3], L. MOLDAWER[2], P. EFRON[2], P. CHAKRABARTY[1];
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Abstract: Inflammation activation in the brain is a critical component of amyloid β (Aβ) and tau neuropathology in Alzheimer's disease (AD). The identification of immune-related genes as risk factors in AD reinforces the notion that immune activation is etiologically linked to the neurodegenerative cascade in AD. However, whether peripheral immune activation influences this cascade remains controversial. In a previous study using a modified cecal ligation puncture (CLP) protocol, we observed increased Aβ deposition in septic *APPswe/ind* transgenic TgCRND8 mice. Following up on this study, here we tested if CLP-induced sepsis would exacerbate tauopathy in the *MAPT* transgenic PS19 line expressing human P301S mutant tau. Initiating the septic protocol in 6-month-old PS19 mice, we examined the brains and spleens either at 8 months of age ("prodromal cohort") or until the onset of bilateral hindlimb paralysis ("survival cohort"). Comparisons were made with sex-matched naïve control animals. In the prodromal cohort, splenic flow cytometry showed robust immune changes, including lymphopenia characterized by reduced $CD8^+$ T cells in septic females, and elevated myeloid-derived suppressor cells in both sexes indicating persistent immunosuppression. Despite these immune alterations, we did not observe significant differences in AT8-postive tau pathology in the hippocampus or cortex between the septic and control PS19 mice, though there were high levels of inter-sample variability. In the survival cohort, spleen cell counts remained lower in the septic animals, indicating continuing impaired immune function; however, lymphopenia was no longer evident in septic survivors. Septic PS19 mice had the same lifespan as their sex-matched control cohorts. Interestingly, region-specific analysis of AT8-positive tau revealed that the septic PS19 males exhibited lower AT8-ptau burden in the hippocampus, whereas cortical and brainstem levels remained comparable to those of sex-matched control mice. Overall, these findings suggest that peripheral inflammation does not increase the vulnerability of PS19 mice to tau-mediated neurodegeneration. Together with our previous data on TgCRND8 mice, our results indicate that peripheral inflammation has a larger role in amyloid deposition and has only modest effects on tau neuropathology.

Disclosures: Q. Vo: None. **D. Nacionales:** None. **K. Biswas:** None. **A. Iturbe:** None. **C. Gorski:** None. **L. Moldawer:** None. **P. Efron:** None. **P. Chakrabarty:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.09/D33

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01AG069447

Title: Lps-induced systemic inflammation exacerbates cognitive function by downregulating cilia function in a mouse model of alzheimer's disease

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Abstract: Background: Evidence suggests that systemic inflammation promotes Alzheimer's disease (AD) progression and may initiate AD-like pathophysiology. Peripheral administration of LPS has been widely used to investigate the effect of systemic inflammation on neuroinflammation in rodents. MyD88 is an essential adaptor molecule for LPS-induced inflammation. In our preliminary findings, whole-body MyD88 gene deficiency improves spatial cognitive deficits and enhanced learning functions in an AD mouse model. However, the mechanisms by which systemic inflammation affects AD are currently unclear. OBJECTIVE: The purpose of this study is to investigate the effects of chronic, LPS-induced systemic inflammation on AD-like learning and memory in mouse models with or without peripheral immune cell-specific MyD88 deficiency (Pko or Pwt, respectively). We hypothesize that peripheral MyD88-deficient immune cells limit the pathophysiology of AD in 3xTg mouse models directly or indirectly by suppressing LPS induced inflammation. METHODS: Elevated plus-maze data was analyzed by 2x2 ANOVAs for 2 days of testing. Unpaired t-test was used for the probe test of the Morris water maze and a 2×5 ANOVA with repeated measurements for 5-day acquisition. Hippocampal brain tissue was harvested from mice for RNA-seq to compare gene expression among experimental groups. RESULTS: In elevated plus-maze, injection of LPS (n=13) increased anxiety in PwtCwt3xTg mice by decreasing open duration ($F(1, 24) = 7.476$, $p = 0.012$) and open duration ratio ($F(1, 24) = 7.575$, $p = 0.011$), such effects were not observed in PBS control mice (n=13). LPS treatment did not affect anxiety and activities in PkoCwt3xTg mice. In the water maze acquisition phase, there is a trend of increase in latency in LPS PwtCwt3xTg group (n=12) compared to PBS PwtCwt3xTg group ($F(1, 23) = 3.456$, $p = 0.076$). In the probe trial, LPS-injected mice spent less time in the target quadrant than control mice ($F(1, 23) = 4.812$, $p = 0.039$). LPS treatment did not affect the learning ability and memory in PkoCwt3xTg mice. In RNA-seq results, LPS down-regulated the function of cilia in

PwtCwt3xTg, but not in PkoCwt3xTg mice by Gene Set Enrichment Analysis (GSEA). Conclusions: Peripheral MyD88 knockout was able to protect mice from LPS inflammation induction induced changes in learning ability. A possible mechanism is reduced function of cilia in the setting of chronic LPS-induced systemic inflammation.

Disclosures: R. Rong: None. **A. vallejos:** None. **C. Holas:** A. Employment/Salary (full or part-time): University of Illinois College of Medicine. **J. Yang:** A. Employment/Salary (full or part-time): University of Illinois College of Medicine. **K. Fukuchi:** A. Employment/Salary (full or part-time): University of Illinois College of Medicine.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.10/D34

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RO1 AG068394
NIH R21 AG077521

Title: Amyloid-β-induced neuroimmune alterations drive gut dysfunction in Alzheimer's Disease

Authors: *K. KIM, H. NAMKOONG, J. YE, M. JANAKIRAMAN, L. BECKER;
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Abstract: **Background** Amyloid-β (Aβ) accumulation, a hallmark of Alzheimer's disease (AD), disrupts brain neuroimmune interactions contributing to disease progression. Microglia, resident brain macrophages, function to clear Aβ, however, this causes them to assume a disease-associated microglia (DAM) phenotype associated with loss of homeostatic function and immune activation. Notably, Aβ also accumulates in guts of individuals with AD and AD animal models, but gastrointestinal (GI) manifestations have been poorly characterized. The goal of this study is to examine AD GI involvement with a focus on whether Aβ-driven neuroimmune alterations contributes to gut dysfunction. **Methods**
Experiments were performed on both sexes of APP/PS1 (B6;C3-Tg(APPswe/PSEN1dE9)85Dbo/Mmjax) mice, as well as C57BL/6 mice injected with Aβ fibrils. Whole gut transit time (WGTT) by carmine red dye and colonic transit by bead expulsion were assessed. Immunohistochemistry was performed on small intestine (SI) and colon muscularis tissue. Single-cell RNA-sequencing (scRNA-seq) and flow cytometry were used to characterize the macrophage phenotypes and functions. Anti-colony-stimulating factor-1 receptor (CSF1R) antibody was administered by IP injection for 2 months (mos) to deplete macrophages. **Results**
Although no differences were observed at 5 mos age, APP/PS1 mice at 8 mos exhibited reduction in Hu^+ enteric neuron density ($p<0.05$) and percent $nNOS^+$ inhibitory motor neurons ($p<0.05$) in SI and colon compared to WT mice. APP/PS1 mice had increased WGTTs ($p<0.05$) and colonic transit ($p<0.001$) compared to WT at 8 mos but not 5 mos. Aβ aggregates were

detected in muscularis macrophages (MMs), gut macrophages with functional similarities to microglia, exclusively in APP/PS1 mice. scRNA-seq of SI muscularis revealed an expansion of a DAM-like MM subset in APP/PS1 mice (8 mos). Sorted ($F4/80^{+}CD11b^{+}$) MMs from APP/PS1 mice at 8 mos but not 5 mos demonstrated elevated expression of DAM markers CD9 ($p<0.0001$) and CD11c ($p<0.05$) and decreased expression of homeostatic genes (*cx3cr1* and *p2yr12*, $p<0.05$) compared to those from WT. Aβ fibrils injected into colon of WT mice recapitulated delayed colonic transit ($p<0.0001$), reduced enteric neuron density ($p<0.05$) and increased CD9 and CD11c MM expression ($p<0.001$). Administration of anti-CSF1R antibody but not isotype control accelerated delay in gut transit and enteric neuron loss in APP/PS1 but not WT mice, highlighting a neuroprotective role for MMs in AD. **Conclusions** Our findings demonstrate that gut Aβ accumulation causes neuroimmune alterations and promotes GI dysfunction. Peripheral immune modulation offers a potential therapy for AD.

Disclosures: K. Kim: None. **H. Namkoong:** None. **J. Ye:** None. **M. Janakiraman:** None. **L. Becker:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.11/D35

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF-2022R1A2C1092997
RS-2023-00262321

Title: Early Olfactory Dysfunction and Immune Alterations in the Olfactory Epithelium of 5xFAD Mice

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Abstract: Olfactory dysfunction is a well-established early symptom of Alzheimer’s disease (AD), yet the underlying mechanisms remain poorly understood. In the central olfactory pathway, early pathological hallmarks—such as amyloid-beta and tau accumulation—have been observed in regions including the olfactory bulb, piriform cortex, and frontal cortex. In the peripheral olfactory system, studies have reported reductions in olfactory sensory neurons, decreased expression of olfactory receptor proteins, and impaired epithelial regeneration within the olfactory epithelium (OE). Despite these findings, it remains unclear how early olfactory alterations in the OE interact with central nervous system (CNS) pathology during the progression of AD. Recent studies have identified age-associated impairments in nasopharyngeal lymphatic drainage, which may disrupt local immune homeostasis in the OE. Based on this, we investigated whether such immune dysregulation in the OE contributes to early olfactory deficits

and interacts with the pathogenesis of Alzheimer's disease. We employed 5-month-old male 5xFAD transgenic mice, which are widely used as a model of Alzheimer's disease, at a stage preceding overt cognitive impairment. Behavioral assessments included the Y-maze test to evaluate spatial working memory and the peanut butter (PB) preference test to assess olfactory function, quantified as the PB/non-PB time ratio. To investigate immune alterations in the OE, $CD45^+$ immune cells were isolated and analyzed using single-cell RNA sequencing (scRNA-seq). While Y-maze performance was comparable between 5xFAD and control mice, 5xFAD mice showed a significantly reduced PB/non-PB ratio, indicating early olfactory impairment. At this stage, scRNA-seq analysis of the OE revealed marked alterations in immune cell populations, including changes in activation states and increased expression of pro-inflammatory cytokines across multiple immune subsets. These findings demonstrate that olfactory deficits emerge prior to cognitive impairment in AD model mice and are accompanied by early immune alterations in the OE. Although a direct functional link between immune changes in the OE and olfactory impairment was not established in this study, our results suggest that the peripheral immune environment may play a role in AD-related olfactory dysfunction. These insights provide a foundation for future investigations to clarify functional mechanisms and explore the potential of olfactory immune signatures as early diagnostic or therapeutic targets in AD.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.12/D36

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant R21AG08168501
Alz. Association Grant AARG-NTF-22-974072

Title: Oral Contraceptive Exposure on Neuroimmune Dynamics and Alzheimer's Disease

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Abstract: Women represent two-thirds of patients diagnosed with Alzheimer's disease (AD) cases, which suggests that sex-dependent factors which contribute to disease development. Of particular interest, ovarian hormone loss during menopause is associated with increased risk of AD while population studies show a decreased risk of AD in previous oral contraceptive (OC) users. We are interested in understanding how OC use may act as a resilience factor to delay or protect against AD-related pathologies and how OCs may alter neuroimmune dynamics. We first examined the impact of OC exposure on neuroimmune signaling at baseline and following immune challenge. Nine-week-old female C57Bl6 mice were treated for one month with daily

OC (ethinyl estradiol/EE; 0.02µg and levonorgestrel/LVNG 0.75µg) in 10% sucrose before injection of a single strand RNA TLR7 agonist (R848 in 4% DMSO and PBS; 1000 µg/kg) or a vehicle injection (4% DMSO and PBS;1000 µg/kg). Brain tissue was collected at 2 hours, 6 hours, and 24 hours post injection and cytokines were quantified in the dorsal and ventral hippocampus, hypothalamus, and prefrontal cortex. In the dorsal hippocampus, we observed that OC-treated animals showed a smaller increase in cytokines CXCL-10, IL-6, and CXCL-1 after acute immune challenge mice. In contrast, in the ventral hippocampus, the same OC-treated animals showed increases in CXCL-10 and CXCL-2 after immune challenge. In the PFC, we observed a decrease in CXCL-10 between control and OC treated mice at baseline. We generated cytokine networks which showed that OC treatment modified neuroimmune patterning at baseline and after immune challenge. These data demonstrate complex modulation of neuroimmune function in response to immune challenge by OC exposure. Based on the OC modulated neuroimmune dynamics, and protective effects of lifetime estrogen exposure, we hypothesized that OC treatment will slow AD-associated behavioral changes and pathologies including aggregation of Aβ plaques and neuroimmune activation in APP/PS1 mice. Together, this work emphasizes how hormonal states, including but not limited to OC use, can interact with risk and resilience factors like neuroimmune dysregulation to confer resilience against long term disease states like AD.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Program #/Poster #: PSTR435.13/D37

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 5R01AG054070

Title: Altered Adaptive Immune Response in Middle-Aged Adults with a Parental History of Dementia

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Abstract: The innate and adaptive immune response is dysregulated in individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD). However, the relationship between parental AD history, a well-established risk factor, and adaptive immunity in adults has been unexamined. We hypothesized that individuals with a parental history of AD have increased

cytotoxic and senescent T cells compared with individuals without parental AD. We performed flow cytometry using a 29-color antibody panel on peripheral blood mononuclear cells (PBMCs) from 113 adults aged 29-81 (mean 54.8±12.3), including non-Hispanic White (n=20), non-Hispanic Black (n=68), and Hispanic (n=25) men and women from the Offspring Study who are the adult children of participants aged 65 and older in the Washington Heights Inwood Columbia Aging Project in New York. Parents were diagnosed with AD, MCI, or normal cognitive function by an expert consensus case conference. Linear regression models tested the associations between parental AD status and the frequency of peripheral immune cells, adjusting for age and sex. We also correlated the frequency of immune cells with plasma biomarker concentrations of amyloid beta, phosphorylated tau, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP), and MRI-derived measures of cortical thickness, hippocampal volume, and atrophy. Offspring participants with a parental history of AD had lower frequencies of $CD4^+$ T cells (p=0.003), higher frequencies of $CD8^+$ T cells (p=0.0031), and decreased $CD4^+/CD8^+$ T cell ratio (p=0.0043) compared to those without a parental history of AD. Within the CD8 compartment, parental history of AD was associated with decreased frequency of central memory (TCM) $CD8^+$ T cells (p=0.046) and increased frequency of terminally differentiated effector memory (TEMRA) $CD8^+$ T cells (p=0.022). Among individuals with parental history of AD, a lower frequency of $CD8^+$ TCM cells was associated with higher NfL concentration (r=-0.29, p=0.038), while in individuals without parental history of AD, this relationship was reversed (r=0.22, p=0.037). In individuals with parental history of AD, higher levels of $CD8^+$ TEMRAs were associated with higher NfL concentrations (r=0.42, p=0.008). Immune cells were not associated with MRI measures, regardless of parental AD status. Our findings suggest that parental history of AD is associated with alterations in the adaptive immune response, specifically in the $CD8^+$ T cell compartment. These alterations are related to plasma markers of neurodegeneration. Longitudinal data are needed to determine the pathways through which adaptive immunity contributes to the increased risk of AD.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.14/D38

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH (NIA) 1RF1AG062496 to A. Dedeoglu and A. Kantarci
TÜBİTAK 2219-1059B192202848 to Z. Guney

Title: Effects of Periodontitis on Memory and Neuroinflammation in the PSAPP Murine Model of Alzheimer’s Disease

Authors: *C. M. TOGNONI[1,3], Z. GUNEY[4,5], E. H. DE SOUZA OLIVEIRA[4,6], P. ZIMMERMAN[4], N. I. KACAMAK[4,7], I. CARRERAS[1,3,2], A. KANTARCI[4,8,6], A. DEDEOGLU[1,3,9];
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Abstract: Alzheimer's disease (AD) and periodontal disease (PD) are two of the most prevalent diseases in the aging population, and evidence from our lab and others suggest they are linked bidirectionally. Previously, we demonstrated that ligature-induced experimental PD results in significant neuroinflammation as measured by Iba1-stained microglia in wildtype (WT) mice and causes dysregulation of plaque-associated microglia (PAMs) alongside elevated levels of Aβ42 in the 5xFAD mouse model of AD. Additionally, 5xFAD mice exhibit more alveolar bone loss compared to WT mice at baseline, and PD increases alveolar bone loss in both WT and 5xFAD mice. In this study, we tested the hypotheses that 1) PD induces cognitive deficits that are not normally present and may exacerbate learning and memory impairments in AD, and 2) inflammation is central to this bidirectional link between PD and AD, such that treatment with specialized pro-resolving mediators of inflammation (SPMs; e.g., lipoxins and resolvins) will restore homeostasis to improve brain health. PD was induced via ligation from 8-9 months of age in WT mice and PSAPP mice, an AD mouse model that has a relatively slow disease progression compared to 5xFAD mice. A subset of animals received SPMs (RvE1+LXA4, 1.5 μg/kg) via oral gavage 3x/week. Non-ligated and vehicle-treated animals served as controls. To examine the effects on learning and memory, mice were evaluated on the Morris water maze (MWM). At the age of 9 months, WT and PSAPP mice displayed similar acquisition of the MWM task across 4 days of 4 training trials. Interestingly, PD introduced slower acquisition of the task in both WT and PSAPP mice. Treatment with SPMs did not significantly alter learning. During a memory probe 1h following the last training trial, PSAPP mice displayed a memory deficit compared to WT mice in terms of having a reduced average proximity to the target location. In WT mice, PD resulted in deficits measured by the proximity to the target and percent time in the target quadrant, in which the latter was partially rescued by SPM treatment. In PSAPP mice, neither PD nor SPMs affected 1h probe performance. Similar trends were observed on a 24h probe. Changes in Aβ42 and microglia parallel these behavioral differences. Thus far, these results indicate that PD introduces cognitive deficits in both WTs and PSAPPs in middle age, and that SPMs may reverse the PD-induced impairment in WT but not PSAPP mice. These findings add support for the consequences of PD on the aging brain and the development of early treatment strategies using SPMs to prevent vulnerabilities to age-related memory decline and dementia, rather than a post-onset AD treatment.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Topic: C.02. Alzheimer"s Disease and Other Dementias

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Technological Research Council of Türkiye (TÜBİTAK) 2219-1059B192202848 to Z. Guney

Title: Effect of Periodontal Disease on the Blood-Brain Barrier Integrity in Murine Models of Alzheimer's Disease

Authors: Z. GUNEY[1,2], C. M. TOGNONI[3,4], K. LAUWENS[5,1], E. DE SOUZA OLIVEIRA[6,1], N. YAKAR[1], C. ALVAREZ RIVAS[7,1], O. UNLU[8,1], N. MAHATUMARAT[1], M. YU[1], G. TEZCAN[9,1], P. ZIMMERMAN[1], E. DEMIR[10,1], S. MOHAMMADI[1], A. MOHAMMADI[1], N. MEHRNIA[1], M. DAVEY[1], I. CARRERAS[4,3], A. DEDEOGLU[4,3], ***A. KANTARCI**[11,1,6];
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Abstract: Disruption of the blood-brain barrier (BBB), which maintains brain homeostasis through tight junctions (TJs), is an early event in Alzheimer's disease (AD) progression. Chronic systemic inflammation contributes to BBB breakdown. Periodontitis, a common oral inflammatory disease, elevates circulating proinflammatory cytokines that can disrupt TJs. Although the periodontal-epithelial barrier and BBB differ structurally, both rely on TJ integrity, suggesting that peripheral inflammation may influence central nervous system vulnerability. Evidence from our lab and others links periodontitis to increased cerebral beta-amyloid (Aβ) accumulation, microglial activation, and cognitive decline. To test the hypothesis that periodontal inflammation exacerbates BBB disruption and AD pathology, we used two transgenic AD mouse models (PSAPP and 5xFAD) and wild-type (WT) mice subjected to ligature-induced periodontitis (LIP) for 25 days from 8-9 months of age; a subset received specialized pro-resolving mediators (SPMs:1.5ug/kg RvE1 and LXA4) via oral gavage 3x/week. Non-ligated animals served as controls. Bone loss was assessed using morphometry and micro-computed tomography, and Aβ42 deposition was measured via immunohistochemistry. BBB integrity was evaluated in hippocampal sections by immunofluorescence for TJ proteins (occludin, claudin-5, tricellulin, and zonula occludens-1) with colocalization analysis using ImageJ. Hippocampal and cortical lysates were analyzed for hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), chitinase-3-like protein 1 (YKL-40), matrix metalloproteinase-2 (MMP-2), and interleukin-10 (IL-10) by Luminex assay. LIP caused significant bone loss in all models ($p < 0.0001$-0.05), which was reversed by SPMs in WTs ($p < 0.01$). Aβ42 levels increased in PSAPP and 5xFAD mice after LIP ($p < 0.05$), with reductions observed from SPMs. TJ protein expression was lowest in AD mice at baseline, further reduced by LIP, and was restored in 5xFADs by SPMs ($p < 0.0001$). Claudin-5 colocalization shifted

from occludin to tricellulin with LIP, which was reversed by SPMs. HGF, YKL-40, and MMP-2 were elevated post-LIP in 5xFAD brains; IL-10 rose across all models. These findings indicate that periodontal inflammation exacerbates BBB dysfunction and AD pathology, particularly in 5xFAD mice, and that resolving peripheral inflammation may offer therapeutic benefit by preserving BBB integrity and slowing disease progression.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.16/D40

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BrightFocus A2025015S
NIH R01AG076610-01

Title: Disruptions of Gut Niacin Biosynthesis exacerbates Alzheimer's Disease Pathology

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Abstract: Alzheimer’s disease (AD) is the most common form of dementia for which there is no effective treatment. Increased intake of niacin (or nicotinic acid - NA) has been correlated with a reduced risk of AD, suggesting a protective role in disease. NA crosses the blood-brain barrier and promotes a microglial neuroprotective response through the activation of the niacin receptor HCAR2. While NA can be acquired through dietary intake, it is also synthesized in the gut through the bacterial enzyme PncA (nicotinamidase), which converts NAM (niacinamide) to niacin (NA). This conversion is a determinant factor in the systemic availability of NA. Given that imbalances in gut microbiome composition have been associated with AD progression, we hypothesized that gut dysbiosis observed in AD underlies a deficit in the biosynthesis of niacin by the gut microbiome, resulting in a deficient supply of niacin to the brain, and promoting disease progression. To understand if there is an association between gut NA biosynthesis and AD progression, we analyzed the genetic abundance of bacterial enzymes involved in NA synthesis in the gut microbiome of AD patients using the human dataset AlzBiom. Furthermore, we investigated how modulation of gut-derived NA affects the progression of AD pathology in

the amyloid mouse model 5xFAD using two complementary strategies: (1) pharmacological inhibition of PncA through pyrazinecarbonitrile (PCN), and (2) gut bacterial colonization with genetically modified *E. coli* overexpressing PncA. The activity of PncA in fecal lysates from control and 5xFAD mice was also analyzed. Our preliminary data suggest that the biosynthesis of NA is disrupted in AD, which reduces the supply of endogenous NA to the brain and contributes to disease progression, possibly by dampening microglia response. These results also open the possibility of activating gut-derived niacin production as a therapeutic strategy to alleviate neurodegenerative pathophysiology in AD.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Jim and Bruce Eck Fund
Strang Neuroscience Research Award

Title: The Role of m^6A-RNA Methylation in Alzheimer's Disease Related Neuroinflammation

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Abstract: N6-methyladenosine (m^6A) is one of the most abundant and dynamic RNA modifications in eukaryotic cells, playing critical roles in regulating RNA stability, translation, and splicing. While m^6A RNA methylation has been reported to regulate peripheral immune responses, including both adaptive and innate immunity, its specific role in the central nervous system remains largely unexplored. Glial cells serve as the brain's primary immune effectors, maintaining homeostasis and responding to pathological insults. Growing evidence implicates neuroinflammation as a central driver of neurodegenerative diseases, including Alzheimer's disease (AD), where chronic glial activation leads to neuronal dysfunction and cognitive decline. However, the molecular mechanisms by which RNA modification, such as m^6A, regulate glial activation and neuroinflammation during AD pathogenesis remain to be elucidated.In this study, we sought to investigate the involvement of m^6A RNA methylation in glial activation associated with AD progression. We employed two transgenic mouse models of AD pathology: the P301S

tau model, which expresses a mutant form of human tau that promotes neurofibrillary tangle formation and neurodegeneration, and the APP-SAA knock-in model, which harbors patient mutations in amyloid precursor protein leading to amyloid-beta accumulation. Brain tissues from aged mice of these models were analyzed to assess cell type-specific changes in m^6A RNA methylation in astrocytes and microglia using immunofluorescence labeling and sequencing techniques. Our results suggest an increase in m^6A modification levels in both astrocytes and microglia as disease pathology progressed, suggesting that m^6A RNA methylation may be involved in driving glial responses during neurodegeneration. To further investigate the functional role of m^6A in regulating glial activation, we utilized STM2457, a selective small-molecule inhibitor of the m^6A "writer" enzyme METTL3, which catalyzes the methylation of adenosine residues on RNA. Treatment with STM2457 in primary glial cultures exposed to oligomeric tau species—a toxic form implicated in tau spreading—suggested that reduction of m^6A methylation attenuated activation of both astrocytes and microglia. This was evidenced by decreased secretion of inflammatory cytokines and diminished morphological changes associated with activation phenotypes.These findings highlight a potential therapeutic avenue in which modulating RNA methylation could alleviate neuroinflammation and glial-mediated toxicity in Alzheimer's disease.

Disclosures: A. Tucker: None. **C. Sepehri:** None. **D. Patel:** None. **Q. Wang:** None. **S. Yuan:** None. **E. Sherman:** None. **A. Downey:** None. **D. Goldberg:** None. **L. Jiang:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.18/D42

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Sex-specific angiogenin regulation in alzheimer's disease reveals divergent inflammatory profiles and molecular subtypes in females

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Abstract: Alzheimer's disease (AD), the most common neurodegenerative disorder characterized by progressive cognitive decline and dementia, affects approximately 15% of individuals over 65 and over 50% of those over 80. Despite extensive research, AD pathogenesis remains incompletely understood, and effective treatments are still lacking. Recent studies highlight the ribonuclease angiogenin (ANG) and tRNA-derived fragments (tRFs) as emerging players in pathological aging and AD development, both of which are associated with mitochondrial dysfunction, oxidative stress, and chronic neuroinflammation. ANG, a stress-responsive ribonuclease, inhibits apoptosis, partly through generating 5′-tiRNA fragments that suppress caspase activation. However, its expression patterns and regulatory mechanisms in aging and AD remain poorly defined. In this study, we investigated ANG expression and regulation across

cellular and animal models of aging and AD, postmortem human brain tissue, and large-scale transcriptomic datasets (n=644). Using [^{32}P]-Northern blotting, RT-qPCR, and Western blotting, we found that ANG is dysregulated in a sex-dependent manner in both aging and AD, leading to altered levels of 5′-tiRNA$^{Gly-GCC}$. In a subset of females, reduced levels of inflammasome markers such as NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) and the downstream pro-inflammatory cytokine interleukin-1β (IL-1β) suggest the presence of a neuroprotective mechanism that attenuates neuroinflammation. In contrast, in male AD patients, increased oxidative stress appears to drive ANG downregulation, potentially impairing its protective effects and exacerbating inflammation. These results support a sex-specific model where ANG and its cleavage product, 5′-tiRNA$^{Gly-GCC}$, exert anti-inflammatory effects in female AD. Furthermore, using large-scale transcriptomic clustering approaches such as UMAP and HDBSCAN, we identified three female-specific ANG-associated, AD-related molecular subtypes: a Neuroinflammatory subtype, an Intermediate Protective subtype with a distinct microglial profile, and a Strongly Protective/Homeostatic subtype characterized by active microglial phagocytosis. These subtypes highlight ANG's potential role in modulating disease progression in females. Our findings position ANG as a key regulator of neuroinflammation and apoptosis in AD, offering a promising new road for the development of early biomarkers and targeted therapeutic strategies.

Disclosures: M. Joerg: None. **K. Friedland:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Carnosine modulates oxidative stress, inflammation, and phagocytosis in an in vitro Alzheimer's disease model

Authors: *S. BARBATI[1,2], V. CARDACI[3], L. DI PIETRO[4], M. ZUPAN[7], A. GRAZIANI[1], K. PARTSINEVELOS[5], G. CAROTA[4], A. PRIVITERA[4], S. M. LUNTE[8], A. AMORINI[4], F. CARACI[6], M. HARTLEY[7], G. CARUSO[1,9];
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Abstract: Carnosine (β-alanyl-L-histidine) is an endogenous dipeptide widely distributed in excitable tissues including the brain. It has antioxidant, anti-inflammatory, and anti-aggregation properties, and it could be used to treat pathologies characterized by oxidative stress such as Alzheimer's disease (AD). Glial cells, particularly microglia and astrocytes engage in a fine-tuned and tight crosstalk and represent the major players in the neuroinflammatory response occurring in AD. In the present study, we evaluated the effect of carnosine on primary mixed glia cultures - composed by astrocytes and microglia - exposed to Aβ1-42 oligomers. Countess 3 FL Automated Cell Counter together with MTT and LDH assays were used to investigate the toxic effect of Aβ1-42 oligomers and the therapeutic potential of carnosine in a mixed glia culture. Cell Counter and microchip electrophoresis were employed to measure the production of key elements related to oxidative/nitrosative stress, namely nitric oxide (NO) and total ROS. Variability in single cell morphology (circularity and size) as well as NO and ROS production was studied using Matlab R2021b. qRT-PCR and Western Blot were used to measure expression of genes and proteins related to oxidative stress and inflammation, while fluorescent latex beads were employed to investigate phagocytosis process.Our data show that Aβ1-42 oligomers decreased metabolic activity of mixed glia cultures without affecting cell viability, with astrocytes being more sensitive than microglia to Aβ1-42 oligomers treatment. This metabolic alteration was paralleled by a significant increase in cell oxidative stress status evaluated through intracellular levels of NO and total ROS, which were both significantly counteracted by carnosine treatment. This protective activity was paralleled by reduction in inflammatory mediator levels and enhancement of phagocytosis, with astrocytes showing greater responsiveness.All together our findings open a new path to exploring the therapeutic potential of carnosine in oxidative stress and neuroinflammation leading to neurodegenerative disorders such as AD.

Disclosures: S. Barbati: None. **V. Cardaci:** None. **L. Di Pietro:** None. **M. Zupan:** None. **A. Graziani:** None. **K. Partsinevelos:** None. **G. Carota:** None. **A. Privitera:** None. **S.M. Lunte:** None. **A. Amorini:** None. **F. Caraci:** None. **M. Hartley:** None. **G. Caruso:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.20/D44

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Ipsc-derived cerebral organoids to advance drug discovery for neuroinflammation and alzheimer's disease

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Abstract: Emerging as a translational model, 3D cerebral organoids derived from induced pluripotent stem cells (iPSCs) recapitulate human brain developmental processes and disease-

associated phenotypes. Cerebral organoids reflect human brain biology with a physiologically relevant microenvironment that surpasses traditional 2D neuronal cultures. These features make cerebral organoids valuable for studying neurodegenerative diseases like Alzheimer's disease and neuroinflammation. In this study, we evaluated the expression of neural lineage markers in mature cerebral organoids including astrocytes, oligodendrocytes, dopaminergic neurons, mature neurons, and immature neurons, collectively demonstrating that cerebral organoids can be successfully developed with cortical-like organization containing abundant mature neurons and astrocytes. Using this model, we investigated two major disease mechanisms. First, we examined Aβ accumulation and the efficacy of anti-Aβ drug in Alzheimer's disease pathogenesis. We employed a chemical induction strategy targeting the posttranslational processing of amyloid precursor protein using the Aβ42 inducer Aftin-4. During 14 days of treatment, we observed increased Aβ42 fragment secretion and elevated Aβ42/Aβ40 ratios. The BACE1 inhibitor LY2886721 significantly attenuated Aβ42 secretion and restored Aβ42/Aβ40 ratios. Second, treatment of cerebral organoids with a cytokine mixture (TNF-α, IL-1α, and IL-1β) robustly induced neuroinflammatory responses. Cytokine-treated cerebral organoids showed significantly elevated secretion of inflammatory mediators (IFN-γ, IL-6, IL-8, and IL-13) with dose-dependent increases. Correspondingly, mRNA levels of inflammatory markers (MCP-1, IL-6, and IL-8) were altered in parallel with secreted cytokine profiles. Taken together, we demonstrated cytokine-driven neuroinflammation and Aftin-4-induced Alzheimer's-like pathology models in cerebral organoids, with pharmacological intervention effectively reversing disease phenotypes. This organoid-based platform shows translational potential for accelerating therapeutic development against neuroinflammation and Alzheimer's disease.

Disclosures: B. Wang: None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.21/D45

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Research Foundation of Korea (NRF) No. 2022R1A2C209333612
Welfare and Ministry of Science and ICT, Korea (HU21C0086

Title: Leucine-rich α-2-glycoprotein (LRG1) promotes IL-6-mediated oAβ aggregation and LCN2 secretion in the Alzheimer disease mice model

Authors: *S. KIM[1], Y. LEE[2], S. KIM[3];
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Abstract: Leucine-rich α2-glycoprotein (LRG) is an approximately 50-kDa glycoprotein that has been found to be elevated in the sera of patients with several types of disease. LRG directly binds to transforming growth factor beta 1 (TGFβ1) and modulates TGFβ1 signaling in BBB pericyte and endothelial cells; however, the precise function of LRG in cancer remains unclear. This study aimed to investigate the role of LRG in Alzheimer disease (AD). AD mice (APP/PS/Tau) hardly expressed LRG. The expression of LRG1 in the AD mice was significantly increased compared with wild-type (WT) mice. Conversely, downexpression of LRG significantly inhibited the oAβ and LCN2 secretion in WT mice. In the presence of LRG, IL-6, TGFβ1 significantly inhibited the growth of Hippocampal cells and endothelial cell line, bEND3 cells in vitro by inducing apoptosis via the potent activation of gp-130 and its downstream signaling pathway. Furthermore, administration of a IL-6 inhibitor significantly enhanced the growth of neuronal cells in WT mice compared with AD mice via inhibition of apoptosis. We propose that LRG potentiates the effect of TGFβ1 and IL-6 in neuronal cells and whose growth is suppressed and induced oAβ and LCN2 secretion in the presence of IL-6 and TGFβ1.

Disclosures: S. Kim: A. Employment/Salary (full or part-time): bundang hospital in seoul national university. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Research Foundation of Korea (NRF), Korea Health Industry Development Institute. **Y. Lee:** None. **S. Kim:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.22/D46

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

Support: 5R01NS114130
R01AG075820

Title: Type 1 and Type 2 IFN dependent signatures exhibit divergent age and Alzheimer's Disease related trajectories in the mammalian brain

Authors: *A. DABDAB BRANDELLI, R. KUMARI, P. KUMAR, U. SRIVASTAVA, S. RANGARAJU;
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Abstract: Neuroinflammation, either in a casual or consequential role, is a hallmark of Alzheimer's Disease (AD). Interferons (IFN), the master regulators of innate immune responses, are one of the critical mediators of neuroinflammation. Several studies have identified IFN specific signatures in microglia in aging and AD. However, the IFN subtypes (Type 1 and Type 2) specific responses to aging and pathological progression of AD are not well characterized. In

this study we performed RNA sequencing on mouse-derived primary microglia and immortalized microglial cell line (BV2) post exposure to Type 1 (1000 U/ml) and Type 2 (100 ng/ml), to derive molecular signatures of Type 1, Type 2 and shared Type 1/2 IFN signatures. We then mapped trajectories of these IFN signatures with aging and AD pathologic progression in wild-type (WT) and amyloidosis (5xFAD) mouse (1.8-14 months) brains, and with pathology in human postmortem AD brains. Type 1 IFN upregulated 2,322 and 1,974 downregulated genes. As expected, several genes associated with innate immune responses like *Stat1* and *Ifi207*, known for positive regulation of Type 1 IFN signaling, are being upregulated, while *Ifi27*, a negative regulator of RIG1 mediated IFN signaling, is downregulated. Similarly, in Type 2 IFN, 2,140 upregulated and 2,652 downregulated genes were identified. Classic antigen processing genes like *Cd14* and *H2-DMa* were differentially regulated upon Type 2 IFN treatment. Interestingly, Type 1 and Type 2 IFN have differential effects on *Samhd1*, a potent antiviral protein. Overall, the level of concordance between Type 1 and Type 2 IFN-induced changes were surprisingly small with only 111 genes increased in both, with a 2.6% overlap on DEGs. We used an eigenprotein approach to measure Type 1 (n= 825), Type 2 (n= 913) and shared (n= 111) IFN signatures in mouse brain proteomes from WT and 5xFAD mice. The Type 1 IFN signature showed similar age-dependent decline, while type 2 IFN signature increased with age, in both WT and 5xFAD brain. Surprisingly, only the shared Type 1/2 IFN signature showed a more pronounced age-dependent induction in 5xFAD as compared to WT brain, suggesting amyloidosis-driven mechanisms. In human brain proteomes from AD-dementia, asymptomatic AD and non-pathology controls, we found that Type 1, Type 2 and shared IFN signatures decreased in AD cases, as compared to controls. In summary, we have defined distinct and overlapping Type 1 and Type 2 IFN signatures in microglia. We observed that aging decreases Type 1 and increases Type 2 IFN signatures in the brain, independent of amyloidosis with a small group of Type 1 and Type 2 IFN shared signatures specifically upregulated in 5xFAD.

Disclosures: A. Dabdab Brandelli: None. **R. Kumari:** None. **P. Kumar:** None. **U. Srivastava:** None. **S. Rangaraju:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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

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NIH 5P30CA138292

Title: Repurposing FDA-Approved Drugs to Disrupt the p38/MK2 Complex and Suppress Neuroinflammation in Alzheimer’s Disease

Authors: J. GRALLA[1], P. FLEMING[1], K. NEGRÓN[1], E. J. MILLER[1], T. BEYETT[1], Z. WEN[2], Y. DU[1], H. FU[1], *A. A. IVANOV[1];
[1]Pharmacol. and Chem. Biol., Emory Univ. Sch. of Med., Atlanta, GA; [2]Departments of Psychiatry & Behavioral Sciences, Cell Biology, Neurology, and Human Genetics, Emory, Sch. of Med., Atlanta, GA

Abstract: Neuroinflammation is a central driver of Alzheimer's disease (AD) pathogenesis and represents a compelling target for therapeutic intervention. The interaction between p38 mitogen-activated protein kinase (p38) and MAPK-activated protein kinase 2 (MK2) forms a critical regulatory node in microglial cytokine production, orchestrating the translation of proinflammatory mediators such as TNF-α, IL-1β, and IL-6. Despite the central role of this axis, existing p38 and MK2 inhibitors have not yet achieved FDA approval, underscoring the need for alternative therapeutic strategies to disrupt this interaction. We present an integrative platform that combines modeling, virtual screening, and high-throughput assays to identify p38/MK2 disruptors, with a focus on repurposing approved drugs for the treatment of neuroinflammation. Computational mapping and peptide competition assays confirmed the p38 docking groove as a ligandable and functionally essential interface. Virtual screening prioritized Nilotinib, a clinically approved BCR-ABL inhibitor, as a putative disruptor of the p38/MK2 complex. Molecular dynamics simulations revealed a stable binding pose within the docking groove, stabilized by hydrogen bonding and solvent-mediated interactions. Biochemical assays confirmed that Nilotinib binds p38, displaces MK2, and attenuates cytokine production in human microglial cells. Structure-activity relationship (SAR) analysis of Nilotinib analogs identified key aromatic moieties and hydrogen bond features critical for activity, informing future scaffold optimization. To expand beyond the Nilotinib chemotype, we developed a lysate-based time-resolved FRET (TR-FRET) assay compatible with ultra-highthroughput screening. This platform identified additional active compounds, including the FDA-approved α_1-adrenergic receptor antagonists Doxazosin, Terazosin, and Alfuzosin, which similarly disrupted the p38/MK2 interface and suppressed cytokine responses in microglia. Together, these findings reveal a non-ATP-competitive strategy to modulate microglial activation and demonstrate the potential of drug repurposing to accelerate the development of neuroimmune therapies for Alzheimer's disease.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Program #/Poster #: PSTR435.24/D48

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

Support: L. Calvier was supported by TARCC grant

Title: Identify and target mediators of the brain-periphery crosstalk to treat neuroinflammation and cognitive decline in advanced Alzheimer's disease.

Authors: S. WU[1], C. R. WASSER[2], J. HERZ[1], ***L. CALVIER**[1];
[1]UT Southwestern Med. Ctr., Dallas, TX; [2]UT Southwestern Med. Ctr., Fort Worth, TX

Abstract: Alzheimer's disease (AD) is characterized by two core pathologies: amyloid β plaques and neurofibrillary tangles. Despite therapeutic efforts focusing on these pathologies, success in the clinic has been limited. To address this challenge, alternative mechanisms are under investigation, and the presence of a low-grade, presymptomatic but sustained immune response has emerged as a third core pathology. This unresolved neuroinflammation relies on the activation of resident microglia and the recruitment of circulating leukocytes through a leaky blood-brain barrier (BBB). We hypothesize that restoring BBB integrity through targeted intervention, focusing on the circulating endothelial factor Reelin, will reduce neuroinflammation and improve AD outcomes. Here, we uncover key mediators of a previously underestimated brain-periphery communication axis, wherein Aβ deposition activates skull bone marrow niches via the glymphatic system, driving the secretion of circulating Reelin, a glycoprotein that exacerbates BBB dysfunction, leukocyte infiltration, and neuroinflammation. Using the anti-Reelin antibody CR-50, we selectively depleted circulating Reelin in preclinical AD models, preserving its protective functions in the central nervous system (CNS). This approach restored BBB integrity, reduced neuroinflammation, and improved cognitive performance in both early and advanced stages of disease in 5xFAD and APP^{NL-F} mouse models. Our findings challenge the traditional view of inflammation as a linear process in AD, showing instead that inflammation peaks during early Aβ deposition, after which a subset of inflammatory factors, including Reelin, remain persistently elevated and sustain chronic disease progression. Importantly, we demonstrate that Reelin depletion does not impair CNS Reelin expression or neuronal function, ensuring therapeutic safety. Our study challenges traditional views on brain-peripheral immune communication, revealing the activation of skull bone marrow niches during AD. It identifies new circulating factors from the skull bone marrow, such as Reelin, that propagate neuroinflammation and may serve as therapeutic targets to disrupt the chronic inflammatory loop in AD.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Program #/Poster #: PSTR435.25/D49

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

Support: 1RF1AG074256-01A1

Title: Human hiPSC-NSC-Derived EVs Treatment in the Advanced Stage of Alzheimer's Disease Can Diminish Neuroinflammation and Improve Neurogenesis and Cognitive Function

Authors: ***S. REDDY**[1,2], L. N. MADHU[2], Y. SOMAYAJI[2], V. RAO[2], G. SHANKAR[2], S. ATTALURI[2], A. NANGIA[2], X. RAO[2], C. FAN[3], S. RAO[2], B. SHUAI[2], A. K. SHETTY[2]; [1]Cell Biol. and Genet., Texas A&M, College Station, TX; [2]Inst. For Regen Med, Texas A&M Univ. Coll Med., College Station, TX; [3]Inst. For Regen Med, Texas A&M Univ. Coll Med., College station, TX

Abstract: Cognitive and memory impairments worsen with time in Alzheimer's disease (AD), likely due to increased deposition of amyloid plaques, activation of multiple neuroinflammatory signaling cascades, elevated hyperphosphorylation of tau, and progressively increasing loss of synapses and neurons. Previous studies in our laboratory have shown that intranasal (IN) interventions with extracellular vesicles (EVs) from human induced pluripotent stem cell (hiPSC)-derived neural stem cells (NSCs) in the early phase of AD can maintain better cognitive and mood function in the later phase of disease in 5xFAD mice, a model of rapidly progressing AD (Madhu et al., Journal of Extracell Vesicles, 2024). In this study, we investigated the effects of IN administration of hiPSC-NSC-EVs starting from 7 months of age in 5xFAD male and female mice, an age when these mice exhibit significant amyloid plaque accumulation, pronounced chronic neuroinflammation, and cognitive deficits. We intranasally administered hiPSC-NSC-EVs or the Vehicle (VEH) monthly for 3 months (20 or 60 billion EVs per month). One month after the final administration (i.e., at 10 months of age), we interrogated mice using multiple neurobehavioral tests to evaluate cognitive function. In comparison to significant cognitive impairments in AD mice receiving VEH in all cognitive tests performed, AD mice receiving higher (60 billion) monthly doses of hiPSC-NSC-EVs displayed an improved proficiency for object recognition memory, associative recognition memory, pattern separation, and spatial memory in various object-based tasks and a Y-maze test. In contrast, AD mice receiving the lower (20 billion) dose of hiPSC-NSC-EVs per month exhibited impairments across most of these cognitive tasks. Furthermore, brain tissue analysis revealed reductions in amyloid beta plaques, astrocytic hypertrophy, microglial clusters, and percentages of microglia displaying inflammasome complexes in male and female 5xFAD mice receiving higher doses of hiPSC-NSC-EVs. Analysis using 5'-bromodeoxyuridine (BrdU) labeling of newly born cells and BrdU and neuron-specific nuclear antigen dual immunofluorescence and confocal microscopy revealed reduced net hippocampal neurogenesis in both male and female 5xFAD mice receiving vehicle treatment. However, male 5xFAD mice receiving higher doses of EVs presented elevated levels of net hippocampal neurogenesis. Thus, intermittent hiPSC-NSC-EVs treatment commencing in the advanced stage of AD can also improve cognitive function in 5xFAD mice, in association with reduced neuroinflammation and amyloid plaques, as well as enhanced neurogenesis in a dose-dependent manner.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.26/D50

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

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Title: Sex Dysmorphism in Alzheimer's Disease: Estrogen Receptor-Beta Deficiency is associated with Increased Retinal and Cerebral Inflammation in Female Patients

Authors: *S. SHAHIN[1], B. GAIRE[1], A. RENTSENDORJ[2], D.-T. FUCHS[3], M. DAVIS[3], E. ROBINSON[3], N. SWERDLOW[3], A. KISSEL[2], L. HAGERMAN[1], A. WILLIAMS[2], K. BLACK[4], L. SCHNEIDER[3], Y. KORONYO[3], M. KORONYO-HAMAOUI[3];
[2]Dept. of Neurosurg., [3]Dept. of Neurosurgery, Maxine Dunitz Neurosurgical Res. Inst., [4]Dept. of Neurosurgery, Maxine Dunitz Neurosurgical Res. Institute,, [1]Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Women have a greater lifetime risk (1 in 5) of developing Alzheimer's disease (AD) than men (1 in 10), underscoring sex-related differences in prognosis, biomarkers, and risk factors. However, how sex interacts with AD is understudied. The hallmark AD pathologies, amyloid-beta (Aβ) deposits and hyperphosphorylated tau (pTau) forming neurofibrillary tangles (NFTs), extend to the retina, but the impact of sex on retinal AD pathology is unknown. We performed multiple analyses of over 20 histopathological AD biomarkers in the retina of male and female patients with mild cognitive impairment (MCI due to AD; n=18) or AD dementia (n=86), compared to aged matched cognitively normal controls (NC; n=30). Statistical tests included 2-way ANOVA with Bonferroni's post-test correction for over 3-group and Student's *t*-test for 2-group comparisons. Pearson's correlation coefficient (*r*) analysis was used to determine the association of retinal AD markers with retinal and brain parameters. Female AD brains exhibited significant increase in NFT severity and retinas showed a trend toward increased pTau and NFTs (MC1~1.69-fold) compared to males, with no sex difference in cerebral and retinal Aβ burden. In males, but not females, retinal $A\beta_{42}$ and oligomeric Aβ strongly associated with brain Aβ plaques (*r=0.62-0.74),* and more strongly corelated with cognition (*r=-0.66-0.70)*. In females, but less in males, retinal Oligo-tau strongly correlated with cognitive status (*r=-0.69)*. Intriguingly, retinal vascular $A\beta_{40}$ deposition was significantly higher (~1.7-fold) in AD males and its burden was strongly linked to retinal microgliosis (*r=0.8)* in females. Notably, significant increases in retinal gliosis (IBA1~1.4-fold; GFAP~1.2-fold) were observed in AD females *vs* males. Furthermore, in females, but not males, both retinal micro- and macro-gliosis very strongly associated with retinal $A\beta_{42}$ and Oligo-tau forms (*r=0.83-0.90)*. Given the increased gliosis in female AD patients, the expression of estrogen receptor-β (ER-β), a female sex

hormone receptor that regulates neuroinflammation and confers neuroprotection, was investigated. For the first time, we identified a significant ~50% reduction in ER-β in MCI and AD ($p<0.0001$) retinas, with a greater decline in both the retina and brain of AD females *vs* males ($p<0.05$), particularly in astrocytes. Overall, this study reveals sex dimorphism in the AD retina, with females showing increased inflammation and marked astrocytic ER-β loss, suggesting a critical role of estrogen signaling and chronic gliosis in mediating disease progression, and underscores the importance of incorporating sex as a biological variable in AD research.

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Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

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Program #/Poster #: PSTR435.27/D51

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

Title: Sex chromosomes and gonadal hormones contribute to lymphocyte brain localization and inflammatory responses in a mouse model of Alzheimer’s Disease

Authors: *H. ZUPPE[1], B. CASALI[2], E. G. REED[3];
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Abstract: There are approximately 6.7 million cases of Alzheimer’s Disease (AD) in the US, with 1 in 3 seniors dying from AD or another dementia. Women are disproportionally affected by AD, making up two-thirds of patients, and there are notable sex differences in disease onset and progression. Understanding of the mechanisms contributing to these differences remains elusive. The *overall objective* of this work is to identify the contribution of sex chromosomes and gonadal hormones to the brain localization and inflammatory response of lymphocytes by using the Four Core Genotype (FCG) mouse model, which separates chromosomal and gonadal sex, coupled with the 5xFAD model of AD. The presence of ovaries drives $CD3^+$ cell infiltration into the brain parenchyma compared to testes-bearing mice, while the sex chromosomes have no effect. Sex chromosomes seem to drive the production of antibodies by B cells and the overall inflammatory milieu of the brain as defined by notable T cell cytokines, as XY mice are more inflammatory than XX mice. However, gonadal sex also plays a role as ovary-bearing mice were more inflammatory than testes-bearing mice. Our results suggest sex chromosomes and gonadal hormones both influence the inflammatory response of AD but may influence each other in previously unknown ways.

Disclosures: H. Zuppe: None. **B. Casali:** None. **E.G. Reed:** None.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.28/D52

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1R43AG082625-01A1
NIH Grant R44ES029898

Title: Reproducible planar organoids for the study of AD-associated neuroinflammation

Authors: N. Y. YUAN, W. RICHARDS, K. PARHAM, S. VISURI, ***R. GORDON**, C. LEBAKKEN;
Stem Pharm, Inc., Madison, WI

Abstract: The role of neuroinflammation in neurodegeneration has been increasingly implicated as a critical driver of disease development and progression. As the resident immune cells of the CNS, glia play a critical role in the production and propagation of inflammatory mediators such as cytokines, chemokines, reactive oxygen species, and bioactive lipids. The study of the activation, resolution, and failure of resolution of neuroinflammation by glial cells is of significant interest. Elucidating this process will further our understanding of neurodegenerative diseases and aid in the development of therapeutic treatments. Most research on neurodegenerative disorders takes a neuro-centric approach to modeling the disease, and therapeutic intervention focuses on neuroprotection. Further, most research is performed in either 2D or 3D *in vitro* systems having only neural lineage cells. Recent advances in differentiation of human induced pluripotent stem cells (hiPSCs) have enabled great strides in generating models with greater recapitulation of the multi-cellular components present in the human brain. Stem Pharm's multicellular cerebral organoids contain neurons, astrocytes, endothelial cells, and microglia and are ready for research use within 21 days. Bulk and single cell RNA-seq analysis of these organoids demonstrate high intraclass correlation and low coefficients of variation between biological replicates. Stem Pharm's organoid system eliminates much of the inherent variability in organoids by leveraging a proprietary synthetic hydrogel platform which facilitates formation of reproducible glia-containing organoids with responsive astrocytes and microglia. Herein, we characterize and describe the neuroimmunological response of Stem Pharm's organoids containing either APOE3/3 or APOE4/4 microglia to recombinant rAPOE4 protein (rAPOE4) and amyloid beta (Aβ) as a model for Alzheimer's Disease (AD)-associated neuroinflammation. Analyses include immunofluorescence staining and imaging, cytokine and biomarker quantification, and transcriptional analysis. Complex multicellular neural organoid systems bridge the gap between the *in vitro* to *in vivo* and can provide crucial and fundamental information leading to therapeutic development with high translational relevance.

Disclosures: **N.Y. Yuan:** A. Employment/Salary (full or part-time): Stem Pharm. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm. **W. Richards:** A. Employment/Salary (full or part-time): Stem Pharm. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm. **K. Parham:** A. Employment/Salary (full or part-time): Stem Pharm. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm. **S. Visuri:** A. Employment/Salary (full or part-time): Stem Pharm. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm. **R. Gordon:** A. Employment/Salary (full or part-time): Stem Pharm. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm. **C. Lebakken:** A. Employment/Salary (full or part-time): Stem Pharm. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm.

Poster

PSTR435: Neuroimmune Mechanisms of Alzheimer's Disease II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.29/D53

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

Support: NIH Grant 1R15NS125564-01
The Wooten Family Initiative for Brain Health Research

Title: Neuroimmune Mechanisms of Rab10 in Alzheimer’s Disease

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Abstract: Rab10, a small Rab GTPase with a crucial role in vesicular trafficking, has been implicated in Alzheimer’s disease (AD) and Parkinson’s disease (PD). A rare functional Rab10 variant, which leads to reduced activity, confers resilience against AD even for high-risk individuals. To identify the mediators of Rab10-dependent neuroresilience, we developed Rab10 heterozygous knockout mice ($Rab10^{+/-}$). Transcriptome profiling of $Rab10^{+/-}$ mice revealed elevated activation of pathways associated with neuronal metabolism, structural integrity, neurotransmission, and neuroplasticity, and reduced activation of the pathways involved in neuroinflammation and aging. In the brain of $Rab10^{+/-}$ mice, the baseline activation status of the microglia (Iba1-immunoreactivity) in the hippocampus was significantly reduced. Next, we analyzed the baseline activation status of peripheral immune cells in $Rab10^{+/-}$ mice. We evaluated the activation state and the immunophenotype of specific immune cells isolated from the spleen using flow cytometry. The % of natural killer (NK) cells was significantly

downregulated in the spleen of $Rab10^{+/-}$ mice compared to $Rab10^{+/+}$ littermates. There was no difference between genotypes in total cell numbers for CD8 and CD4 lymphocytes; however, the % of CD8 effector cells was significantly lower, and the % of CD4 effector cells was significantly higher in $Rab10^{+/-}$ mice. Therefore, our data suggest a role for Rab10 in innate immunity that has been shown to contribute to AD progression. To gain mechanistic insights, we treated $Rab10^{+/-}$ and $Rab10^{+/+}$ organotypic hippocampal slices with oligomeric amyloid (oAβ42) or scrambled Aβ peptide as a control, followed by measurement of cytokine release into the culture medium using the Luminex multiplex assay. We found that the release of IL1-β, TNFα, and IFNγ from $Rab10^{+/-}$ hippocampal slices treated with oAβ42 was significantly lower compared to littermate $Rab10^{+/+}$ slices of the same treatment. We conclude that by attenuating neuroinflammation and modulating immune cell phenotypes, Rab10 reduction offers a promising therapeutic avenue for prevention or treatment of AD.

Disclosures: W.P. Bunner: None. **K. Surabhi:** None. **J. Carver:** None. **A. Didonna:** None. **E. Szatmari:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.01/D54

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CIHR Grant PJT- 173540
PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research, and funding partners listed on the PPMI website

Title: Evaluating APOE4's effect on gray matter structure and its link to cognitive function in Parkinson's disease: A PPMI cohort study

Authors: *A. E. ROSAL[1,2], E. TORRES CARMONA[2,1], S. L. MARTIN[1,3], I. BOILEAU[1,2], A. GRAFF-GUERRERO[4,2,1], A. P. STRAFELLA[1,2,5];
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Abstract: Cognitive impairment is a well-established non-motor symptom of Parkinson's Disease (PD), yet the underlying factors that lead to its development in PD subjects remain elusive. *Apolipoprotein E4* (*APOE4*), a genetic risk factor of Alzheimer's Disease, has been associated with PD-related cognitive impairment, though its contribution to this symptom is unclear due to inconsistent findings. Gray matter abnormalities, specifically reduction in gray

matter volume (GMV) and cortical thickness (CTh), have been observed in both subjects with PD-related cognitive impairment and *APOE4* carriers independently. However, limited studies have explored *APOE4's* impact on these gray matter measures and its association with cognitive function in a PD cohort. This study aimed to assess the role of *APOE4* on cognitive function in PD by analyzing its effects on GMV and CTh using Parkinson's Progression Markers Initiative (PPMI) data (https://www.ppmi-info.org). Baseline T1-weighted MRI scans of 51 PD *APOE4* carriers (58.75 ± 9.11 years; 16 females, 35 males) and 120 PD *APOE4* non-carriers (62.96 ± 9.15 years; 48 females, 72 males) were processed using FreeSurfer 7.1 to extract GMV and CTh measures. Primary analyses examined these measures for 7 bilateral *a priori* and 6 exploratory regions of interests associated with PD-related cognitive impairment. Secondary analyses examined GMVs of hippocampal subregions due to prior evidence of their atrophy in PD subjects with cognitive deficits. ANCOVA models in RStudio controlling for age, sex, disease duration, and total intracranial volume (TIV) revealed increased GMV in the left angular gyrus (AnG) and decreased GMV in the left nucleus accumbens (NAcc) of PD *APOE4* carriers compared to non-carriers ($p < 0.05$). However, these differences did not survive multiple comparison correction. No group differences were observed for regional CTh measures and hippocampal subregion GMVs. Follow up Pearson correlations in RStudio showed that the GMV of the left AnG was positively correlated with visuospatial function in both groups, but it did not remain significant after covariate adjustment using regression analyses. GMV of the left NAcc was also positively correlated with visuospatial ability as well as executive function and working memory, but only in PD *APOE4* non-carriers with and without covariate adjustment. These findings suggest that *APOE4* may not affect GMV and CTh in a way that impacts cognitive function in early PD. Future work will conduct longitudinal analyses to confirm these controversial findings and determine whether the observed GMV differences represent early changes that precede PD-related cognitive impairment.

Disclosures: A.E. Rosal: None. **E. Torres Carmona:** None. **S.L. Martin:** None. **I. Boileau:** None. **A. Graff-Guerrero:** None. **A.P. Strafella:** F. Consulting Fees (e.g., advisory boards); A.P.S serves on the Board Directors of Parkinson Canada and Canadian Academy Health Sciences. A.P.S was a past consultant for Hoffman La Roche. Other; A.P.S received honoraria from GE Health Care Canada LTD, Hoffman La Roche.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.02/D55

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Apoe ε4 genotype predicts increased hippocampus-olfactory tract connectivity

Authors: T. BITHER[1], ***T. IKUTA**[2];
[1]Univ. of Miami, Coral Gables, FL; [2]Univ. of Mississippi, Oxford, MS

Abstract: Olfactory dysfunction is one of the earliest non-cognitive signs of Alzheimer's disease (AD) and may reflect early network-level changes preceding clinical symptoms. This study investigates whether genetic risk for AD, specifically APOE ε4 carriage, is associated with altered functional connectivity between the hippocampus and olfactory-related brain regions. Resting-state functional MRI data were analyzed from 126 older adults (mean age = 71.8 ± 6.9 years; 53% female) obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Participants represented a spectrum of clinical diagnoses, including cognitively normal individuals and those with mild cognitive impairment or Alzheimer's disease. Functional connectivity was computed between the bilateral hippocampi and four predefined olfactory regions: anterior piriform cortex, posterior piriform cortex, olfactory bulb, and olfactory tract. Multiple linear regressions assessed whether APOE ε4 allele count, age, sex, and clinical diagnosis predicted connectivity strength. APOE ε4 carriage was significantly associated with increased hippocampal connectivity to both the olfactory bulb ($p = .026$) and olfactory tract ($p = .022$), independent of diagnosis and age. No significant associations were found in the piriform regions. Age was also positively associated with connectivity in the olfactory tract. These findings suggest that hippocampus-olfactory tract connectivity may serve as an early neural signature of genetic vulnerability to AD, potentially preceding overt clinical decline. The olfactory-hippocampal network represents a promising target for future biomarker development and early intervention strategies in at-risk populations.

Disclosures: T. Bither: None. **T. Ikuta:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.03/D56

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Reliable Antibodies for Neuroscience: APOE4 as a Case Study of Abcam's Enhanced Validation Framework

Authors: J. TANJORE RAMANATHAN[1], C. HIRST[1], A. KARPATI[2], A. GALLI[1], W. HOWAT[3], ***S. SBACCHI**[1];
[1]Abcam Ltd, Cambridge, United Kingdom; [2]Abcam Inc., Cambridge, United Kingdom; [3]Abcam, Cambridge, United Kingdom

Abstract: Reliable antibody performance is essential for neuroscience research, particularly when investigating disease-associated targets such as Apolipoprotein E4 (APOE4), a key genetic risk factor for Alzheimer's disease (AD). Conventional antibody validation methods often fall short in addressing the complexity of human tissue expression and disease heterogeneity. To overcome these limitations, an enhanced validation framework was developed that integrates disease-relevant tissue profiling. This approach combines multiple validation steps, including isoform-specificity testing and generating detailed IHC expression profiles in selected formalin-

fixed paraffin-embedded (FFPE) human tissue microarrays (TMA) using automated immunohistochemistry (IHC) platforms. As a case study, a recombinant rabbit monoclonal antibody (RabMab®) targeting APOE4, clone EPR24181-64 (ab279714), was validated across multiple IHC automated platforms. The antibody demonstrated high specificity, effectively distinguishing APOE4 from the closely related APOE2 and APOE3 isoforms. In AD brain tissues, it revealed distinct expression patterns in amyloid-beta plaques and neurovascular compartments, with minimal background staining in normal brain and peripheral tissues. Additional profiling across nervous system tumours and multi-cancer TMAs confirmed its selectivity and utility in a range of pathological contexts. This study highlights the value of enhanced antibody validation in de-risking reagent selection and ensuring robust, reproducible results in neuroscience research. The APOE4 case exemplifies how rigorous Abcam's antibody validation can accelerate discovery and translational applications in neurodegenerative disease.

Disclosures: J. Tanjore Ramanathan: A. Employment/Salary (full or part-time): Abcam. **C. Hirst:** A. Employment/Salary (full or part-time): Abcam. **A. Karpati:** A. Employment/Salary (full or part-time): Abcam. **A. Galli:** A. Employment/Salary (full or part-time): Abcam. **W. Howat:** A. Employment/Salary (full or part-time): Abcam. **S. Sbacchi:** A. Employment/Salary (full or part-time): Abcam.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.04/D57

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Davos Alzheimer's Collaborative (DAC) Global Cohorts program

Title: Apoe, sex, and alzheimer's disease: investigating their interplay in the egyptian population

Authors: *M. OTHMAN;
Inst. of Global Hlth. and Human Ecology, Sch. of Sci. and Engineering, The American Univer, Cairo, Egypt

Abstract: This study investigates the interplay between the APOE gene, sex, and Alzheimer's Disease (AD) within the Egyptian population, addressing a significant gap in current research. As Egypt faces a rising prevalence of dementia due to an ageing population, understanding genetic risk factors becomes crucial. We explore the distribution of APOE alleles (ε2, ε3, ε4) and their association with Alzheimer's Disease, emphasizing the gene's role as a predominant genetic risk factor, particularly the ε4 allele. Study findings indicate APOE ε3 is common in Egyptians, variability of ε2 and ε4 alleles, and potential sex contribution to disease risk despite statistical insignificance. This research aims to elucidate how genetic predispositions and geographical factors intertwine, ultimately guiding targeted prevention strategies tailored to the unique genetic

context of Egypt. By examining these connections, we aspire to contribute to a deeper understanding of dementia risk and inform healthcare practices in the region.

Disclosures: M. Othman: None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.05/D58

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Apoe4 mice show reduced glymphatic clearance and impaired neurovascular coupling

Authors: *K. GUSAROVA[1], C.-Y. YANG[2], M. H. MURDOCK[3], M. KAHN[4], J. PARK[5], N. LAVOIE[7], M. R. ZOLLER[6], D. PARK[8], Z. KE[3], K. GALANI[3], L.-H. TSAI[3,9];
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Abstract: The glymphatic system clears waste from the brain via cerebrospinal fluid (CSF) influx along perivascular spaces, a process modulated by vasomotion and astrocytic water channels. Prior studies show that non-invasive audiovisual stimulation at 40 Hz (gamma frequency) enhances glymphatic clearance in Alzheimer's disease (AD) mouse models. However, it is unknown whether APOE4, a major genetic risk factor for late-onset AD, disrupts this response. Here, we investigated how APOE4 affects glymphatic function and its modulation by 40 Hz stimulation in young, pre-symptomatic mice. We used 6-month-old mice expressing humanized ApoE isoforms—either the Alzheimer's-associated APOE4 allele or the control APOE3 allele. A cranial window over the frontal cortex enabled in vivo two-photon imaging to assess CSF influx from arterial perivascular spaces into the brain parenchyma and arteriolar vasomotion. Vascular and CSF tracers were introduced via retro-orbital injection to monitor the CSF influx. Two-photon imaging was conducted under Ketamine-Xylazine anesthesia and in awake mice before and during 40 Hz audiovisual stimulation (light flicker and auditory clicks). Following imaging, aquaporin-4 (AQP4) polarization at astrocytic endfeet was analyzed via immunofluorescence staining. Under KX anesthesia, APOE4 mice exhibited reduced CSF influx into both the perivascular space and parenchymal compartments, along with diminished arteriolar vasomotion at ultraslow frequencies (<0.1 Hz), compared to APOE3 controls. AQP4 polarization at astrocytic endfeet surrounding arterioles was also impaired in APOE4 mice. In awake APOE3 mice, 40 Hz stimulation markedly increased both CSF influx and vasomotion. In contrast, APOE4 mice exhibited only minimal changes, indicating a blunted neurovascular response. Our results indicate that the APOE4 allele impairs glymphatic function and neurovascular dynamics at an early, pre-symptomatic stage. The attenuated response to

multisensory stimulation suggests deficits in neurovascular coupling, potentially contributing to early vulnerability and progression of Alzheimer's disease in APOE4 carriers.

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Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.06/D59

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG086313
NIH Grant AG059762

Title: Apoer2 splicing and APOE isoforms drive distinct gene expression in the brain: understanding mechanisms underlying Alzheimer's disease risk

Authors: *S. A. KISTLER[1,3], C. M. GALLO[3,1], R. BOZADJIAN[2], M. DOWGIEWICZ[1], W. OO[1], U. BEFFERT[1], A. HO[1];
[1]Biol., [2]Computing & Data Sci., Boston Univ., Boston, MA; [3]Pharmacology, Physiol. & Biophysics, Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: The two largest risk factors for Alzheimer's disease (AD) are age and the ε4 allele of apolipoprotein E (*APOE*). APOE is involved in neuronal lipid homeostasis and binds to several transmembrane lipoprotein receptors, including APOER2. APOER2 is a synaptic receptor which undergoes extensive alternative splicing. Recent studies have implicated aberrant RNA splicing changes in AD pathogenesis, particularly within *APOER2*. Notably, human *APOER2* exon 18 inclusion is reduced in AD brains compared to non-cognitively impaired controls, suggesting APOER2 isoforms may have isoform-specific roles in AD susceptibility. Supporting this, enhancing *Apoer2* exon 19 inclusion (murine exon 19 = human exon 18) via antisense oligonucleotide in an amyloid mouse model rescues spatial learning deficits. This exon encodes a proline-rich cytoplasmic domain critical for Reelin-induced hippocampal long-term potentiation, highlighting the functional significance of alternative splicing in synaptic plasticity and cognition. Despite this, the interplay between APOE isoforms and APOER2 splice variants, and how they together impact neuronal and brain function, is still not well understood. To investigate this, we generated four novel mouse lines by crossing *Apoer2* +ex19 or Δex19 (excludes exon 19) knock-in mice with humanized *APOE3* and *APOE4* targeted replacement mice resulting in the following homozygous lines: *Apoer2* $+ex19^{\varepsilon3/\varepsilon3}$, $+ex19^{\varepsilon4/\varepsilon4}$, $\Delta ex19^{\varepsilon3/\varepsilon3}$, and $\Delta ex19^{\varepsilon4/\varepsilon4}$. Bulk RNA sequencing of hippocampi from 3-month-old males followed by gene ontology (GO) and ingenuity pathway analysis (IPA) revealed that *Apoer2* at exon 19 drives widespread transcriptomic changes, with distinct exon 19 and APOE-dependent effects. When comparing $+ex19^{\varepsilon3/\varepsilon3}$ vs $\Delta ex19^{\varepsilon3/\varepsilon3}$ mice, differentially expressed genes (DEGs) were enriched in GO terms

related to serine-type endopeptidase activity and humoral immune response pathways. When we compared +ex19$^{\varepsilon4/\varepsilon4}$ vs Δex19$^{\varepsilon4/\varepsilon4}$ mice, most DEGs were associated with DNA-binding transcription activator and peptidase inhibitor activities. Validation by qPCR across both sexes and multiple brain regions confirmed DEGs linked to serine-type endopeptidase activity, suggesting potential alteration in microglial responses and neuroinflammation. Future studies will investigate DEG expression patterns in the brain and examine differences in microglial morphology across these mouse lines. In summary, *Apoer2* exon 19 splicing regulates global transcriptomic profiles in the brain, which are further modulated by *APOE* isoforms, potentially influencing AD risk through pathways involved in neuroinflammation and synaptic plasticity.

Disclosures: S.A. Kistler: None. **C.M. Gallo:** None. **R. Bozadjian:** None. **M. Dowgiewicz:** None. **W. Oo:** None. **U. Beffert:** None. **A. Ho:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.07/D60

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CBR-FABRIC Grant

Title: Group 1 mGluR stimulation rescues apoe4-mediated translation defect in neurons

Authors: *B. K RADHAKRISHNA, R. MUDDASHETTY;
Ctr. For Brain Research, IISc, Bengaluru, India

Abstract: Apolipoprotein E4 (APOE4) is the most recognized risk factor for Alzheimer's disease, implicated in early neurodegeneration and impaired synaptic plasticity. In neurons, APOE4 treatment disrupts basal and NMDAR-mediated calcium signaling, further disrupting translation response. mGluRs, another major class of glutamate receptors, also play a critical role in synaptic plasticity through activity-dependent protein synthesis. Here, we examine neuronal translation response to mGluR stimulation in the presence of APOE4. In DIV15 primary cortical neurons, APOE4 treatment induces translation inhibition, rescued by stimulation of mGluRs for 5 minutes. This mGluR-mediated rescue is driven by phosphorylation of RPS6, downstream of the mTOR pathway, which is abolished by rapamycin treatment. This rescue is independent of calcium-mediated translation inhibition induced by APOE4, demonstrating an independent role for mTORC1 activity in maintaining mGluRs' translation capacity under APOE4 exposure. A potential mGluR-mediated compensation for the effects of APOE4 suggests a dynamic mechanism for the induction of plasticity in human APOE4 carriers. This study provokes the critical need to explore the synaptic dynamics in the presence of APOE4 and its impact on cognition.

Disclosures: B. K radhakrishna: None. **R. Muddashetty:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.08/D61

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association ABA-22-974612 to CYP
NIH-NIA F31AG079540 to AKL

Title: Differential Regulation of APOE4-Mediated Astrocytic Lipid Metabolism by BMP Signaling Exacerbates Alzheimer's Disease Pathologies

Authors: *C.-Y. PENG[1], A. LINDEN[1], A. AFFANEH[2], J. A. KESSLER[1];
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Abstract: The two greatest risk factors for Alzheimer's Disease (AD) are Apolipoprotein E4 polymorphism (APOE4) and aging, yet how these factors interact remain unclear. In this study, we investigate how bone morphogenetic protein (BMP) signaling, which increases with age, contributes to APOE4-induced lipid metabolic dysfunctions using induced-pluripotent stem cell (iPSC)-derived astrocytes and cocultured neurons. Surprisingly, BMP signaling differentially altered lipid droplet formation, cholesterol synthesis and breakdown, and fatty acid-oxidation in APOE4 compared to APOE3 astrocytes, and increased secretion of oxidized LDL (oxLDL). Furthermore, neurons cocultured with BMP4-treated APOE4 astrocytes showed altered transcriptomic profiles based on scRNA-seq as well as increased tau phosphorylation (p-tau). oxLDL treatment similarly increased p-tau and reduced neuronal survival. Conversely, lipid uptake inhibition in neurons rescued the BMP4/APOE4 astrocyte-induced neuronal phenotype. These data demonstrate key interactions between APOE4 and aging-associated molecular signaling in AD pathogenesis and establish a causal linkage between astrocytic lipid metabolism and neuronal tau hyperphosphorylation.

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Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.09/D62

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG055770
RF1AG076124
R01AG067063
R01AG054434
R21AG056518
P30AG066530
GC-201711-2014197

Title: Cellular senescence induced by cholesterol accumulation is mediated by lysosomal ABCA1 in APOE4 and AD

Authors: *S. WANG[1], B. LI[3], B. E. KERMAN[2], D. A. BENNETT[4], Z. ARVANITAKIS[5], H. N. YASSINE[1];
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Abstract: Background: Cellular senescence, a hallmark of aging, has been implicated in Alzheimer's disease (AD) pathogenesis. Cholesterol accumulation is known to drive cellular senescence; however, its underlying mechanisms are not fully understood. ATP-binding cassette transporter A1 (ABCA1) plays an important role in cholesterol homeostasis, and its expression and trafficking are altered in APOE4 and AD models. However, the role of ABCA1 trafficking in cellular senescence associated with APOE4 and AD remains unclear. Methods: We examined the association between cellular senescence and ABCA1 expression in human postmortem brain samples using transcriptomic, histological, and biochemical analyses. Unbiased proteomic screening was performed to identify the proteins that mediate cellular ABCA1 trafficking. We created ABCA1 knock out cell lines and mouse models to validate the role of ABCA1 in cholesterol-induced mTORC1 activation and senescence. Results: Transcriptomic profiling of the human dorsolateral prefrontal cortex from the Religious Order Study/Memory Aging Project (ROSMAP) cohort revealed the upregulation of cellular senescence transcriptome signatures in AD, which correlated with ABCA1 expression and oxysterol levels. Immunofluorescence and immunoblotting analyses confirmed increased lipofuscin-stained lipids and ABCA1 expression in AD brains and an association with mTOR phosphorylation. Discovery proteomics identified caveolin-1, a sensor of cellular cholesterol accumulation, as a key promoter of ABCA1 endolysosomal trafficking. Greater caveolin-1 expression was observed in APOE4-TR mouse models and AD human brains. Oxysterol induced mTORC1 activation and senescence were regulated by ABCA1lysosomal trapping. Treatment of APOE4-TR mice with cyclodextrin reduced brain oxysterol levels, ABCA1 lysosome trapping, mTORC1 activation, and attenuated senescence and neuroinflammation markers. Conclusions: Oxysterol accumulation in APOE4 and AD induced ABCA1 and caveolin-1 expression, contributing to lysosomal dysfunction and increased cellular senescence markers. This study provides novel insights into how cholesterol metabolism accelerates features of brain cellular senescence pathway and identifies therapeutic targets to mitigate these processes.

Disclosures: S. Wang: None. **B. Li:** None. **B.E. Kerman:** None. **D.A. Bennett:** None. **Z. Arvanitakis:** None. **H.N. Yassine:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.10/D63

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01 AG082315

Title: Apolipoprotein E (APOE) Modulates Microglial Stress Response via TFEB-Mediated Transcription

Authors: *X. LI[1], D. VILLALVA[2], L. STREHLE[1], J. FREIMAN[4], K. L. TAMASHIRO[3], R. LEE[5];
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Abstract: Apolipoprotein E (APOE), particularly the ε4 allele, is a major genetic risk factor for late-onset Alzheimer's Disease (AD). It is thought that the ε4 allele is a hypomorph with reduced function such as lipid transport and clearance. Studies have shown a pronounced stress response in mice that harbor a knockout of APOE and in humans that carry two copies of the risk allele, yet the molecular impact of ε4 on the stress response remains incompletely understood. FKBP5 and NR3C1 are stress response genes that are central to glucocorticoid signaling and neuroinflammatory regulation. Here, we examined whether APOE modulates expression of these genes through TFEB, a key transcription factor for lysosomal and autophagy genes. The mouse BV-2 microglial cell line, a well-characterized in vitro model, exhibits microglial properties in maintaining neural homeostasis through processes like autophagy and inflammatory regulation. Dysregulation of these functions is implicated in the pathogenesis of neurodegenerative diseases such as AD.We used mouse BV-2 microglial cells with APOE knockdown via three siRNA constructs. qRT-PCR confirmed >70% APOE suppression across all three constructs (p 0.001). APOE knockdown significantly elevated *Fkbp5* expression and decreased *Nr3c1* expression (p 0.05). Correlation analysis across knockdown and control samples showed that APOE expression negatively correlated with *Fkbp5* ($p = 0.03$) and positively with NR3C1 ($p = 0.005$).To understand underlying mechanisms, we conducted ChIP assay using TFEB antibody. APOE knockdown samples showed detectable DNA-protein complexes (72-174 ng/ml), while scrambled controls showed no detectable DNA after immunoprecipitation. These results suggest that APOE reduction enhances TFEB binding to DNA, potentially at TFEB-binding CLEAR motifs within *Fkbp5* and *Nr3c1* regulatory regions. We are currently sequencing these ChIP products to identify gene-sets and pathways involved with APOE knockdown and TFEB activation. Together our data suggest that APOE may inhibit TFEB-mediated transcription under basal conditions, and its knockdown removes this inhibition, leading to altered levels of autophagy- and stress-related genes with implications for neuroinflammation and neurodegeneration in AD.

Disclosures: X. Li: None. **D. Villalva:** None. **L. Strehle:** None. **J. Freiman:** None. **K.L. Tamashiro:** None. **R. Lee:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.11/D64

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MJFF grant #023040
MJFF grant #024855

Title: Discovery of agonists for the APOE4 regulated gene GPR4 for Alzheimer's disease therapy

Authors: *R. URFER, A. URFER-BUCHWALDER;
Selonterra, Inc., San Mateo, CA

Abstract: The apolipoprotein E gene variant APOE4 is the most clinically significant genetic risk factor for late onset Alzheimer’s disease. We previously showed that the single nucleotide polymorphism that defines APOE4 (i.e. a C/T transition) creates a de novo binding motif for nuclear respiratory factor NRF1. This suggests that APOE4 could act as a transcriptional enhancer for genes located in its chromosomal vicinity. The present study was designed to first identify these APOE4 dysregulated genes using human neurons derived from induced pluripotent stem cells (iPSC) and then investigate how these genes affect pathways dysfunctional in AD. We identified a key gene, GPR4, located on human chromosome 19 about 0.68 Mb downstream of APOE4, that is downregulated in both isogenic and Alzheimer’s disease patient-derived neuronal lines homozygous for APOE4. GPR4 is a pH-sensitive G-protein-coupled receptor that signals through the cAMP and RhoA pathways. We validated this new target by using pharmacological (GPR4 antagonist and GPR4 agonist tool compound) and molecular (siRNA) tools and established a link of GPR4 function with the expression of YAP1, a transcription factor coactivator that is downregulated in early AD and controls key AD pathways. We performed a high throughput screening campaign and identified a potent and selective small molecule GPR4 agonist lead compound (SLC2101). This compound restored gene expression dysfunction and levels of well-established disease markers (amyloid beta and phosphorylated tau) in human iPSC-derived APOE4 neurons. SLC2101 improved long-term potentiation (LTP) deficits in hippocampal slices of two independent Alzheimer’s disease genetic animal models (APOE4 targeted replacement mice and APP Swedish transgenic mice) suggesting effectiveness in addressing early pathological events. We then engaged in a medicinal chemistry effort to optimize SLC2101 and identified the compound SLC2443 that is metabolically stable in murine systems, shows higher potency as a GPR4 agonist and restored the LTP deficit at a lower concentration. Further lead optimization and generation of in vivo data will allow us to select the best compound to enter into IND-enabling studies. In conclusion, GPR4 agonists offer

exceptional opportunities for the chronic therapy of Alzheimer's disease and other neurodegenerative diseases with cognitive impairments such as Parkinson's disease.

Disclosures: R. Urfer: A. Employment/Salary (full or part-time): Selonterra, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Selonterra, Inc. **A. Urfer-Buchwalder:** A. Employment/Salary (full or part-time): Selonterra, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Selonterra, Inc..

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.12/Web Only

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Transcriptomic Analysis Reveals Lipid Neurotransmitter Pathways Underlying APOE2-Specific Neuroprotection in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD), the most prevalent form of dementia, is characterized by progressive neurodegeneration and brain atrophy. The apolipoprotein E (APOE) gene, encoding a lipid transporter expressed in the central nervous system and the periphery, is the strongest genetic risk factor for sporadic AD. Among the three major human APOE isoforms, APOE4 confers the highest AD risk, APOE2 is associated with reduced risk and APOE3 is generally considered risk-neutral. Despite these associations, the molecular mechanisms by which APOE isoforms modulate AD susceptibility remain incompletely understood.To explore isoform-specific pathways, we analyzed transcriptomic data from RNA-seq datasets (GSE18867, GSE234711) from brains of APOE-targeted replacement (TR) mice expressing human APOE2, APOE3, or APOE4. RNA was extracted from 12- and 18-month-old hemibrains to assess gene expression. Using a false discovery rate < 0.05 and $|\log_2$ fold change$| > 0.25$, we identified 250 upregulated and 464 downregulated genes in APOE2 TR mice relative to APOE3, and 1,021 upregulated and 993 downregulated genes in APOE4 TR mice.Several lipid-signaling related genes were differentially expressed among APOE genotypes. *Pla2g4e*, a phospholipase A2 enzyme that generates N-acyl phosphatidylethanolamines (NAPEs), was significantly upregulated in APOE2 brains at both timepoints in comparison with APOE3 and APOE4, while NAPE-degrading enzymes *Faah* and *Naaa* were unchanged, suggesting potential NAPE accumulation. NAPEs and their derivatives, N-acyl ethanolamines (NAEs), are lipid neurotransmitters with anti-inflammatory and neuroprotective functions. *Cyp2j13*, which converts arachidonic acid to epoxyeicosatrienoic acids (EETs) - lipid messengers with neuroprotective properties - was also upregulated in APOE2 mice. Other lipid signaling genes

with anti-inflammatory, antioxidant functions *(Pafah2*, *Ubiad1*, *Ech1*, *Me1)*, were also upregulated in APOE2 mice*,* whereas *Nnmt* and *Bco2,* which are pro-inflammatory, were downregulated.Together, this study reveals novel isoform-specific modulation of lipid neurotransmitters in aging brains. The upregulation of anti-inflammatory, neuroprotective lipid messengers and suppression of pro-inflammatory ones in APOE2 mice supports the model in which APOE2 confers neuroprotection through lipid-mediated signaling pathways. The upregulation of *Pla2g4e* and *Cyp2j13* in APOE2 mice suggests a mechanistic link between APOE genotype and a neuroprotective lipid environment, highlighting *PLA2G4E* and *CYP2J13* as promising therapeutic targets for mitigating AD progression.

Disclosures: L. Wang: None. **Q. Wang:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.13/E1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Characterization of induced pluripotent stem cell (iPSC)-derived Apolipoprotein E models of Alzheimer's Disease

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Abstract: Alzheimer’s disease (AD) is the most common form of dementia; however, modeling this disease has proven incredibly challenging. The generation of human induced pluripotent stem cells (iPSCs) and the subsequent development of complex human cell culture systems can be leveraged to improve the translation of AD research to clinical trials. These models can be used to represent both sporadic and familial disease populations, with sporadic AD (sAD) comprising the majority of patients. In order to model the sAD population, we focused on the major genetic risk factor for late-onset Alzheimer’s Disease (LOAD), Apolipoprotein E4 (ApoE4). ApoE is a lipid transporter, and ApoE4 has a reduced ability to bind to lipids compared to the other isoforms. ApoE4 has also been associated with multiple pathological processes involved in AD, such as amyloid-beta (Aβ) and tau pathology. Therefore, we utilized iPSC-derived neurons, astrocytes and microglia to investigate the role of ApoE4 in AD pathology. Specifically, we examined mitochondrial function, lipid and cholesterol metabolism, as well as Aβ production and clearance. We identified differences in lipid accumulation between non-AD associated (ApoE3/E3) and ApoE4/E4 iAstrocytes and preliminary data suggests increased Aβ40 and Aβ42 peptide production in ApoE4 iNeurons. ApoE4 is also known to drive an altered inflammatory phenotype in astrocytes and microglia. Thus, we examined the addition of ApoE4 astrocyte conditioned media (ACM) and microglia conditioned media (MCM) on iPSC-derived

neurons and its effect on viability, as well as amyloid and tau pathogenesis. Going forward, these models will be used to test potential novel therapeutic compounds for the treatment of AD.

Disclosures: G. Sonsalla: A. Employment/Salary (full or part-time): MSD (UK) Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MSD (UK) Limited. **K. Hawkins:** A. Employment/Salary (full or part-time): MSD (UK) Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MSD (UK) Limited. **J. Howden:** A. Employment/Salary (full or part-time): MSD (UK) Limited. **B. Timkova:** A. Employment/Salary (full or part-time): MSD (UK) Limited. **A.T. Wolman:** A. Employment/Salary (full or part-time): Merck & Co., Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck & Co., Inc. **J. Brownlees:** A. Employment/Salary (full or part-time): MSD (UK) Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MSD (UK) Limited.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.14/E2

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Apoe4-mediated glial lipid dysregulation disrupts brain circuitry and exacerbates neurological dysfunction following isoflurane exposure

Authors: *Y. LI[1], Y. JI[3], C. UZUN[4], S. T. ISLAM[5], H. LEE[2], Z. WANG[6], H. LI[1], J. JONES[3], S. LIU[7], J. WU[8];
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Abstract: General anesthesia (GA), while essential for surgical and diagnostic procedures, has been linked to olfactory and cognitive impairments and may increase the risk of Alzheimer's disease (AD). Apolipoprotein E4 (APOE4), the strongest genetic risk factor for AD, is present in up to 65% of patients and contributes to disease pathogenesis through lipid dysregulation. However, the impact of GA and surgery (GA/OP) on APOE-associated neurological vulnerability remains poorly understood, highlighting the need to elucidate the underlying mechanisms. To investigate this, we utilized humanized APOE4 and APOE3 mice subjected to laparotomy combined with a 2-hour exposure to isoflurane. We assessed lipid composition,

molecular changes, and functional outcomes using liquid chromatography-tandem mass spectrometry (LC-MS/MS), bulk RNA sequencing (RNA-seq), and behavioral testing. Initial analysis of the olfactory bulb (OB) via LC-MS/MS revealed elevated levels of fatty acids and lipid peroxidation in APOE4 mice at 7 days post-GA/OP. Notably, APOE4 mice also displayed consistently lower triglyceride levels in the OB compared to APOE3 controls, signaling the disruption of lipid homeostasis. In contrast, the hippocampus (HI) exhibited a broad downregulation of hexosylceramides and cardiolipins, indicative of disrupted bioenergetics and mitochondrial dysfunction. Cell type-specific lipid profiling further revealed more pronounced lipid perturbations in microglia and astrocytes isolated from the OB and HI of APOE4 mice at 7 days post-GA/OP. Complementary *in vivo* electrophysiological recordings from the OB and HI showed exacerbated neural circuit disruptions and altered neuronal excitability in APOE4 mice relative to APOE3 mice following GA/OP. Behavioral assessments demonstrated persistent deficits in odor memory lasting up to 83 days post-procedure. These were accompanied by transient reductions in olfactory sensitivity at 12 and 37 days post-GA/OP, as well as impaired motor coordination on the rotarod during weeks 1 and 2. While immediate cognitive impairments were not observed, APOE4 mice developed delayed deficits in learning and memory, as evidenced by impaired Y-maze performance. Finally, RNA-seq analysis of the OB at 90 days post-GA/OP revealed downregulation of genes involved in lipid metabolism and atherosclerosis pathways in APOE4 mice compared to APOE3 counterparts. Collectively, these findings provide molecular, cellular, and circuit-level insights into the mechanisms underlying olfactory impairments and delayed cognitive dysfunction in humanized APOE4 mice following isoflurane exposure and surgery.

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Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.15/E3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA RF1AG057933
NIA R01AG055798

Title: Influence of apolipoprotein E and amyloid-associated proteins on Arctic amyloid beta deposits in an App knock-in mouse model

Authors: *C. ANGELLE[1], G. XU[2], K. N. MCFARLAND[3], A. ITURBE[4], P. SACILOTTO[7], S. FROMHOLT[5], S. PROKOP[6], P. CHAKRABARTY[5], D. R. BORCHELT[5];
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Abstract: Apolipoprotein E (apoE), the strongest genetic risk factor for late-onset Alzheimer's disease, (AD) facilitates the deposition of amyloid β (Aβ) in the brain. ApoE and other proteins co-deposit with Aβ, potentially modulating the maturation and pathologic features of Aβ plaques in Alzheimer's disease. Knowledge from such studies can provide insight into the role of apoE and related family of proteins in the deposition, evolution and maturation of parenchymal Aβ pathology. We used hAbetaSAA (Jax Labs Strain 034711) mice crossed with human *APOE* targeted replacement mice (Patrick Sullivan, Duke University) to create hAbetaSAA mice homozygous for human *APOE* E2 (SAA-APP/E2), *APOE* E3 (SAA-APP/E3) or *APOE* E4 (SAA-APP/E4). Neuropathological examination of mouse brain tissue was conducted via immunohistochemistry and immunofluorescence; gene expression analysis was performed with NanoString Neuropathology codesets. Protein colocalization analysis was conducted by creating overlays of consecutive sections of immunohistochemically-stained mouse brain tissue. We examined mice at ages of 5, 8 and 13 months, finding that SAA-APP/E4 showed higher Aβ deposition relative to SAA-APP/E3 and SAA-APP/E2 mice. SAA-APP mice expressing mouse *Apoe* had the highest Aβ plaque deposition across ages, supported by increased astrocytosis and gene expression patterns related to the DAM phenotype. We did not observe sex-dependent variations in Aβ deposition in any of these four lines. However, female SAA-APP/E4 mice showed a faster rate of Aβ deposition compared to male SAA-APP/E4 mice, indicating a possible sex, genotype and age interaction. Deletion of mouse *Apoe* resulted in reduction in Aβ deposition when tested at early ages up to 11 months. SAA-APP/E4 mice had larger plaque sizes on average compared to SAA-APP/E3 and SAA-APP/E2 mice, though ubiquitin staining revealed similar morphological attributes. We also examined colocalization of apoE, Aβ deposits, and proteins recently identified as amyloid associated proteins (AAP's). C1qtnf4 immunostaining with Aβ deposits was the same across all *APOE* genotypes, while apoD immunostaining was relatively increased in deposits in the SAA-APP/E3 mice. Consistent with previous data in *APP* transgenic mice, we show that SAA-APP knock-in mice expressing an Arctic variant of Aβ follows the expected amyloid burden and inflammatory profile of Apoe>>APOE4>APOE2~APOE3>>>Apoe KO. Whether association with specific brain AAP's found in Alzheimer's disease patients imparts functional differences across apoE isoforms relevant to Aβ deposition remains to be investigated.

Disclosures: C. Angelle: None. **G. Xu:** None. **K.N. McFarland:** None. **A. Iturbe:** None. **P. Sacilotto:** None. **S. Fromholt:** None. **S. Prokop:** None. **P. Chakrabarty:** None. **D.R. Borchelt:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.16/E4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Intravenous delivery of a bi-functional AAV gene therapy to reduce endogenous ApoE4 and express ApoE2 in ApoE4 humanized mice

Authors: *M. GRANNAN[1], C. COLPAN[1], M. DALRYMPLE[1], M. PARANJPE[1], G. RIVERA[1], J. STUDER[1], J. ROUTHIER[1], D. SHAH[1], A. JOHNSON[1], Y. ITO[3], J. THOMPSON[1], M. NONNENMACHER[1], T. CARTER[2], R. SIVASANKARAN[1];
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[3]Voyager Therapeutics, Inc, Lexington, MA

Abstract: Apolipoprotein E (ApoE) genotype represents the most significant genetic risk factor for Alzheimer's disease (AD), with distinct allelic variants exerting differential effects on disease susceptibility and progression. The ApoE2 allele is associated with a reduced risk and offers a protective effect, whereas the ApoE4 allele markedly elevates the risk of developing AD and is linked to an earlier onset of symptoms. Consequently, therapeutic strategies aimed at modulating ApoE expression, such as adeno-associated virus (AAV)-mediated delivery of the protective ApoE2 isoform and/or knockdown of ApoE4 expression, are emerging as promising avenues for intervention in AD pathogenesis. Here, we describe identification of siRNAs targeting APOE in silico, confirmation of potent siRNAs in vitro, and subsequent vectorization using proprietary amiRNA cassettes for in vivo evaluation. We then demonstrate IV delivery of investigational AAV therapeutic candidates that combine expression of human APOE-targeting artificial microRNAs with concomitant ApoE2 expression via single dose IV-delivery using Voyager's proprietary, VCAP-Gen2 BBB-penetrant capsid. We observed significant reduction of endogenous ApoE4 in key AD-relevant brain regions of ApoE4 knock in mice, while significantly increasing expression of the ApoE2 isoform. We conclude that utilization of a novel BBB-penetrant capsid delivering a bi-functional payload effectively modulates the level of ApoE2 and 4, and is a viable approach that will be further evaluated in pre-clinical studies.

Disclosures: M. Grannan: A. Employment/Salary (full or part-time): Voyager Therapeutics. **C. Colpan:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **M. Dalrymple:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **M. Paranjpe:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **G. Rivera:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **J. Studer:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **J. Routhier:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **D. Shah:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **A. Johnson:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **Y. Ito:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **J. Thompson:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **M. Nonnenmacher:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **T. Carter:** A. Employment/Salary (full or part-time): Voyager Therapeutics. **R. Sivasankaran:** A. Employment/Salary (full or part-time): Voyager Therapeutics.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.17/E5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Apoech variant improves therapeutic efficacies of ipsc-derived mesenchymal stromal cells against neurodegeneration

Authors: *P. RODRIGUEZ MARTINEZ[1], A.-C. RAULIN[2], A. R. YSLAS[1], S. BAKER[1], T. KANEKIYO[3];
[1]Neurosci., [2]Mayo Clin., Jacksonville, FL; [3]Neurosci., Mayo Clin. Jacksonville, Jacksonville, FL

Abstract: Title: APOE3Ch variant improves therapeutic efficacies of iPSC-derived mesenchymal stromal cells against neurodegenerationAuthors: Paula Rodriguez Martinez, Ana-Caroline Raulin, PhD., Meeia Parsons, Aria R. Yslas, PhD., Samantha K. Baker, Takahisa Kanekiyo, M.D. PhD.Background: The use of mesenchymal stromal cells (MSCs) has been identified as a potential cell-based therapy for the treatment of neurodegenerative diseases such as Alzheimer's Disease (AD) due to their anti-inflammatory and promotion of neurogenesis. A rare variant of the apolipoprotein E (APOE) gene known as APOE3 Christchurch mutation (APOE3Ch), which encodes for the p.R136S mutation within the receptor binding domain of APOE3, has been shown to be protective against the familial AD cases carrying PSEN1 p.E280Amutation. We aim to investigate the therapeutic properties of induced pluripotent stem cell (iPSC)-derived MSCs (iMSCs) with APOE3 or APOE3Ch.Methods: We differentiated two isogenic PSC lines carrying either APOE3 or APOE3Ch into iMSCs. The effects of APOE3Ch on the immunomodulatory, angiogenic, and metabolic properties in the iMSCs were investigated using multiple functional assays. We also assessed their ability to support endothelial barrier integrity by measuring Transendothelial Electrical Resistance (TEER) in vitro. In addition to that, their effect on neurite growth and neuronal survival was assessed through a series of assays.Results: Our results found that APOE3Ch iMSCs have higher mitochondrial activity than those with APOE3 through Seahorse XF. APOE3Ch iMSCs had greater immunomodulatory capabilities, as shown by a greater reduction in the LPS-induced inflammatory response of human monocyte THP1 reporter cell line. Furthermore, hBMEC/D3 endothelial cells were more prone to assemble into tubular networks when co-cultured with APOE3Ch iMSCs than with APOE3 iMSCs, suggesting that the APOE3Ch variant has a stronger angiogenic effect. Additionally, preliminary results suggest that endothelial barrier integrity was improved when in contact with APOE3Ch iMSCs. Similarly, survival and neurite growth of iPSC neurons were facilitated by the exposure to the secretome of APOE3Ch iMSCs.Conclusions: Our findings support the notion that the APOE3Ch variant improves the immunomodulator and neurotrophic role of iMSCs, suggesting additional protective mechanisms associated with APOE3Ch against neurodegeneration in AD.

Disclosures: P. Rodriguez Martinez: None. **A. Raulin:** None. **A.R. Yslas:** None. **S. Baker:** None. **T. Kanekiyo:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.18/E6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Evaluating the role of ApoE4 on insulin resistance in Alzheimer's Disease

Authors: *E. ANGELES[1], M. BOCARSLY[2];
[1]Rutgers New Jersey Med. Sch., Newark, NJ; [2]Pharmacology, Physiol. and Neurosci., Rutgers NJMS, Newark, NJ

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder, and its prevalence is only expected to increase as a result of the increasing life expectancy. The apolipoprotein E4 (ApoE4) allele has been identified as a major genetic risk factor for AD. Although only ~20% of humans are ApoE4 carriers, these individuals account for up to 65% of all AD cases. The scope of ApoE4's contribution to AD remains unclear, but recent research suggests that it may impair neuronal insulin signaling by trapping insulin receptors in endosomes. Insulin dysregulation and insulin resistance are associated with AD and have been shown to have a significant negative effect on brain function. The goal of this study is to investigate the role of ApoE4 in AD pathology by determining its impact on insulin signaling and identifying possible therapeutic strategies. We hypothesize that ApoE4 contributes to AD pathology by impairing insulin signaling. This investigation adopts a dual-pronged approach, encompassing both *in vitro* and *in vivo* studies. Three specific aims seek to (1) establish the extent of insulin-signaling dysregulation in the context of ApoE4-induced AD, (2) determine whether long-acting insulin treatment can ameliorate pathology caused by ApoE4 and (3) link the signaling dysregulation to the cognitive decline of AD. Understanding the intricate relationship between ApoE4 and insulin signaling has the potential to significantly advance our understanding of how ApoE4 contributes to neurodegeneration and unveil novel therapeutic strategies for AD in a critical-need population.

Disclosures: E. Angeles: None. **M. Bocarsly:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.19/E7

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

Support: Program Project grant 2P01AG0124, R01AG08447211-21 A1, NIH Grant R01AG084472

Title: When two worlds collide: the contribution and association between genetics (APOEε4) and neuroinflammation (IL-1β) in Alzheimer neuropathogenesis

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Abstract: Abstract INTRODUCTION: There is one causative factor and one abettor in Alzheimer neuropathogenesis; i) interleukin-1β (IL-1β) is causative as it drives synthesis of βAPP for Aβ plaques, and of MAPKp38-phosphorylation of tau for neurofibrillary tangles (NFTs), the two cardinal features of AD; and ii) the Alzheimer gene (APOEε4), which downregulates lysosomal autophagy furthering aggregation. **METHODS:** RT-PCR, immunoblotting and immunohistochemistry assessed brain levels of IL-1β and it's signaling cascade in ADε4,4, ε3,3, age-matched controls (AMC), and ApoE3 or ApoE4-treated NT2 cells. **RESULTS:** Levels of IL-1β, and its downstream signaling proteins TLR-2, MyD88, NF-κB, COX-1 and COX-2 were greater in tissue from ADε4,4 than ADε3,3 or AMC. Cathepsins B, D and L, necessary for lysosomal autophagy, were less in ADε4,4 than ADε3,3, or AMC. IL-1β levels were higher and cathepsins lower in APOE4-treated NT2 cells. **CONCLUSIONS:** IL-1β is the principal driver in AD neuropathogenesis, especially in those who inherit APOEe4, abetted by APOEe4.

Disclosures: J. Narasimhappagari: None. **M. Balasubramaniam:** None. **S. Ayyadevara:** None. **S.T. Griffin:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.20/E8

Topic: B.09. Glial Mechanisms

Title: Interaction Between ApoE Isoforms and Tau in Regulating Microglial Phagocytosis in BV2 Cells

Authors: *S. PARK[1,2,3], Y. KIM[1,2,3], S. PARK[2,1,3,4];
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Abstract: Alzheimer's disease (AD) is the most general neurodegenerative disorder. In this disease, hyperphosphorylated and aggregated tau proteins are primarily observed. Among the various risk factors for the onset and progression of AD, the apolipoprotein E4 (ApoE4) isoform is recognized as the strongest genetic risk factor. Microglia, the resident immune cells of the central nervous system (CNS), contributes to maintaining homeostasis through phagocytosis and immune responses. Upon tau hyperphosphorylation and aggregation, microglia activates and attempts to clear pathological tau aggregates. ApoE is known for regulating microglial immune responses importantly. In this study, we aimed to mimic AD-like pathophysiological conditions

via overexpressing both human tau and ApoE in microglia, therefore investigating how tau and ApoE interact microglial phagocytic function at the cellular level. First, we optimized lentiviral vector-based gene delivery in BV2 cells, a murine microglial cell line which is typically resistant to conventional transduction. Human 2N4R tau (wild-type or P301S mutant) and ApoE3 or ApoE4 were overexpressed either individually or in combination. Gene expressions were confirmed using western blotting and immunofluorescence staining. Phagocytic activity was assessed using non-degradable latex beads. As a result, Phagocytic activity gradually increased in the order of ApoE4, ApoE3, P301S, P301S+ApoE4, and P301S+ApoE3. These results suggest that the interaction between tau pathology and ApoE isoforms differentially modulates microglial phagocytic function. Notably, ApoE4 tended to suppress phagocytic activity both alone and in combination with tau expression. To summarize, we demonstrated stable co-expression of tau and ApoE in BV2 cells. This provides experimental evidence that the interaction between ApoE isoforms and tau pathology may contribute to microglial dysfunction under AD-like conditions.

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

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.21/E9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH NIA T32 AG052374
NIA 1RO1AG061879
5P01AG066591
T32 AG000266
1S10 OD028654

Title: Apoe2-driven eif4a1 upregulation enables synaptic regulation and shifts translation away from disease-associated mrnas

Authors: *T. L. M. MCHUGH[1,2], N. T. MARKOV[1], J. BONS[1], L. WU[1], C. GALICIA[1], S. K. MAK[1], G. KAUWE[1], K. WILSON[1], K.-T. TSHILENGE[1], D. FURMAN[1], B. SCHILLING[1], T. E. TRACY[1,2], L. M. ELLERBY[1,2];
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Abstract: Apolipoprotein E4 (*APOE4*) is the strongest genetic risk factor for late-onset Alzheimer's disease (AD), while *APOE2* is associated with exceptional longevity. Neuronally produced *APOE4* has been recognized as a pathological initiator of AD. To investigate the molecular mechanisms underlying APOE2's neuroprotection, we generated isogenic *APOE2/2, APOE3/3*, and *APOE4/4* induced pluripotent stem cells (iPSCs) using CRISPR/Cas9 and differentiated them into glutamatergic neurons. Multi-electrode array recordings revealed that

APOE2 neuronal networks exhibited significantly reduced burst frequency, but increased synchrony compared to APOE4 networks. Immunocytochemistry analysis demonstrated that 7-week-old APOE4 neurons displayed aberrantly increased synaptic density relative to both APOE2 and APOE3 neurons, as measured by the colocalization of the postsynaptic marker PSD95 and the presynaptic marker Synapsin. Supporting this data, we measured by whole-cell voltage-clamp electrophysiology that APOE4 neurons have an increased frequency of miniature excitatory post-synaptic currents (mEPSCs) compared to APOE2 and APOE3 neurons. To further explore whether alterations in neuronal network activity across APOE genotypes could be attributed to differences in intrinsic excitability, we conducted whole-cell current clamp recordings. We found that the number of action potentials elicited by incremental current injections was similar across APOE2, APOE3, and APOE4 neurons, indicating no significant differences in intrinsic excitability, suggesting that the altered network activity is primarily driven by synapse number. Unbiased proteomic analysis by mass spectrometry identified eukaryotic translation initiation factor 4A1 (EIF4A1) as the key protein driving distinct proteomic clustering of the three APOE isoforms. EIF4A1 overexpression in APOE4 neurons rescued the aberrant synaptic density phenotype by enhancing translation of C-terminal binding protein 1 (CTBP1), a transcriptional corepressor known to restrict synaptogenesis. To identify other mRNAs regulated by EIF4A1, we performed polysome profiling in APOE4 neurons with EIF4A1 overexpression. This revealed a selective shift away from the translation of mRNAs involved in amyloid fibril formation, mitochondrial dysfunction, and endosomal transport. These findings suggest that APOE2 mediates its neuroprotective effects by upregulating EIF4A1-dependent translation, positioning it as a novel AD-resilience protein that facilitates early regulation of synaptic homeostasis while reducing translation of disease-associated mRNAs.

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Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.22/E10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RF1AG076124
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NIH Grant R01AG067063

Title: Apoe4 is associated with increased cPLA2 activity and cerebral amyloid angiopathy in Alzheimer’s disease

Authors: *B. E. KERMAN, G. LAZZARINO, B. LI, S. WANG, J. SY, H. N. YASSINE; USC, Los Angeles, CA

Abstract: Cerebral amyloid angiopathy (CAA) is characterized by amyloid-beta (Aβ) accumulation in the vessel walls. CAA affects approximately 25% of the elderly and coexists with the onset of Alzheimer's disease (AD) pathology in at least 50% of AD cases. CAA-related inflammation (CAA-ri) includes not only radiological symptoms but also histological features such as vasogenic edema, microbleeds, blood-brain barrier (BBB) breakdown, and neurovascular inflammation. CAA has been linked to Amyloid-Related Imaging Abnormalities (ARIA). Histological findings in ARIA show inflammatory responses around Aβ-laden vessels. APOE4 genotype is among the strongest risk factors for both AD and CAA, influencing both Aβ deposition and neurovascular inflammation.
cPLA2 (cytosolic phospholipase A2) is an enzyme that regulates lipid metabolism, inflammation, and oxidative stress. cPLA2 activation is a prominent feature of vascular diseases. Both APOE4 and Aβ oligomers drive the overactivation of cPLA2. cPLA2 activation triggers the release of arachidonic acid (AA), which is metabolized into inflammatory eicosanoids like prostaglandin E2 (PGE2). PGE2 controls blood flow and matrix metalloproteinase-9 (MMP9). MMP9, also activated by APOE4, degrades the BBB integrity.
Thus, we investigated the role of cPLA2 in neurovascular inflammation in CAA. Immunohistochemical analysis of 22 brain samples (stratified by clinical AD and APOE genotype) showed that cPLA2 activity in cerebral vessels increased with increasing CAA, which was associated with APOE4 ($R2 = 0.35$, $p = 0.044$). Among the high CAA samples, APOE4 carriers had significantly higher cPLA2 activation in the blood vessels than APOE3 homozygotes ($p = 0.053$). In addition, cPLA2 activity correlated with Aβ load in the cerebral vessels, specifically in APOE4 carriers ($R2 = 0.76$, $p = 0.024$). To determine if cPLA2 activity was associated with inflammatory lipid metabolism, we analyzed single-nucleus RNA-sequencing (snRNAseq) of 427 human brain tissues from ROSMAP. AA metabolism scores in microglia and vascular cells were strongly correlated with AD pathology and neuroinflammation. In conclusion, we demonstrated that APOE4 increased CAA and cPLA2 activation in the blood vessels and that in APOE4 carriers, cPLA2 activity surrounding the cerebral vessels increased with increasing CAA and neuroinflammation.

Disclosures: B.E. Kerman: None. **G. Lazzarino:** None. **B. Li:** None. **S. Wang:** None. **J. Sy:** None. **H.N. Yassine:** None.

Poster

PSTR436: ApoE and Associated Pathways in Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.23/E11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1RF1 AG088226-01
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Title: Aged APOE ε4-targeted replacement mice exhibit a dichotomy in extent of brain atrophy

Authors: *W. CULLINA[1], A. LIZINCZYK[1], J. PANKIEWICZ[1,2], E. LECHOWICZ[1], H. KEPPENS[1], K. PARRA[1], M. SADOWSKI[1,2,3];
[1]Neurol., [2]Biochem. & Mol. Pharmacol., [3]Psychiatry, New York Univ. Grossman Sch. of Med., New York, NY

Abstract: The apolipoprotein E (*APOE*) gene, present in the global population as three allelic variants, is the strongest factor modulating the risk of late-onset Alzheimer's Disease (AD). Some studies have demonstrated that *APOE* genotype may also be responsible for modulating an "aging" phenotype, promoting age-related cognitive decline and atrophy in the absence of AD pathology. Still, the underlying mechanism of this is unclear. We hypothesized that, in mice, targeted replacement with *APOE ε4* would result in an accelerated aging phenotype, enabling mechanistic investigation. We aged female mice, homozygous for targeted replacement of endogenous *APOE* with *APOE ε4* and *APOE ε3*, to 24 mos.-roughly equivalent to age 70 in humans-and measured the volume of the posterior lateral ventricle (PLV) as a surrogate marker of brain atrophy. Interestingly, we found a divergence in PLV volumes within the 24 mos. *ε4* group, with some mice (n=8) exhibiting values consistent with the range seen in 24 mos. *ε3* mice (mean±2SD) and the other group (n=7) exhibiting PLV volumes 2.4-fold larger than the former (p<0.0001). Thus, we split the 24 mos. *ε4* group into two bins: large PLV (L-PLV) and small PLV (S-PLV). We found significant differences in the PLV volume of L-PLV *ε4* mice relative to both 3 mos. *ε4* mice (5.3-fold increase, p<0.0001, n=16) and 24 mos. *ε3* mice (5.3-fold increase, p<0.0001, n=22). There was much less enlargement in PLV volume of S-PLV *ε4* mice relative to 24 mos. *ε3* mice (2.2-fold increase, p=0.0002). There was no significant difference between PLV volume in *ε3* mice at 3 and 24 mos. To localize the atrophy observed in L-PLV *ε4* mice, we conducted volumetric analysis of structures surrounding the PLV. In the L-PLV *ε4* group, we found marked decreases in the volumes of both the entorhinal cortex (16% reduction, p<0.0001) and amygdala (19%, p<0.0001) relative to 24 mos. *ε3* mice, but no differences in hippocampal volume. Investigating the mechanism underlying this *ε4* allele-associated aging dichotomy, we utilized NanoString nCounter technology to conduct transcriptomic analysis in the entorhinal cortex. We found the most pronounced expression differences between L-PLV *ε4* and combined 3 mos. *ε3+ε4* mice in myelin-related genes (*Myrf*, *Mag*, *Mog*, *Mal*, and *Mbp*). Additionally, we observed increases in the expression of pro-inflammatory genes in microglia (*C1qa*, *C1qb*, *C1qc*, *C4a*, *Csf1*, and *Irf8*) and astrocytes (*C3*). We are now pursuing spatial transcriptomics to more effectively evaluate regional gene expression patterns in the most affected anatomical structures. Our goal is to identify genes interacting with the *ε4* allele with hopes of attenuating its deleterious pro-neurodegenerative effect.

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Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.01/E12

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: NIH/NIA P01AG026572 to RDB
Center for Innovation in Brain Science to RDB

Title: Addition of humanized APP reduces regional brain volume in a mouse model of Alzheimer's Disease: A voxel-wise analysis

Authors: *A. BHATTRAI[1], A. RAIKES[2], R. D. BRINTON[2];
[2]Ctr. for Innovation in Brain Sci., [1]Univ. of Arizona, Tucson, AZ

Abstract: Prominent preclinical models of Alzheimer's Disease (AD), while exhibiting strong pathology, have risk factors more closely associated with familial AD, which accounts for <5% of the clinical AD population, rather than the more prevalent late-onset AD (LOAD). Apolipoprotein (APOE) ε4 is the strongest LOAD genetic risk factor, in addition to other relevant risk genes such as the amyloid precursor protein (APP). Clinically, APOE ε4 is associated with lower overall brain volume and decreased white matter integrity (WMI) in AD. Preclinical studies reporting these clinically relevant disease indicators are lacking, limiting translatability of investigated models. Herein, we investigated the additive impact of humanized *APP* (h*APP*) and humanized *APOE* on brain volume and WMI in a preclinical mouse model. Aged h*APP*/*APOE* and h*APOE* mice (ε3/3, ε3/4, and ε4/4; N=124, mean age=23.5 months) underwent high-resolution ex-vivo structural (T2-weighted RARE; 75 microns isotropic) and diffusion-weighted (200 microns isotropic) MRI. Deformation based morphometry was used to identify voxel-wise differences in local brain volume. WMI was quantified using fractional anisotropy and analyzed voxel-wise in a white matter mask. Mice were classified as ε4 carriers (at least one allele) or non-carriers (ε3/ε3). Linear modeling was used to identify main effects of ε4 genotype and h*APP* carrier status. Statistical significance was set at FDR corrected $p < 0.05$.h*APP*/*APOE* mice had lower brain volume across both cortical and subcortical regions, with greatest difference observed in bilateral parieto-temporal lobes, bilateral midbrain, thalami, hypothalamus and left amygdala. In comparison, h*APOE* mice had lower brain volume in parts of left parieto-temporal lobe, frontal lobe and olfactory bulb. h*APP*/h*APOE* mice exhibited greater FA in parts of bilateral corpus callosum(superior), right cerebral peduncle, internal capsule and fimbria while hAPOE mice had greater FA in parts of corpus callosum(inferior), arbor vita of cerebellum and bilateral internal capsule.In a mouse cohort at a comparative human age of 70 years, lower brain volume with the addition of hAPP points to greater atrophy, irrespective of the ε4 genotype. This points to the dominant influence of h*APP* on local brain volume and provides a meaningful insight into the neurological impact of modeling these risk genes together. Lower mean FA in cerebellar white matter in *APP*/*APOE* mice is consistent with recent work identifying lower cerebellar mean FA in AD patients. Future work will focus on

quantifying the translational correspondence of the *APP*/*APOE* brain imaging results to clinical outcomes.

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Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.02/E13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA
NINDS
Alzheimer's Association
Brightfocus Foundation
Kleberg Foundation

Title: Using small molecules to increase endolysosomal acidification and prevent Alzheimer's disease

Authors: *J. HERZ, M. DURAKOGLUGIL, M. LAMBERT, S. WU, L. CALVIER;
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Abstract: Apolipoprotein E4 (ApoE4) is the most significant genetic risk factor for late-onset Alzheimer’s disease, yet its underlying mechanisms remain unclear. Our research demonstrates that ApoE4 disrupts cargo trafficking in early endosomes by binding to ApoE receptors, causing a “traffic jam” that delays receptor recycling and normal ApoE processing for hours. This disruption is likely due to a phase transition of ApoE4 at the mildly acidic pH of early endosomes, where the pH matches ApoE4’s isoelectric point, hindering its dissociation from receptors. By partially inhibiting the Na/H exchanger 6, the main proton leak channel in these compartments, we accelerated and modestly increased endosomal acidification. This intervention resolved the trafficking delay and normalized recycling of both ApoE and glutamate receptors. Enhanced acidification also extended to the lysosome, increasing autophagic flux and promoting the degradation of amyloid beta and tau aggregates. To determine the importance of time-coordinated early endosomal acidification, we have measured AMPA receptor recycling in the mouse hippocampus. Our findings reveal previously unknown roles for APP, amyloid-β, ApoER2/LRP8 and γ-secretase in the coordination of early endosomal acidification and sorting. These findings suggest that targeting excessive proton leak from endolysosomal compartments—often exacerbated by impaired vATPase activity with aging—may offer a promising strategy to preserve neuronal functions that are critical to its survival and thus prevent or slow Alzheimer’s disease progression.

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Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.03/E14

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Patient-derived ipsc neuronal models reveal alzheimer’s disease-associated pathology and provide a platform for drug discovery.

Authors: ***Y. C. ANZABI**, A. SAADIN, C. MYERS, K. TUTTIS RODRIGUES, N. ECKERT; Elixirgen Scientific Inc., Baltimore, MD

Abstract: Background: Understanding the cellular mechanisms driving sporadic Alzheimer’s disease (AD) pathology is crucial for developing effective therapeutics. Induced pluripotent stem cell (iPSC)-derived neurons and glia provide a patient-specific, human-relevant system for studying sporadic AD-related phenotypes. We have developed an AD Panel consisting of differentiated neurons, microglia and astrocytes produced from iPSCs derived from AD patients, to systematically evaluate disease-associated phenotypes and assess therapeutic interventions.Methods: We differentiated iPSCs from AD patients and healthy controls into excitatory neurons and glia and assessed key AD-related phenotypes, including Aβ secretion and accumulation, tau hyperphosphorylation, synaptic integrity, and electrophysiological activity. Neurons were characterized using high-resolution immunofluorescence imaging, ELISA, and MEA. Tri-culture of neurons and glial cells was set up to evaluate a more complex model of sporadic AD.Results: AD patient-derived neurons exhibited increased secretion and accumulation of amyloid peptides, an elevated Aβ42/Aβ40 ratio and increased pTau/Tau ratio in AD patient derived neurons. Mature AD neurons had altered electrophysiological activity, suggesting functional deficits. To evaluate the therapeutic potential of GSK3β and β-secretase inhibitors (BACEi), we tested their effects on pTau and Aβ42 levels across multiple healthy and AD patient iPSC-derived neuronal lines. Our data revealed a consistent reduction in pTau and Aβ42 levels in AD and healthy lines, while the response to both compounds was donor-dependent, underscoring the importance of patient-specific models for drug testing. We have found that coding variants in ABCA1 transporter may be responsible for sensitivity to the GSK3β inhibitor. MEA and ICC data suggests that older AD neurons have diminished activity due to loss of synaptic connections in our model.Conclusions: Our iPSC-based AD Panel provides a robust, human-relevant model for studying sporadic AD pathophysiology. The ability to recapitulate key AD hallmarks in patient-derived neurons supports their use in target

validation, biomarker identification, and personalized drug screening. This scalable model facilitates therapeutic discovery and precision medicine approaches in AD research.

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Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.04/Web Only

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Use of a Novel Drosophila Model to Study the Effects of Exercise and Ellagic Acid Supplementation on Alzheimer’s Disease Traits

Authors: *M. MORGAN, Z. LOPEZ, R. E. HARTMAN;
Psychology, Loma Linda Univ., Loma Linda, CA

Abstract: Non-pharmacological lifestyle factors such as regular physical activity and nutrition may protect against cognitive decline associated with neurodegenerative diseases. This study investigated the effects of ellagic acid (EA) supplementation and exercise on climbing, learning/memory, and lifespan in a Drosophila melanogaster model of Alzheimer’s disease (AD). In terms of climbing, flies that exercised for 120 minutes climbed significantly higher ($M = 3.1$ cm) than those that exercised for 30 minutes ($M = 1.8$ cm; $p < .001$), indicating improved motor performance. However, in terms of memory performance, flies in the 30-minute exercise group performed best ($M = 44.2\%$), outperforming the 60-minute ($M = 6.4\%$) and 120-minute ($M = 10.6\%$) groups ($p < .001$), suggesting a hormetic effect, meaning a moderate level of exposure of exercise was more beneficial than a higher level of exercise exposure. Similarly, a hormetic pattern was observed with EA supplementation. Flies that consumed 0.24 mg/ml EA lived longest ($M = 34.8 \pm 1.0$ days), outliving both the 1.2 mg/ml EA group by 5.9 days ($p < .001$) and the control group by 4.6 days ($p = .007$). Among exercise groups, flies in the 60-minute condition lived the longest ($M = 34.5 \pm 1.0$ days), exceeding the control group lifespan by 4.9 days ($p = .008$). Overall, these findings highlight the potential for optimized levels of exercise duration and dietary EA supplementation concentrations to enhance cognitive function and longevity in the presence of AD traits.

Disclosures: M. Morgan: None. **Z. Lopez:** None. **R.E. Hartman:** None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.05/E15

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Endosomal Dysregulation in RIN3 W63C Mutant Mice: Implications for Early-Onset Alzheimer's Disease

Authors: *J. SONG[1,2], S. YAN[1], C. WU[3], K. SUNG[3], L. SHI[2];
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[3]Neurosciences, Sch. of Medicine, UC San Diego, La Jolla, CA

Abstract: Alzheimer's disease (AD), encompassing early-onset (EOAD) and late-onset (LOAD) forms, is a neurodegenerative disorder driven by genetic, environmental, and lifestyle factors. In this study, we focus on synaptic proteins (ARC, PSD95, Synaptophysin), Rab proteins (Rab7, Rab21, Rab31, Rab38), and Ras and Rab Interactor 3 (RIN3), a guanine nucleotide exchange factor, due to their roles in AD. The RIN3 W63C mutation is a genetic risk factor for EOAD. We investigated synaptic proteins for their roles in synapse modulation, neuronal network formation, and neurotransmitter regulation, and Rab proteins for their involvement in vesicle trafficking and endosomal degradation dysfunction. Our hypothesis posits that the RIN3 W63C mutation triggers increased endosomal recycling and trafficking as a compensatory response to EOAD, followed by late endosomal dysfunction, which subsequently impacts synaptic proteins, contributing to dementia.
Brain samples from eight one-month-old mice, four wild-type WT and four transgenic TG with the RIN3 W63C mutation, were collected and homogenized. Western blots were performed to quantify differences in protein levels of synaptic and Rab proteins between WT and TG samples. After performing Western blots and quantifying the proteins detected by the target antibodies, we observed no significant differences in protein levels of synaptic proteins between WT and TG samples. However, we detected differences in protein levels for Rab31 and Rab7 within the Rab protein family, with p-values less than 0.1.
Our hypothesis posits that EOAD triggers an early response involving increased endosomal recycling and trafficking, mediated by elevated Rab31 levels, which regulate endosomal recycling. Subsequently, late endosomal dysfunction increases, driven by Rab7 upregulation due to compensatory mechanisms and pathological accumulation. Our results support this hypothesis, as one-month-old mice harboring the RIN3 W63C mutation exhibited elevated Rab protein levels compared to wild-type WT mice. However, no differences in synaptic protein levels were yet observed, likely due to the young age of the mice, equivalent to approximately 3-4 years of human age.

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Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

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Program #/Poster #: PSTR437.06/E16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P01AG026572
T32AG082631
Center for Innovation in Brain Science

Title: Altered mitochondrial function and inflammation in humanized APP/APOE mouse model of Alzheimer's Disease risk

Authors: *M. BANTUGAN[1], Y. SHANG[2], T. WANG[2], G. TORRANDELL[2], H. VAN ROSSUM[3], R. D. BRINTON[4];
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Abstract: Mitochondrial dysfunction and neuroinflammation are early hallmarks and critical drivers of neurodegenerative diseases, including Alzheimer's disease (AD). Age, female biological sex, and *APOE4* carriership are predominant unmodifiable risk factors for AD and may disproportionately exacerbate mitochondrial dysfunction and neuroinflammation in the aging female brain. We utilized transcriptomics to investigate how biological sex and *APOE* genotype may modulate bioenergetic and neuroinflammatory pathways in an aged mouse model of AD risk. We conducted bulk RNA sequencing on hippocampi isolated from 18-month-old humanized (h) h*APP* x h*APOE3/3* (*APOE3*) and h*APP* x h*APOE4/4* (*APOE4*) mice (n=4-5 per sex and genotype). Differentially expressed genes (DEGs) were analyzed via Gene Set Enrichment Analysis (GSEA) and Ingenuity Pathway Analysis (IPA) to identify and predict key functional pathways associated with biological sex and *APOE* genotype. Outcomes of gene expression analyses indicated significant alterations in immune- and mitochondrial-related genes and signaling pathways. Specifically, DEG analysis revealed increased transcriptomic differences in immune- and mitochondrial-associated genes in *APOE4* mice compared to *APOE3*, with greater changes in females relative to males. Notably, female *APOE4* mice exhibited the greatest alterations of these genes compared to male *APOE4* mice. GSEA indicated overrepresentation and activation of inflammatory gene sets in *APOE4* mice relative to *APOE3*, with the highest enrichment observed in female *APOE4* mice. Pathway analysis predicted downregulated oxidative phosphorylation and metabolic substrate utilization and upregulated redox stress response pathways in *APOE4* compared to *APOE3* mice. These patterns were preserved when stratified by sex. Activated inflammatory pathways were consistently predicted in *APOE4* mice, most prominently in female *APOE4* mice compared to male *APOE4* mice by IPA, corroborating the GSEA findings. In contrast, comparisons between female and male *APOE3* mice revealed relatively fewer differences in canonical pathways and biological processes.
These findings indicate elevated expression of neuroinflammatory-related genes and pathways in the hippocampi of *APOE4* mice, particularly in female *APOE4* mice, may significantly impact AD pathogenesis in a sex- and *APOE*-dependent manner. The biological mechanisms at the intersection of altered mitochondrial function and elevated inflammation remain to be understood. These results highlight the importance of considering both sex and genotype when investigating neuroinflammatory and mitochondrial function in AD.

Disclosures: M. Bantugan: None. **Y. Shang:** None. **T. Wang:** None. **G. Torrandell:** None. **H. Van Rossum:** None. **R.D. Brinton:** E. Ownership Interest (stock, stock options, royalty, receipt

of intellectual property rights/patent holder, excluding diversified mutual funds); NeuTherapeutics, LLC..

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.07/E17

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Evaluating amyloid related imaging abnormalities (ARIA) in the 5xFAD mouse model of Alzheimer's disease after treatment with the anti-amyloid antibody 3D6

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Abstract: Amyloid-related imaging abnormalities (ARIA) is a term used to cover a variety of magnetic resonance imaging (MRI) findings in patients receiving anti-amyloid beta (Aβ) immunotherapies for Alzheimer disease (AD). The findings are broadly categorized into ARIA characterized by edema and effusion (ARIA-E) and ARIA characterized by microhemorrhages and superficial siderosis (ARIA-H). In this study we evaluated the ARIA-like events in the 5xFAD mouse model of AD using T2 and T2star MRI after an 11-week treatment with the anti-amyloid antibody 3D6.
5xFAD mice were treated with the anti-amyloid antibody 3D6 (n=15) or an isotype control antibody (n=8) for 11 weeks, starting from approximately 9 months of age. The ARIA-like events were quantified and characterized using T2 and T2star MRI before the treatment onset and at 3, 7, 9 and 11 weeks of treatment.
At the pre-treatment baseline, the 5xFAD mice showed low number of microbleeds (9±5) but no ARIA-H or ARIA-E lesions. ARIA-E lesions, ARIA-H lesions and increased microbleed load were only detected in groups receiving the Aβ antibody 3D6 starting at 3 weeks after the treatment onset. No ARIA-E lesions, ARIA-H lesions or increased number of microbleeds were detected in control 5xFAD mice. Edemic ARIA-E lesions were transient and a subset of them resolved over time during the MRI follow-up at later time points. Hemorrhagic ARIA-H incidence increased at 7 - 9 weeks in the mice receiving 3D6, and ARIA-H events were detected in these mice at all time points. The number of microbleeds was elevated already at 3 weeks after treatment initiation in the mice receiving 3D6, and the microbleed load increased over time during the follow-up period. After 11 weeks of 3D6 treatment, the incidence of ARIA-E was 77% and ARIA-H 69%, and number of microbleeds 52±38. Taken together, the ARIA-H, ARIA-E and elevated microbleed load were induced by treatment with the murine Aβ antibody 3D6. The optimized MRI assessment serves as a preclinical tool in the development of improved treatment strategies in AD.

Disclosures: **R. Immonen:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **T. Heikkinen:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **M. Yacoub:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **T. Miettinen:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **J. Rytkönen:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **J. Oksman:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **H. Long:** A. Employment/Salary (full or part-time): Alector LLC. **M. Sokolovsky:** A. Employment/Salary (full or part-time): Alector LLC.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.08/E18

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Neuroprotective effect of soursop seed extract on hypothalamic dysfunction in aluminium chloride induced alzheimer disease in rats

Authors: *O. A. BAMGBSE[1], D. O. TAIWO-OLA[3], F. BAMIDELE[1], R. IFARAJIMI[4], P. D. SHALLIE[2];
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Abstract: Background:
The hypothalamus plays a vital role in regulating endocrine and metabolic functions and is increasingly recognized in Alzheimer's disease (AD) pathogenesis. Hypothalamic neurodegeneration disrupts hormone secretion, impairing insulin signaling and glucose metabolism, potentially linking AD with metabolic disorders. This study evaluated the neuroprotective effects of aqueous soursop seed extract on the hypothalamus in an aluminum chloride-induced AD rat model.
Methodology:
Twenty adult Wistar rats (180-220 g) were randomly assigned to five groups (n=5). Treatments were administered orally and concurrently for 28 days: distilled water (control), 100 mg/kg aluminum chloride (Alzheimer’s group), 200 mg/kg soursop seed extract, aluminum chloride plus soursop extract, and aluminum chloride plus Donepezil (10 mg/kg). Cognitive and anxiety-like behaviors were assessed using Morris water maze and elevated plus maze tests. Brain inflammatory and oxidative stress markers (TNF-α, lipid peroxidation) were quantified. Histological analyses employed H&E and cresyl violet staining to assess neuronal integrity.
Results:
Aluminum chloride administration induced significant cognitive deficits and anxiety-like

behavior, along with elevated TNF-α and lipid peroxidation levels, reflecting increased neuroinflammation and oxidative stress. Histological evaluation revealed neuronal vacuolation and degeneration in the hypothalamus. Treatment with soursop seed extract significantly improved behavioral outcomes and preserved neuronal structure, demonstrating neuroprotective effects against AD-related pathology.
Discussion:
Aluminum chloride induces Alzheimer-like cognitive impairment, anxiety, and neuroinflammatory and oxidative stress markers. Soursop seed extract effectively ameliorates these effects and preserves neuronal integrity in critical brain regions, indicating promising therapeutic potential for AD by modulating hypothalamic function and reducing neurodegeneration.
Conclusion:Soursop seed extract mitigated aluminum-induced hypothalamic neurodegeneration, oxidative stress, and neuroinflammation, enhancing cognitive function and neuronal integrity—suggesting its potential as a neurotherapeutic agent in Alzheimer's disease management.

Disclosures: O.A. Bamgbse: None. **D.O. Taiwo-ola:** None. **F. Bamidele:** None. **R. Ifarajimi:** None. **P.D. Shallie:** None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.09/E19

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Generation of a novel Alzheimer disease mouse model with both amyloid-betaand tau co-pathologies

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Abstract: The pathological features of Alzheimer disease (AD) include extracellular senile plaques formed by amyloid-β (Aβ) protein accumulation and intracellular neurofibrillary tangles (NFT) composed of aggregated tau protein. Senile plaques precede dementia onset by 10 to 20 years, followed by NFT formation, which correlates with cognitive decline. To elucidate the pathophysiology of AD, it is necessary to examine the factors of Aβ pathology, tau pathology, and cognitive decline, as well as their interrelationship. Previous AD mouse models, mainly transgenic, face challenges in inducing tau accumulation precisely and require prolonged breeding. While the tau seed injection model can cause the accumulation, it is highly invasive. In this study, we aimed to establish a novel mouse model of AD that chronologically recapitulates Aβ and tau pathology. To induce rapid tau accumulation in the mouse brain at specific times, we transduced the aggregation-prone P301L/S320F mutant (PL/SF) tau (Koller et al., HMG 2019),

associated with familial frontotemporal dementia, using an adeno-associated virus (AAV) vector packaged with a blood-brain-barrier-permeable capsid PHP.eB. Human PL/SF tau was expressed under a neuron-specific synapsin 1 promoter. The recombinant AAV-PHP.eB encoding PL/SF tau was administered into the orbital vein, followed by the analysis of tau pathology in the brains. Immunohistochemical analysis revealed increased tau phosphorylation in neurons in the motor and somatosensory cortices and the hippocampal CA2 region one month post-injection (mpi), with Gallyas-Braak staining. Insoluble tau exhibited increased tau phosphorylation at S396, a hallmark of mature tangle in the late stage of the tauopathy, observed from 1 mpi. Next, to establish a novel AD model mouse with comorbidity of Aβ and tau, PL/SF tau expression was induced in NLGF mice, which develop Aβ deposition at 4 to 6 months old (Saito et al., Nat Neurosci 2014). One month after induction of PL/SF tau expression, dystrophic neurites containing phosphorylated tau surrounding Aβ deposits typical of AD patient brains were induced in the brains of 9-month-old NLGF mice. Currently, using this mouse model, we are conducting RNA sequencing analysis in various cell types (neurons, microglia, astrocytes, and oligodendrocytes) to examine the changes in gene expression profiles with the development of co-pathologies. This novel model mouse offers a valuable tool for investigating tau aggregation mechanisms and AD research applications.

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Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.10/E20

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Swiss National Science Foundation (grant 310030_212322)

Title: Preclinical validation of a pharmacological strategy against Alzheimer’s pathology

Authors: A. M. BADINA[1], K. CEYZÉRIAT[2], L. ABJEAN[1], S. TSARTSALIS[1], P. MILLET[3], ***B. B. TOURNIER**[3];
[2]CIBM Ctr. for Biomed. Imaging, [1]Univ. of Geneva, Geneva, Switzerland; [3]Psychiatry, Univ. of Geneva / Univ. Hosp. of Geneva, Geneva, Switzerland

Abstract: Alzheimer’s disease (AD) is a chronic neurodegenerative disease that represents more than 70% of dementia cases. This makes AD one of the main clinical challenges of the century, as dementia affects 45 million people worldwide and the number of patients is predicted to triple by 2050. AD is characterized by cognitive decline associated with impaired cerebral metabolism, inflammatory responses mediated by astrocytes and microglia, and the accumulation of two primary neuropathological markers: β-amyloid (Aβ) and hyperphosphorylated Tau. Additionally, increased glial reactivity (as shown by the over-expression of the 18kDa translocator protein,

TSPO) has been widely observed, although its precise pathophysiological role remains unclear. The 3xTgAD (APP_{SWE}, $PS1_{M146V}$ and Tau_{P301L}) mice model of AD shows progressive Aβ- and Tau-associated pathologies that mimic the temporal and regional development of AD in humans. We previously observed that knocking out TSPO in 3xTgAD mice significantly reduced Aβ levels and Tau pathology and decreased glial reactivity, as confirmed through gene expression analyses and morphological assessments. In the present study, we investigated the ameliorative effects of a chronic pharmacological treatment (ct) impacted glial cells in 15-month-old 3xTgAD mice (all experiments were conducted blind). The molecule identity and administration methods are confidential as a valorization is under evaluation (Technology Transfer Office of Geneva University, Unitec, Switzerland). The treatment successfully prevented spatial working memory decline compared to vehicle-treated (VEH) 3xTgAD mice, although 3xTgAD mice still showed deficits compared to WT (% of good alternance, WT: 51±7; VEH-3xTgAD: 38±13*; ct-3xTgAD: 50±6; One-way ANOVA, *P<0.05 vs WT and ct-3xTgAD). As compared to VEH-3xTgAD mice, the chronic treatment reduced amyloid deposition by half ($A\beta_{42}$ in pg/µg of protein, VEH-3xTgAD: 0.16±0.11; ct-3xTgAD: 0.07±0.08; Student t-test, P<0.05). Finally, a restoration of cerebral glucose metabolism was also observed (Standard uptake value normalized by blood glucose, WT: 3.9±1; VEH-3xTgAD: 2.8±0.6*; ct-3xTgAD: 3.6±0.4; One-way ANOVA, *P<0.05 vs WT and ct-3xTgAD). The proposed treatment was well-tolerated, did not induce any adverse effect, and led to significant improvements in both cognitive and neurochemical symptoms of AD in mice. Thus, our therapeutic approach could subsequently progress to human clinical trials. Moreover, given that numerous neurodegenerative disorders involve glial reactivity, this treatment has the potential for broad therapeutic applications.

Disclosures: A.M. Badina: None. **K. Ceyzériat:** None. **L. Abjean:** None. **S. Tsartsalis:** None. **P. Millet:** None. **B.B. Tournier:** None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.11/E21

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant

Title: The Mechanism Study of Transcranial Electromagnetic Treatment for Alzheimer’s Disease

Authors: *D. REGMI[1], O. FIHURKA[2], Y. WANG[2], C. CAO[3];
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Abstract: Alzheimer's disease (AD) is the most common cause of dementia. AD is a neurodegenerative disorder characterized by the gradual decline of memory and cognitive

abilities over 2-20 years, driven by the loss and dysfunction of neurons in key brain regions. The disease is rooted in a biological process involving the building up of extracellular plaques and intracellular neurofibrillary tangles in the brain. We have reported that a novel neuromodulatory, non-pharmacologic approach using transcranial electromagnetic (radiofrequency) field as a treatment (TEMT) can prevent or reverse cognitive decline caused by Aβ oligomerization by disrupting the aggregation that is the central hypothesis of several neurodegenerative diseases. Based on the MTT assay results, the best combination of two parameters for increasing N2a/APPswe cell viability is 915 MHz and 1 hour x twice daily at 72 hrs. We investigated that upon EMF exposure, soluble Aβ1-40 level, Aβ1-42 level, and Aβ1-42 /Aβ1-40 ratio was significantly reduced. The data showed that Drp1, Fis1, and MFF expressed a low level in the best combination (915 MHz and 1-hour x twice daily) EMF treatment group. Our recent results demonstrate that TEMT can enhance mitochondria function by reducing oligomer Aβ levels and lead to the increase of cell viability in the N2a/APPswe cell culture model. We hope this non-pharmacological multi-functional approach could be safer and more cost-effective in preventing or reversing cognitive impairment in AD.

Disclosures: D. Regmi: None. **O. Fihurka:** None. **Y. wang:** None. **C. Cao:** None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.12/E22

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: NIA Grant P01AG026572

Title: Impact of combination therapies on Alzheimer's Disease-related outcomes in a humanized APP/APOE AD-risk model during midlife

Authors: *A. K. PARKER[1], G. TORRANDELL[2], H. VAN ROSSUM[3], R. D. BRINTON[4]; [2]Pharmacol., [3]Neurosci., [4]Ctr. for Innov in Brain Sci., [1]Univ. of Arizona, Tucson, AZ

Abstract: Intervening in the preclinical phase of Alzheimer’s disease (AD) represents an opportunity to prevent, reverse, or delay disease progression. During this stage, peripheral inflammation and dysregulated glucose and lipid metabolism drive the accumulation of AD hallmarks, amyloid beta (Aβ) and tau. Targeting these systems of biology with combinations of FDA-approved drugs may reduce early AD risk. Our previous medical informatic analyses indicated that lipid-lowering agents, glucose regulators, and anti-inflammatory drugs were associated with significantly lower risk of developing AD. A late-onset AD risk mouse model expressing humanized (h) *APP x hAPOE3/3 or hAPP x hAPOE4/4* was used to evaluate the effects of combination therapies on AD pathology. 15-month-old mice received either control chow or chow with tofacitinib (TOF), atorvastatin (ATV), pioglitazone (PGZ), or combinations thereof: TOF+ATV, TOF+PGZ, ATV+PGZ, and TOF+ATV+PGZ (TRIPLE). Mice were

evaluated pre- and post-treatment with novel object recognition (NOR), monthly EchoMRI for body composition, and weekly nesting behavior tests. After 90 day-treatment, plasma metabolic markers were measured with a clinical blood analyzer. Flow cytometry assessed immune cells in blood and meninges, microglial activation was evaluated via IHC, and amyloid beta was quantified in plasma (MSD) and brain (IHC). Outcomes of these analyses indicated that each therapeutic effectively targeted its respective biological pathway and their combination produced treatment- and sex-specific effects. ATV, TOF and TRIPLE combination significantly reduced Aβ load in the hippocampus, as assessed by 6E10 labeling and immuno quantification. In addition, combination therapy increased plasma Aβ 42:40 ratio in female-treated mice, consistent with enhanced Aβ clearance. Over the treatment period, control mice exhibited increased body weight, characterized by elevated body fat and reduced lean mass. These changes in body composition were reversed by ATV monotherapy and combination therapies containing ATV, with body weight fat and lean mass maintained after 3 months of treatment. Control mice also exhibited a decline in cognitive performance as assessed by NOR and nesting, which was prevented by all treatments except PGZ. Specifically, TRIPLE-treated female mice exhibited the greatest improvement in nesting scores throughout the study. Overall, these findings support the therapeutic potential of pathway-specific combination therapy that collectively target multiple biological systems involved in Alzheimer's disease pathology and highlight the importance of accounting for sex as a biological variable.

Disclosures: A.K. Parker: None. **G. Torrandell:** None. **H. Van Rossum:** None. **R.D. Brinton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuTherapeutics, LLC..

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.13/E23

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: UK DRI-Edin0010
Dunhill Medical Trust Fund PhD Scholarship

Title: Using amyloid-beta to recapitulate and study dendritic spine loss and compensation in Alzheimer's disease.

Authors: *Y. CHANG[1,2], P. OPAZO[2,1];
[1]The Univ. of Edinburgh, Edinburgh, United Kingdom; [2]UK Dementia Res. Inst., Edinburgh, United Kingdom

Abstract: Synapse loss is a key feature of many neurodegenerative diseases involving cognitive deficits, and is also the strongest correlate of cognitive decline in Alzheimer's disease (AD). In addition, the integrity of dendritic spines, the post-synaptic sites of excitatory synapses, has been

shown to play a key role in cognitive resilience against AD. Given the critical role of synaptic loss in cognitive decline, we hypothesized that synaptic compensation and repair play a vital role in counteracting synapse loss and as a consequence, in delaying the onset of cognitive deficits. The aim of our study is to induce spine loss in order to study the emergence of compensatory mechanisms over time using longitudinal imaging. To this end, we use 2-photon microscopy to image dendritic spines in an *in-vitro* model system: rat organotypic hippocampal slice cultures. To induce spine loss, we added either synthetic amyloid-beta peptides (Aβ(1-42)), or pathologically relevant human brain homogenates to our slice cultures. By imaging the same dendrite over time, we visualise structural changes in dendritic spines in both the spine loss phase and the following compensation phase. In our preliminary data, we show the optimization of this system to induce spine loss, and its ability to promote the emergence of synaptic compensation over days. Following this, we plan to look into the transcriptional landscape at relevant time points to elucidate the mechanisms of spine compensation.

Disclosures: Y. Chang: None. **P. Opazo:** None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

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Program #/Poster #: PSTR437.14/E24

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant T32AG061897
NIA Grant R37AG053589

Title: Single-nuclei sequencing in ovariectomized rat hippocampus identifies estrogen-sensitive brain cell sub-populations and pathways

Authors: *J. W. MCLEAN[1], T. WANG[2], Y. SHANG[2], R. D. BRINTON[2];
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Abstract: Estrogen coordinates metabolic, immune, and neuronal homeostasis in the female brain. Loss of estrogen across menopause is associated with declining brain glucose metabolism and increasing neuroinflammation, which may contribute to neuronal vulnerability and the doubled lifetime risk for Alzheimer’s disease (AD) in women. However, the neuronal and glial cell type-specific responses to estrogen deficiency in the hippocampus, a brain region critically affected in AD, is incompletely understood. To identify hippocampal cells and pathways affected by estrogen loss, 5-month-old female Sprague Dawley rats were assigned to sham ovariectomized (SHAM), ovariectomized plus vehicle (OVX), or OVX with 17β-estradiol (OVX+E2) conditions and sacrificed 5 weeks post-surgery. Nuclei isolated from dorsal hippocampi were pooled from two biological replicates per treatment group. A 10X Genomics Chromium Single Cell 3’ kit was used to generate a single-nuclei cDNA library for each condition. Libraries were sequenced on an Illumina NovaSeq6000, and demultiplexed FASTQ

files were analyzed downstream using CellRanger and Loupe Browser. After a quality-control step filtering out nuclei with more than 5% mitochondrial reads, established cell type-specific marker genes allowed annotation of distinct clusters of major brain cell types including excitatory and inhibitory neurons, astrocytes, oligodendrocytes, oligodendrocyte precursor cells (OPCs), microglia, and endothelial cells. Single-nuclei transcriptomics identified reduced cell percentage of the neuron cluster (Exc1) expressing *Slc17a6* (vGlut2) in OVX hippocampus (10%), which was partially mitigated in OVX+E2 (17%), relative to SHAM (37%). Additional cell types with treatment-associated population shifts included changes in inhibitory and other excitatory neuron clusters, as well as oligodendrocytes. Gene set enrichment analysis of differentially expressed genes within estrogen-sensitive neuronal subpopulations indicated a reduction in oxidative phosphorylation and upregulation of inflammatory response in OVX compared to both SHAM and OVX+E2, while glial cells exhibited a more heterogenous response. These findings extend previous reports of estrogen loss affecting bioenergetics, specifically oxidative phosphorylation, as well as neuroinflammation and potentially synaptic function. Ongoing studies aim to identify further cell-type specific pathway contributions. Outcomes will advance an understanding of brain cell-specific responses to estrogen loss and help identify AD-relevant drivers of brain vulnerability in the estrogen-deficient postmenopausal female brain.

Disclosures: J.W. McLean: None. **T. Wang:** None. **Y. Shang:** None. **R.D. Brinton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuTherapeutics, LLC.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.15/E25

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ed and Ethel Moore Alzheimer's Disease Research Program
NIH Grant 5R01AA029674-03

Title: The Novel beta-lactam, MC-100093, Mimics the Neurodegenerative Phenotype of swip-10 mutation in C. elegans

Authors: *M. ASIF[1], P. RODRIGUEZ[2], M. FENOLLAR FERRER[1], W. E. CHILDERS, Jr.[3], M. ABOU-GHARBIA[3], R. D. BLAKELY[1];
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Abstract: IIn a prior genetic screen, the Blakely lab identified the gene *swip-10* in *C. elegans* as a determinant of dopamine (DA) signaling and health. Deletion of *swip-10* results in a glutamate (Glu)-dependent elevation of DA neuron excitability accompanied by premature degeneration

that can be mimicked by genetic loss of Glu transporters (GLTs) in wildtype animals. The putative mammalian ortholog of SWIP-10, MBLAC1, possesses a single structural feature, a metallo-beta-lactamase domain (MBD) that shares high homology with SWIP-10. Notably, the MBD of SWIP-10 is the site of a mutation recovered in our screen, consistent with a loss of SWIP-10 enzymatic activity. MBDs are evolutionarily ancient, having arisen to support the enzymatic hydrolysis of β-lactam antibiotics. The MBD structural fold has been repurposed by other organisms, including humans, to hydrolyze a range of molecules. The presence of an MBD in SWIP-10, whose glial activity is required for normal DA neuron function and viability, reminded us that the β-lactam antibiotic ceftriaxone (Cef) can act in cultured mammalian cells and the brain to modulate glia-dependent neuronal excitability and viability. Following this lead, we previously used back-scattering interferometry and immunodepletion approaches to evaluate Cef protein binding, generating strong evidence that the protein MBLAC1 is a major, if not exclusive, CNS target for Cef. Unfortunately, the antibiotic activity of Cef precludes a test of our hypothesis in *C. elegans.* An opportunity to overcome this problem arose through the work of Childers and Abou-Gharbia in creating novel, CNS-penetrant β-lactam structures that exhibit Cef-like actions in addiction models but lack antibiotic activity. Working together, we have tested the monocyclic *β*-lactam, MC-100093, for its ability to mimic the biochemical, cellular, and behavioral properties of a loss-of-function *swip-10* mutation. We observe that treatment of worms with MC-100093 induces significant degeneration of DA neurons in a dose-dependent manner. We also observed altered expression of *glt-1* mRNA levels, consistent with a conserved mechanism of Cef and MC-100093 involving altered GLU signaling. Ongoing efforts aim to model the interaction of MBLAC1 and SWIP-10 with Cef and MC-100093 to gain further insights into the physical basis of their interactions and differential *in vivo* capacities. We believe these efforts can yield further insights into the opportunities provided by MBLAC1-targeted pharmacology as a potential path for novel treatments given GWAS findings of an association of the MBLAC1 gene with risk for Alzheimer's disease with cardiovascular disease comorbidity.

Disclosures: M. Asif: None. **P. Rodriguez:** None. **M. Fenollar Ferrer:** None. **W.E. Childers:** None. **M. Abou-Gharbia:** None. **R.D. Blakely:** None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.16/E26

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Plga-encapsulated auranofin nanoparticles attenuate aluminium-induced neurotoxicity in a rodent model of alzheimer's disease

Authors: *R. ARORA, JR;
CLINICAL HEMATOLOGY, Christian Med. Col. and Hosp., Ludhiana, India

Abstract: Background: Effective treatment of neurodegenerative disorders like Alzheimer's disease (AD) remains a major challenge, primarily due to the limited blood-brain barrier (BBB) permeability of therapeutic agents. Nanotechnology-based delivery systems offer a promising solution to enhance CNS drug delivery.
Objective: This study aimed to develop and evaluate poly(lactic-co-glycolic acid) (PLGA) nanoparticles encapsulating auranofin for neuroprotection against aluminium chloride ($AlCl_3$)-induced AD in rats.
Methods: Auranofin-loaded PLGA nanoparticles were formulated and characterized for particle size (101.5 ± 10.3 nm), zeta potential (27.5 ± 5.10 mV), polydispersity index (0.438 ± 0.12), entrapment efficiency (98%), and drug loading (76%). In vivo, rats received $AlCl_3$ (100 mg/kg, oral) for 21 days to induce AD-like pathology. Auranofin (5 and 10 mg/kg) and its nanoparticle formulation (2.5 and 5 mg/kg) were co-administered for 14 days. Post-treatment, hippocampal tissues were analyzed for cognitive performance, oxidative stress markers, and neuroinflammatory cytokines.
Results: Auranofin-loaded nanoparticles significantly reversed $AlCl_3$-induced cognitive deficits, oxidative damage, and elevated pro-inflammatory markers more effectively than auranofin alone.
Conclusion: The enhanced neuroprotective efficacy of nanoparticle-encapsulated auranofin may be attributed to improved BBB penetration and sustained release, highlighting its potential as a novel therapeutic approach for modifying Alzheimer's disease progression.

Disclosures: R. Arora: None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.17/E27

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MH128108

Title: Comparative analysis of brain metabolic markers in Alzheimer's Disease and HIV-associated neurocognitive impairment

Authors: *J. A. FIELDS;
UCSD, La Jolla, CA

Abstract: The prevalence of people with HIV (PWH) over the age of 55 is rapidly increasing; however, the effects of aging on HIV neuropathogenesis remain unclear. This study examines changes in glucose metabolism pathways in post-mortem brain tissues from individuals with Alzheimer's disease (AD) and HIV-associated neurocognitive impairment (NCI). Postmortem brain tissues from the frontal cortex were acquired from the National NeuroAIDS Tissue Consortium (n=24) and the San Diego Alzheimer's Disease Research Center (n=40). Specimens were homogenized by sonication, then resolved by SDS page, and immunoblotted with

antibodies against metabolic proteins. Densitometry data were stratified by the progression of AD and HIV-associated NCI. Glucose transporter levels remained unchanged in both conditions, while monocarboxylate transporter (MCT) levels varied; specifically, monomeric MCT1 levels increased, and MCT2 levels decreased in PWH with NCI, whereas MCT4 levels were unaffected. Proteolytic fragments of the insulin receptor changed across the course of HIV-associated NCI, accompanied by a significant decrease in insulin-degrading enzyme levels in PWH with NCI. Glycolytic enzymes hexokinase and pyruvate kinase M2 showed no change in response to disease severity. Notably, truncated variants of the transcription coactivator PGC-1α increased in PWH with NCI. These results highlight shared and distinct mechanisms of metabolic dysfunction in AD and HIV-NCI, providing potential targets for therapeutic interventions.

Disclosures: J.A. Fields: None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.18/E28

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: High throughput in vitro screening of Alzheimer's disease risk factors

Authors: D. AL-AZZEH[1], S. RAO[1], A. RAJAN[2], A. ATAMIAN[2], E. HERGENREDER[3], L. SAAVEDRA[2];
[1]Arc Inst., Palo Alto, CA; [2]Arc Inst., Palo Alto, CA, ; [3]Arc Inst., San Francisco, CA.

Abstract: High throughput in vitro screening of Alzheimer's disease risk factorsDana AL-Azzeh1, Sneha Rao1, Lorena Saavedra1, Akshaya Rajan1, Ipek Tasan2, Harry Bevir2, Kristen Seim2, Po-Yuan Tang3, Maggie Brown3, Nianzhen Li3.
1 Cellular Models Tech Center, Arc Institute 2 Genome Engineering Tech Center, Arc Institute3 Multiomics Tech Center, Arc Institute
Alzheimer's disease (AD) is a complex pathology involving interactions of genetic and environmental factors across different CNS cell types. While patient genetic screens have identified some potential risk factors, not much is understood about the interplay between them and their cellular contexts that can result in disease pathology.
Here we developed a screening platform combining human 3D brain in vitro models with arrayed genetic and environmental perturbations to systematically interrogate microglia function in AD-relevant contexts. Our approach used 3D cellular models containing neurons, astrocytes and microglia, CRISPRi-mediated modulation of AD risk genes, environmental perturbations modeling AD-related insults, inflammation and metabolic stress, and multimodal readouts including single-cell transcriptomics to assess perturbation effects on specific cell types. This platform enables systematic dissection of gene-environment interactions in AD pathogenesis, providing a scalable framework for identifying therapeutically-relevant targets and pathways.

Disclosures: D. AL-Azzeh: None. **S. Rao:** None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.19/E29

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: IUSM Behavioral Phenotyping Core
R01AG064003
K02AG068595
I21BX006307

Title: Chronic migraine via nitroglycerin treatment progresses cognitive decline and amyloid pathology in the 3xTG mouse model of Alzheimer's Disease.

Authors: T. MEYER, D. FRAZAO, C. YAMADA, S. KATNER, ***K. D. FISCHER**;
Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Alzheimer's Disease (AD) is a devastating neurodegenerative disease characterized behaviorally by memory loss typically later in life and is ultimately fatal. AD is commonly associated with other health conditions that increase the risk of developing AD later in life. An understanding of these health conditions that contribute to the onset of AD will promote disease prevention strategies. Migraine disorder is a disabling chronic disease condition that affects over 15% of the general population. Clinical reports show that AD is prevalent in individuals with a history of migraine, and that the incidence of AD is significantly higher in those that suffer from migraine at a younger age. More specifically, females with a history of migraine have a 37% higher risk of developing AD compared to same-age males with a history of migraine. To date, it remains unclear how to address sex-associated migraine disorder in patients with AD due to our limited knowledge of the molecular crosstalk behind these two CNS disorders. A major barrier to progress is that the AD field has not reverse translated this increased AD incidence in migraine patients to preclinical animal models. Here, we combined an AD and migraine mouse model by using the transgenic AD mouse containing three familial AD mutations (3xTG) exposed to the migraine causing agent, Nitroglycerin (NTG). This combined migraine-AD mouse model allowed us to monitor the effect of NTG on the pain threshold, behavioral changes, and pathogenic amyloidogenesis in males and females. We tested the hypothesis that chronic migraine disorder induced by NTG accelerates the development of cognitive decline and amyloid pathology in 3xTG mice. Mice were injected every other day with intraperitoneal injections of NTG or saline for 10 injections total. Using the Von Frey test, we show that 3xTG female and male mice have accelerated pain responses to single acute and chronic NTG injections compared to vehicle treated 3xTG mice. However, only 3xTG female mice exposed to systemic NTG injections displayed deficits in spatial learning and memory and significant accumulation of amyloid beta (Aβ) in histological sections. Collectively, our findings suggest that the migraine

causing agent, NTG, accelerates AD-related cognitive decline and Aβ accumulation in 3xTG mice, with more pronounced effects in female 3xTG mice specifically. This area of research is highly novel to the AD field in that we are the first to reverse translate the increased human AD incidence in chronic migraine sufferers to preclinical animal models.

Disclosures: T. Meyer: None. **D. Frazao:** None. **C. Yamada:** None. **S. Katner:** None. **K.D. Fischer:** None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.20/E30

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Exploring the Influence of Aβ42 on the Hippocampus in Adult and Aging Cynomolgus Monkeys

Authors: *L. CHEN[1,2], X.-J. LI[3], S.-H. LI[4];
[1]Guangdong-Hongkong-Macau Inst. of CNS Regeneration, Guangzhou, China; [2]Jinan Univ., Guangzhou, China; [3]Jinan Univ., Guangdong, China; [4]GHM Inst. of CNS Regeneration, Jinan Univ., Guangzhou, China

Abstract: The pathological mechanisms of Alzheimer's disease (AD) remain poorly understood, and the lack of animal models that accurately replicate the disease's phenotypes poses significant challenges for AD research. We developed a cynomolgus macaque model of AD by overexpressing the Aβ42 peptide through AAV viral injection in the hippocampal region. Our findings indicate a minor influence of Aβ42 overexpression in adult monkeys (7-9 years old), but we observed significant Aβ deposition, Tau tangles, and specific loss of CA1 neurons in aging monkeys (21-23 years old). Additionally, we noted hippocampal volume shrinkage and sleep disturbances in Aβ42-overexpressing older monkeys. To investigate the differences in Aβ42 overexpression between adult and aging monkeys, we performed single-nucleus sequencing on the hippocampal regions of Aβ42-overexpressing monkeys. Our results identified five dominant clusters of pyramidal neurons, with a dramatic decrease in the $COL25A1^{+}TRPS1^{+}$ cluster in the aging monkeys. Furthermore, we observed differences in microglial populations between adult and aging monkeys; specifically, the $GPNMB^{+}$ microglia cluster was reduced in aging hippocampus, potentially leading to impaired Aβ42 clearance and increased toxicity to pyramidal neurons. These findings enhance our understanding the relationship between aging and neurodegeneration in AD, revealing a potential pyramidal neuron subcluster that is particularly sensitive to Aβ42 toxicity. Additionally, the exhaustion of clearance microglial subclusters with aging may contribute to neuronal death in AD. This research provides theoretical and experimental support for early intervention and targeted therapies in AD.

Disclosures: L. Chen: None. **X. Li:** None. **S. Li:** None.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.21/E31

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Spaceflight Reveals Environment-Dependent Maturation and Neurodegenerative Signatures in Human Alzheimer's Brain Organoids

Authors: *N. XIONG[1], R. MIHANI[2], **N. MOREIRA**[3];
[1]Akoya Biosci., San Diego, CA; [2]Akoya Biosci., Marlborough, MA; [3]UCSD, La Jolla, CA

Abstract: Alzheimer's disease (AD) exhibits complex, multifactorial pathology influenced by genetic background and environmental factors. To investigate how an accelerated aging environment impacts AD progression, we cultured cortical brain organoids from patient-derived iPSCs—including both sporadic AD and non-demented control (NDC) lines—and exposed them to microgravity aboard the International Space Station (ISS), with matched controls maintained on Earth. Following spaceflight exposure, organoids underwent multi-omics analysis, including proteomics-based Astral-Orbitrap mass spectrometry and spatial proteomics using Akoya Biosciences' PhenoCycler®-Fusion platform and PhenoCode™ Human Neurobiology Panel. This approach enables spatially resolved protein mapping across neural and glial compartments, capturing the impact of space environment on disease progression. Our data revealed a clear divergence between ISS- and Earth-grown organoids. In control organoids, spaceflight enriched pathways related to neurite outgrowth and membrane organization, suggesting accelerated neuronal maturation under microgravity. In contrast, AD-derived organoids displayed heightened sensitivity to the space environment, with enrichment in chromatin remodeling, DNA recombination, and cell cycle dysregulation—hallmarks of Alzheimer-related cellular stress. These results indicate that microgravity not only promotes neurodevelopmental progression in healthy tissue but also exacerbates disease-specific molecular phenotypes in AD models. This study is among the first to model human neurodegenerative disease in space using patient-derived organoids, offering insights into how aging and AD pathology are modulated by environment and sex. These findings provide a high-resolution, experimental framework for understanding AD heterogeneity and evaluating future neuroprotective strategies under accelerated aging conditions.

Disclosures: **N. Xiong:** A. Employment/Salary (full or part-time): Akoya Biosciences, University of California San Diego. **R. Mihani:** A. Employment/Salary (full or part-time): Akoya Biosciences. **N. Moreira:** A. Employment/Salary (full or part-time): UCSD.

Poster

PSTR437: Alzheimer's Disease: Animal Models and Drug Targets

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.22/E32

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

Support: Supported by a grant from the National Institute on Aging (1RF1AG074256-01A1 to A.K.S.)

Title: Psilocybin Treatment Restrains the Progression of Pathological Alterations and Cognitive Decline in an Early-onset Model of Alzheimer's Disease

Authors: *L. N. MADHU, Y. SOMAYAJI, S. KOTIAN, S. ATTALURI, J. PATEL, P. PANDA, M. KODALI, B. SHUAI, X. RAO, G. SHANKAR, A. K. SHETTY;
Inst. For Regen Med, Texas A&M Univ. Coll Med., College Station, TX

Abstract: Alzheimer's disease (AD) is a neurodegenerative condition typified by the accumulation of amyloid-beta (Aβ) plaques, neurofibrillary tangles, chronic neuroinflammation, synapse loss, and neurodegeneration, and a progressive decline in cognition and mood. This study investigated the efficacy of administering microdoses of psilocybin (PS) in mitigating chronic neuroinflammation, impaired neurogenesis, and cognitive and mood dysfunction in 5xFAD mice, a model of early-onset Alzheimer's disease (AD). Three-month-old male 5xFAD mice received intraperitoneal administrations of PS (0.5 mg/Kg, AD-PS group) or the vehicle (AD-Veh group) once a month for 4 months. A month later (i.e., at 7 months of age), cognitive and mood functions were assessed by a series of neurobehavioral tests. The animals were then euthanized to quantify markers of neuroinflammation, neurogenesis, synaptic proteins, and amyloid plaques. Hippocampus tissue lysates from vehicle- or PS-treated 5xFAD mice were also screened for differentially expressed protein profiles using proteomics. Mice in the AD-PS group displayed improved competency to discern minor changes in the environment in an object location test, episodic-like memory function in a pattern separation test, and associative recognition memory in an object-in-place test, compared to mice in the AD-Veh group. Besides, mice in the AD-PS group displayed no anhedonia in a sucrose preference test compared to significant anhedonia in the AD-Veh group. Notably, such beneficial effects of PS treatment on cognitive and mood function were associated with reductions in astrocytic hypertrophy, inflammasome complexes within microglia, concentrations of mediators, and end products of inflammasome activation, the expression of proteins involved in p38/mitogen-activated protein kinase hyperactivation, and proteins linked to activation of cGAS-STING signaling. Additionally, PS treatment alleviated the decline in hippocampal neurogenesis, pre- and post-synaptic puncta, and BDNF-ERK-CREB signaling. Proteomic analysis revealed the upregulation of 16 proteins and the downregulation of 15 proteins in the AD-PS group compared to the AD-Veh group. Notably, the upregulated proteins have a role in regulating synaptic function, axon extension, restraining neuroinflammation, and inhibiting mTOR signaling. However, PS treatment did not diminish amyloid beta plaques or microglial clusters. Thus, intermittent PS treatment in AD has the promise to maintain better cognitive and mood function for extended periods by reducing adverse neuroinflammatory signaling cascades and alleviating synapse loss and neurogenesis decline.

Disclosures: L.N. Madhu: None. **Y. Somayaji:** None. **S. Kotian:** None. **S. Attaluri:** None. **J. Patel:** None. **P. Panda:** None. **M. Kodali:** None. **B. Shuai:** None. **X. Rao:** None. **G. Shankar:** None. **A.K. Shetty:** None.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.01/E33

Topic: C.03. Parkinson's Disease

Support: CIRM TRAN1-14671

Title: Development of robust and personalized cell replacement therapy for Parkinson's disease

Authors: *M. D. CIRNARU[1], M. T. GOODUS[1], N. YING[1], A. RAMIREZ[2], S. JUNG[7], D. AMBRUZS[3], A. WILSON[4], R. SRIJEMAC[4], A. CORL[2], H. OLIVARES[1], J. PINTOR CUELLAR[1], S. SCHREIBER[1], A. DE LA GARZA RODEA[8], Y. LEE[5], S.-C. ZHANG[9,6]; [2]R&D, [3]Analytical QC, [4]Translational Neurobio., [1]BrainXell Therapeut., SAN DIEGO, CA; [5]R&D, BrainXell Therapeut., San Diego, CA; [6]BrainXell Therapeut., San diego, CA; [7]Analytical QC, BrainXell Therapeut. Inc.,, SAN DIEGO, CA; [8]Med. Affairs, BrainXell Therapeut. Inc, San Diego, CA; [9]Ctr. for Neurologic Dis., Sanford Burnham Prebys, La Jolla, CA

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder caused by the degeneration of the midbrain dopaminergic neurons. Current treatments for PD are limited to targeting the symptoms of the disease and do not modify disease progression. Therefore, the identification of new and restorative therapies to slow down, stop and even reverse PD is critical. Cell replacement is an emerging potential therapeutic treatment for PD. Recent clinical trials of allogeneic transplantation therapy showed safety but with mild efficacy, suggesting a need for improvement in drug products. In addition, few are targeting personalized therapy. Here we define and validate the patient-to-product path for an autologous iPSC-derived PD cell therapy product. For this, we established fibroblast cultures from PD patient skin biopsies that were reprogrammed to iPSCs via mRNA technology. The iPSCs lines were banked and tested for PD mutations and determined to be idiopathic cases. Their genetic integrity was confirmed using Karyostat and aCGH testing. We generated a total of 28 iPSCs lines from normal healthy volunteers and PD patients. Five PD lines were differentiated into highly enriched midbrain dopaminergic progenitors (DAPs) via controlled innovative procedures in 3D PBS mini bioreactors culturing with timed morphogens. The DAPs (drug product) from two of the lines were transplanted into the unilateral 6-OHDA-lesioned RNU rats for the efficacy study with a viability higher than 90% at transplantation. Our in vitro results indicated a robust cell production process with greater than 30% tyrosine hydroxylase positive dopaminergic neurons and consistent on-target/off-target marker expression in all the DAPs. The efficacy of the drug product was evidenced by reduction of amphetamine induced rotations in grafted animals as early as 12 weeks and sustained efficacy up to six months for both cell lines. Thus, we have

established an efficacious, highly reproducible personalized PD cell therapy product that could have life-changing effects on PD patients.

Disclosures: M.D. Cirnaru: None. **M.T. Goodus:** None. **N. Ying:** None. **A. Ramirez:** None. **S. Jung:** None. **D. Ambruzs:** None. **A. Wilson:** None. **R. Srijemac:** None. **A. Corl:** None. **H. Olivares:** None. **J. Pintor Cuellar:** None. **S. Schreiber:** None. **A. de la Garza Rodea:** None. **Y. Lee:** None. **S. Zhang:** None.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.02/E34

Topic: C.03. Parkinson’s Disease

Support: SERB-CRG/2019/006028

Title: Advancing neuroprotective therapies: Mitochondria Targeted Polyglycerol facilitates the organelle specific antioxidant delivery.

Authors: *N. KEETHEDETH, Jr;
Ctr. for Drug Discovery, Inter Univ. Ctr. for Biomed. Res. and Super Specialty Hosp., Kottayam, India

Abstract: Mitochondrial dysfunction is a key contributor to neurodegenerative diseases like Parkinson’s disease. Targeted drug delivery to neuronal mitochondria is hindered by both the blood-brain barrier and the inner mitochondrial membrane. To address this, we developed a neutral, non-toxic, dendritic polyglycerol-based nanocarrier conjugated with triphenylphosphonium, termed as MitoPG, for efficient mitochondrial targeting. In vitro studies of MitoPG were carried out using SH-SY5Y neuronal cells. For studying mitochondrial localisation, MitoPG was tagged with fluorescein isothiocyanate (FITC) and mitochondria were stained by Mitotracker RED. MitoPG demonstrated excellent neuronal uptake, and high mitochondrial accumulation (98%) for any reported dendritic nanoparticle. In vitro toxicity study using MTT assay showed that MitoPG was non-toxic upto 100 μM. At this concentration MitoPG did not induce any mitochondrial ROS generation as indicated by MitoSOX staining and did not alter the mitochondrial membrane potential as indicated by TMRM staining. Subacute toxicity study using C57BL/6 mouse showed MitoPG to be non-toxic upto 100 mg/Kg, as evidenced by histopathological examination of tissues and body weight measurements. MitoPG was conjugated with antioxidants curcumin and quercetin for proof-of concept demonstration of neuroprotective effect. When conjugated with these drugs, MitoPG significantly reduced their toxicity. MitoPG-quercetin and MitoPG-curcumin were 2.5 times less toxic than their respective free forms, even at millimolar concentrations. MitoPG-quercetin provided 90% protection against rotenone-induced neurotoxicity at a quercetin concentration of 60 μM, a dose at which free quercetin exacerbated rotenone-induced cellular toxicity. Similarly, MitoPG-curcumin

exhibited no rotenone-induced neurotoxicity at curcumin concentration of 300 μM, while 300 μM free curcumin was toxic to the cells. Both the MitoPG conjugates effectively reduced rotenone-induced mitochondrial ROS generation, with MitoPG-quercetin (30 μM) and MitoPG-curcumin (100 μM) resulting in 76% and 84% reduction. In conclusion, MitoPG offers a highly efficient and non-toxic platform for delivering drugs directly to neuronal mitochondria, overcoming key barriers in targeted drug delivery in neurodegenerative diseases. By significantly reducing drug toxicity, enhancing neuroprotection, and restoring mitochondrial function, MitoPG holds promise as a novel nanocarrier for targeting mitochondrial dysfunction in neurodegenerative diseases.

Disclosures: N. Keethedeth: None.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.03/E35

Topic: C.03. Parkinson’s Disease

Title: Harnessing Organelles as Targets for Treatment in Neurodegenerative Diseases

Authors: S. DONATO[1], T. SORBO[1], M. SAGGIORO[1], D. BARDELLI[1], S. CORALLINO[1], D. DEL PRETE[1], D. PRESUTTI[1], M. PAINA[1], S. MARTIN[1], A. ROSSETTI[1], S. CAINARCA[1], A. MONDINI[1], F. RICCI[1], ***M. CAMPOGNONE**[2], J. ROLLAND[1];
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Abstract: Organelles are specialized cellular structures essential for maintaining homeostasis. Neurodegenerative diseases such as Alzheimer's (AD), Parkinson's (PD), and amyotrophic lateral sclerosis (ALS) often involve dysfunction of organelles including lysosomes and mitochondria. Lysosomes regulate cellular homeostasis through autophagy and nutrient sensing, while mitochondria provide energy and support metabolism; dysfunction in these organelles contributes to oxidative stress and impaired autophagy observed in these diseases. Dysregulation of the autophagy-lysosome pathway and mitochondrial impairment highlights them as therapeutic targets. Induced pluripotent stem cells (iPSCs) offer a powerful platform to model neurodegenerative diseases by generating relevant neurons that recapitulate disease phenotypes. iPSC-derived neuronal models enable detailed study of organelle dysfunction in a physiologically relevant context and support assay development for drug discovery. In particular, iPSC-derived Apparently Healthy Normal (AHN) iCell® Motorneurons and TDP43-mutated cells, as well as iCell DopaNeurons-derived from AHN engineered SNCAA53T, TMEM175 (M393T, Q65P) and PD donor-derived LRRK2 G2019S or GBA N370S lines (FCDI) were used to develop relevant models for ALS and PD. Cells were cultured in vitro for up to 3 weeks in 384- or 24-well plates for imaging and electrophysiology analysis respectively with at least four replicates per condition. To mimic disease pathologies, cells were treated with various stressors and labelled with organelle-specific dyes (such as LysoTracker Red, MitoTracker Orange), or

antibodies (e.g. LAMP-1) and acquired by High Content Microscopy. Lysosomes were isolated enzymatically for patch-clamp analysis to assess organelle-specific ionic currents involved in neurodegenerative disease (e.g. TMEM175). iCell DopaNeurons and Motorneurons exhibited disease-relevant features, upon triggering with specific stressors, such as alpha-synuclein aggregates and TDP43 mislocalization, respectively. The assays were successfully miniaturized and optimized for high-throughput drug discovery applications. Distinct ionic currents were recorded from lysosomal patches isolated from AHN and mutated cell lines. The integration of disease modelling with organelle-specific readouts enables to use the platform for a comprehensive understanding of subcellular dysfunction in neurodegeneration and facilitates the identification of novel compounds targeting these critical pathways.

Disclosures: S. Donato: A. Employment/Salary (full or part-time): Axxam SpA. **T. Sorbo:** A. Employment/Salary (full or part-time): Axxam SpA. **M. Saggioro:** A. Employment/Salary (full or part-time): Axxam SpA. **D. Bardelli:** A. Employment/Salary (full or part-time): Axxam SpA. **S. Corallino:** A. Employment/Salary (full or part-time): Axxam SpA. **D. Del Prete:** A. Employment/Salary (full or part-time): Axxam SpA. **D. Presutti:** A. Employment/Salary (full or part-time): Axxam SpA. **M. Paina:** A. Employment/Salary (full or part-time): Axxam SpA. **S. Martin:** A. Employment/Salary (full or part-time): Axxam SpA. **A. Rossetti:** A. Employment/Salary (full or part-time): Axxam SpA. **S. Cainarca:** A. Employment/Salary (full or part-time): Axxam SpA. **A. Mondini:** A. Employment/Salary (full or part-time): Axxam SpA. **F. Ricci:** A. Employment/Salary (full or part-time): Axxam SpA. **M. Campognone:** A. Employment/Salary (full or part-time): Axxam Inc. **J. Rolland:** A. Employment/Salary (full or part-time): Axxam SpA.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.04/E36

Topic: C.03. Parkinson’s Disease

Title: Neural spheroids - a platform for neurodegenerative disease modeling across multiple conditions

Authors: M. PENNAUER, *T. LÖFFLER, S. KRASSNIG, I. SCHILCHER, I. PEREZ-RUIZ, S. FLUNKERT, M. PROKESCH;
Scantox Neuro GmbH, Grambach, Austria

Abstract: Three-dimensional (3D) cell culture systems are becoming an increasingly important tool for modelling human diseases and providing new drug discovery platforms. Among them, spheroids, 3D spherical aggregates of neural progenitors or differentiated cells - offer high reproducibility, scalability and relatively short cultivation times. These cellular systems provide a valuable platform for capturing key cellular events and modeling core pathological features of neurodegenerative diseases *in vitro*, making them a suitable tool to bridge the gap in preclinical

research. In our current study, we are exploring 3D spheroids as a model for Alzheimer´s disease, Parkinson´s disease and Aging. Disease phenotypes are induced either through chemical lesions or by cells with the respective genotypes. We have confirmed basic characteristics, such as spontaneous activity, and observed disease-related phenotypes, including increased cell death, alterations in senescence or decreased mitochondrial activity. Neural spheroid models offer a reproducible and scalable platform for disease modelling and drug discovery, enabling the investigation of cellular alterations associated with human pathophysiology.

Disclosures: **M. Pennauer:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **T. Löffler:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **S. Krassnig:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **I. Schilcher:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **I. Perez-Ruiz:** 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

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.05/E37

Topic: C.03. Parkinson’s Disease

Title: Development of iPSC-based Parkinson’s disease model for drug discovery

Authors: C. FORMICA[1], B. SAMSON-COUTERIE[2], K.-C. PITSA[3], C. VAN BERKEL[4], A. DAS[3], ***S. JAIN**[3];
[1]Ncardia Services BV, Leiden, Netherlands; [2]Discovery Technologies, [4]Discovery Technol., [3]Ncardia, Leiden, Netherlands

Abstract: Parkinson’s disease (PD) is the second most common neurodegenerative disorder worldwide, affecting over 10 million individuals. Its prevalence has doubled in the past decades and is projected to double again by 2040. Despite decades of research, disease-modifying therapies remain elusive. One critical challenge is the lack of predictive preclinical models that accurately reflect the complex, multifactorial nature of PD pathology in humans. Rodent models and immortalized cell lines often fail to replicate key molecular and cellular features of the human disease, particularly α-synuclein (α-Syn) aggregation, mitochondrial dysfunction, impaired protein degradation pathways, and synaptic deficits. To address this gap, we developed a robust and scalable human induced pluripotent stem cell (iPSC)-based platform using dopaminergic neurons (iPSC-DNs) derived from healthy donors. Disease pathology was induced by treating cells with recombinant α-Syn pre-formed fibrils (PFFs) or oligomers, leading to the formation of intracellular phosphorylated α-Syn (pS129) aggregates. High-Content imaging quantified a significant increase in pS129 puncta number (> 5 fold), area (3.2-fold), and intensity (3.1-fold) compared to vehicle-treated controls ($p < 0.001$). This pathology was accompanied by

autophagy disruption, including elevated p62 levels, indicating impaired autophagic flux. Furthermore, mitochondrial density and membrane potential were reduced by 40% and 35%, respectively, as measured by high-content and live-cell fluorescent imaging. Proteasomal activity assays revealed a 45% decrease following PFF exposure. Functional neuronal deficits were confirmed using multi-electrode array (MEA) recordings, which showed a 50% reduction in weighted mean firing rate (wMFRm), 30% fewer active electrodes, and significant declines in burst and network burst frequency. Together, these findings demonstrate that our iPSC-derived PD model faithfully recapitulates multiple disease-relevant phenotypes. This platform enables drug discovery teams to screen and characterize compounds with higher translational relevance, offering robust phenotypic endpoints for efficacy and mechanism-of-action studies. Moreover, this model has the potential to reduce reliance on animal studies, supporting ethical and cost-effective approaches in PD research.

Disclosures: C. Formica: A. Employment/Salary (full or part-time): Employment/Salary. **B. Samson-Couterie:** A. Employment/Salary (full or part-time): Employment/Salary. **K. Pitsa:** A. Employment/Salary (full or part-time): Employment/Salary. **C. van Berkel:** A. Employment/Salary (full or part-time): Employment/Salary. **A. Das:** A. Employment/Salary (full or part-time): Employment/Salary. **S. Jain:** A. Employment/Salary (full or part-time): Employment/Salary.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.06/E38

Topic: C.03. Parkinson’s Disease

Title: Elucidating aggregation: a cell-based plate reader assay to model α-Synuclein pathology in neurodegeneration

Authors: G. MARESCA[1], A. CINTI[1], D. DEL PRETE[1], S. VIGANO[1], F. RICCI[1], M. CAMPOGNONE[2], L. REDAELLI[1], T. GRAMMATOPOULOS[3], ***J. ROLLAND**[1];
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Abstract: Alpha-synuclein (α-syn) aggregation is a pathological hallmark of Parkinson’s disease and other synucleinopathies, where intracellular inclusions contribute to neurodegeneration. Understanding and modulating this aggregation is central to the development of disease-modifying strategies in neuroscience. We aimed to develop and optimize a sensitive, reproducible, and scalable FRET (Förster Resonance Energy Transfer) assay enabling detection at plate reader of α-syn aggregation in a human cell background. A biosensor stable HEK-293 cell line expressing α-syn fused to ECFP and EYFP was engineered to generate a FRET signal upon intracellular aggregate formation. The rationale was to enable direct, quantitative assessment of aggregation dynamics for potential use in phenotypic compound screening. A

negative mock cell line expressing only ECFP and EYFP was developed in parallel. To ensure scientific rigor, we conducted assay optimization across multiple parameters: cell density, α-syn seed transduction protocols, DMSO tolerance, and reproducibility across multi-well plate formats. All conditions were tested with intra-plate replication (n=4 wells per condition), using both positive and negative controls, i.e. α-syn seeds and vehicle only, respectively. The assay demonstrated high robustness and sensitivity and is fully suitable for compound profiling in screening campaigns. In parallel to FRET signal detection, we employed high-content imaging with nuclear staining to visualize and quantify aggregate formation at the single-cell level. This platform enables reproducible induction and quantification of α-syn aggregation and represents a robust cellular model for investigating the molecular mechanisms of protein misfolding in neurodegeneration. It is ideally suited for future high-throughput screening efforts aimed at identifying modulators of pathological α-syn species, supporting therapeutic discovery in the field of neurobiology.

Disclosures: G. Maresca: A. Employment/Salary (full or part-time): Axxam SpA. **A. Cinti:** A. Employment/Salary (full or part-time): Axxam SpA. **D. Del Prete:** A. Employment/Salary (full or part-time): Axxam SpA. **S. Vigano:** A. Employment/Salary (full or part-time): Axxam SpA. **F. Ricci:** A. Employment/Salary (full or part-time): Axxam SpA. **M. Campognone:** A. Employment/Salary (full or part-time): Axxam Inc. **L. Redaelli:** A. Employment/Salary (full or part-time): Axxam SpA. **T. Grammatopoulos:** A. Employment/Salary (full or part-time): Axxam SpA. **J. Rolland:** A. Employment/Salary (full or part-time): Axxam SpA.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.07/E39

Topic: C.03. Parkinson’s Disease

Support: Michael J. Fox Foundation for Parkinson's Research Grant ID: 12350

Title: Transglutaminase 2 transamidase activity facilitates alpha-Synuclein pathology in iPSC-derived neurons

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Abstract: Alpha-synuclein (α-Syn) misfolding and aggregation into Lewy bodies and Lewy neurites are hallmark pathological features of Parkinson’s disease (PD) and dementia with Lewy bodies (DLB). Transglutaminase 2 (TG2), a multifunctional enzyme with transamidase activity that catalyzes cross-linking between glutamine and lysine residues, has been implicated in α-Syn aggregation. Our previous work demonstrated that TG2 facilitates the formation of insoluble,

high-molecular-weight (HMW) α-Syn aggregates both in *vitro* and in cell lines. Furthermore, TG2 overexpression enhances α-Syn aggregation and toxicity in α-Syn transgenic mice, whereas TG2 deletion has a protective effect. Given the multifunctional nature of TG2, the present study aimed to determine whether its transamidation activity specifically mediates its contribution to α-Syn pathology in human induced pluripotent stem cell (iPSC) models. To this end, we transduced differentiated dopaminergic neurons from an SNCA triplication bearing iPSC line (SNCA Tri) derived from a PD patient and its isogenic control line with lentiviral vectors expressing either wild-type (WT) human TG2 or transamidase inactive W241A mutant TG2. Immunostaining revealed markedly elevated levels of phosphorylated α-Syn in WT TG2-overexpressing neurons derived from the SNCA triplication line but not in mutant TG2 transduced neurons. Western blot analysis confirmed a significant increase in HMW α-Syn in WT TG2 transduced neurons compared to W241A mutant TG2 overexpressing or control neurons in both SNCA Tri and isogenic lines, with the effect being more pronounced in the triplication bearing line, consistent with the elevated levels of α-Syn. A significant increase in LDH release was observed in WT TG2-transduced SNCA Tri neurons compared to W241A mutant transduced or control neurons, suggesting that the crosslinking activity of TG2 enhances α-Syn aggregation and exacerbates its neurotoxicity in PD patient-derived dopaminergic neurons, particularly in the context of SNCA triplication. Additionally, the exacerbation of HMW α-Syn aggregates and neuronal toxicity were seen in WT TG2 overexpressed iPSC-differentiated neurons challenged with α-Syn preformed fibrils (PFF), but not in mutant TG2 transduced neurons. These findings indicate that the transamidation activity of TG2 is specifically involved in α-Syn aggregation and its downstream neuropathologic consequences, supporting the development of specific TG2 transamidase inhibitors as a disease-modifying therapeutic strategy in α-synucleinopathies.

Disclosures: J. Liu: None. **K. Hassanzadeh:** None. **E. Junn:** None. **M. Mouradian:** None.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.08/E40

Topic: C.03. Parkinson’s Disease

Title: GT-02287, a small molecule allosteric modulator of the lysosomal enzyme glucocerebrosidase (GCase), also affects GCase at the level of the mitochondria

Authors: S. AUZMENDI[1], A. RUANO[1], N. PEREZ[1], A. GARCIA COLLAZO[1], ***J. TAYLOR**[2];
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Abstract: Heterozygous mutations in the GBA1 gene encoding the lysosomal enzyme glucocerebrosidase (GCase) constitute the major genetic risk factor for the development of

Parkinson's disease (PD)[1]. In addition to its well-known function as a lysosomal enzyme, GCase is imported into mitochondria where it promotes the integrity and function of mitochondrial complex 1[2]. Furthermore, GCase mutations that impair its function lead to an increase in mitochondrial oxidative stress. GT-02287 is an orally available and brain penetrant small molecule allosteric modulator of GCase that stabilizes and improves its function in a variety of experimental models. GT-02287 is being developed as a disease-slowing treatment for Parkinson's disease and is currently in a Phase 1b study in people with Parkinson's disease with or without a GBA1 mutation. Previously, we demonstrated that in dopaminergic neurons in which GCase activity was reduced with conduritol B epoxide (CBE), to model GBA1-PD, GT-02287 acts as a neuroprotective compound by alleviating lysosomal pathology, reducing α-synuclein aggregation, and decreasing mitochondrial oxidative stress which resulted in enhanced neuronal survival. Additionally, in a dopaminergic neuronal model of mitochondrial impairment induced by MPP+, a mitochondrial toxin that inhibits mitochondrial complex 1 and used to model PD, GT-02287 reduced levels of mitochondrial reactive oxygen species (ROS), cytochrome C release, lysosomal pathology and α-synuclein aggregation, and increased neuronal survival. We have also demonstrated the ability of GT-02287 to prevent motor deficits and pathophysiological changes in an in vivo model of PD in which rats were treated with mitochondrial complex 1 inhibitor rotenone, as well as in mouse models in which GCase activity was lowered with CBE. In the current study we have examined the ability of GT-02287 to directly affect mitochondrial physiology, including mitochondrial GCase levels and complex 1 activity, in patient-derived cells carrying GBA1 mutations. Taken together, our findings suggest that GT-02287 exerts its neuroprotective effect through improving both lysosomal and mitochondrial function and further support its potential as a therapeutic candidate for Parkinson's disease and related synucleinopathies.[1]Sidransky, E. et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009, 361:1651-1661. https://doi.org/10.1056/NEJMoa0901281 [2]Baden, P. et al. Glucocerebrosidase is imported into mitochondria and preserves complex I integrity and energy metabolism. Nat Commun. 2023, 14: 1930 . https://doi.org/10.1038/s41467-023-37454-4

Disclosures: S. Auzmendi: A. Employment/Salary (full or part-time): Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **A. Ruano:** A. Employment/Salary (full or part-time): Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **N. Perez:** A. Employment/Salary (full or part-time): Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **A. Garcia Collazo:** A. Employment/Salary (full or part-time): Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **J. Taylor:** A. Employment/Salary (full or part-time): Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.09/E41

Topic: C.03. Parkinson's Disease

Support: ASAP-020566

Title: Ptbp1 suppression rescued gene expression in pff-treated primary neurons

Authors: *X. ZUO[1], A. JOHNSTONE[2], W. C. MOBLEY[3];
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Abstract: Mouse primary cortical neurons exposed to α-synuclein PFFs model early neurodegenerative changes, marked by significant shifts in gene expression. We investigated whether PTBP1 knockdown (KD) could rejuvenate these degenerating neurons. Neurons treated with PFFs exhibited upregulation of lysosomal, senescence, and inflammatory response genes, alongside marked downregulation of genes associated with neuronal development and differentiation. PTBP1 and related loop genes showed no intrinsic change. However, PTBP1 antisense oligonucleotide (ASO) treatment effectively downregulated PTBP1, restoring the expression of critical neuronal genes such as MEF2C, MYT1L, and NEUROD2, and suppressing stress-linked pathways. Bulk RNA-seq analysis revealed that PTBP1 KD rescued a cluster of genes associated with neuronal function disrupted by PFFs, as shown by GO term enrichment. These findings underscore the potential of PTBP1 suppression to counteract neurodegenerative gene expression changes and promote neuronal resilience, positioning PTBP1 as a compelling target for early-stage therapeutic intervention.

Disclosures: X. Zuo: None. **A. Johnstone:** None. **W.C. Mobley:** None.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.10/E42

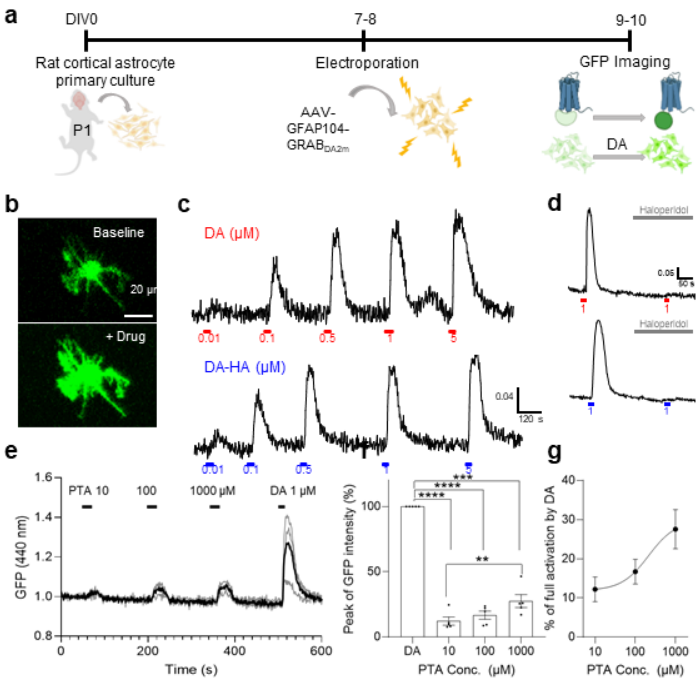
Topic: C.03. Parkinson's Disease

Support: NST Grant GTL24021-000
UST Grant 2024YS03

Title: The development of new dopamine with less toxicity and less autoxidation

Authors: *Y.-J. KIM[1,2], D. WOO[1,2];
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Abstract: Levodopa (L-DOPA), the gold standard drug for Parkinson's disease, supplements dopamine but induces side effect called L-DOPA-induced dyskinesia (LID) because of its toxicity. In our recent study, we proposed dopamine-modified hyaluronic acid (DA-HA) as a dopamine mimetic with less autoxidation and preserved dopamine functionality-two essential criteria for developing safer dopamine replacements. However, DA-HA's high molecular weight limits its permeability to cross the blood-brain barrier (BBB). To resolve these problems, we selected five materials with a similar structure to dopamine. Here, we report a series of evidence that 2-PTA and DA-HA, which are new dopamine candidates, show similar functionality as dopamine and low neurotoxicity with no autoxidation. Using a genetically encoded GPCR-activation-based DA ($GRAB_{DA2m}$) sensor, we evaluate functionality as dopamine. 1 mM 2-PTA as well as 1 μM DA-HA showed identical peak amplitude of GFP transients as 20% GFP transients induced by 1 μM dopamine. However, tyrosine, paracetamol, N-methyltyramine and phenylalanine showed no responsiveness on GFP transients of $GRAB_{DA2m}$. After 72 h incubation, 100 μM DA-HA showed low autoxidation level and 100 μM 2-PTA showed no autoxidation compared to that dopamine did show autoxidation. Moreover, both 100 μM 2-PTA and DA-HA exhibited low neurotoxicity. Our study suggests that 2-PTA and DA-HA, with their dopamine-like functionality and low neurotoxicity, represent promising tools for treating Parkinson's disease.



Disclosures: Y. Kim: None. **D. Woo:** None.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.11/E43

Topic: C.03. Parkinson’s Disease

Title: NRX02067: A noncompetitive LRRK2 inhibitor with disease-modifying potential in Parkinson's Disease

Authors: *E. KIM, H.-Y. HWANG, H. PARK, W. SON, D. LEE;
Central Res. Institute, Novorex, Inc., Seongnam-si, Gyeonggi-do, Korea, Republic of

Abstract: Parkinson’s disease (PD) is a progressive neurodegenerative disorder with an urgent unmet need for disease-modifying therapies (DMTs). Gain-of-function mutations in leucine-rich repeat kinase 2 (LRRK2), such as G2019S, are well-established genetic risk factors for both familial and sporadic PD. The pathophysiological role of LRRK2 is increasingly being elucidated, particularly its involvement in autophagy, mitochondrial homeostasis, and lysosomal function—processes critical for mitigating α-synuclein-mediated neuronal cell death. These findings support LRRK2 as a promising target for DMTs in PD. NRX02067, a recently discovered noncompetitive LRRK2 inhibitor, exhibits compelling mechanisms of action and superior efficacy compared to a reference compound. Kinase panel assays confirmed that NRX02067 is a selective LRRK2 inhibitor, with off-target effects limited to kinases whose inhibition may be beneficial in PD, suggesting a favorable pharmacological profile. The cellular potency of NRX02067 was evaluated via LRRK2 phosphorylation sites in HEK293 cells overexpressing either LRRK2 G2019S or wild-type LRRK2, yielding half-maximal inhibitory concentrations equivalent to or better than those of the reference drug. In SH-SY5Y cells overexpressing LRRK2 G2019S, NRX02067 restored lysosomal integrity by enhancing GCase activity, again outperforming the reference drug. Additionally, NRX02067 mitigated rotenone-induced 4-HNE production across various cell types. Mechanistically, we found that NRX02067 exerts its protective effects by inhibiting LRRK2-$p47^{phox}$ interactions. Collectively, these findings support NRX02067 as a promising disease-modifying therapeutic candidate that counteracts key pathological features of PD, providing strong rationale for its further preclinical development as a next-generation LRRK2-targeted therapy.

Disclosures: **E. Kim:** A. Employment/Salary (full or part-time): NOVOREX Inc. **H. Hwang:** A. Employment/Salary (full or part-time): NOVOREX Inc. **H. Park:** A. Employment/Salary (full or part-time): NOVOREX Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NOVOREX Inc. **W. Son:** A. Employment/Salary (full or part-time): NOVOREX Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NOVOREX Inc. **D. Lee:** A. Employment/Salary (full or part-time): NOVOREX Inc..

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.12/E44

Topic: C.03. Parkinson's Disease

Title: Investigating the Therapeutic Potential of Ophthalmic Acid-Producing Escherichia coli in Cellular model of Parkinson's Disease

Authors: *S. SHARMA[1], A. ALACHKAR[2];
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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by characteristic motor deficits, including bradykinesia, rigidity, and resting tremors, primarily resulting from the degeneration of dopaminergic neurons in the substantia nigra. Building upon our preliminary findings, we hypothesize that ophthalmic acid (OA), a glutathione analog with established antioxidant properties, may exert neuroprotective effects in PD, particularly when endogenously synthesized by gut-resident microbes. In our study, we identified *Escherichia coli*, a common gut commensal, as a potential microbial producer of OA. When cultured in M9 minimal medium supplemented with OA precursors (2 mM glycine, 4 mM 2-aminobutyrate, and 2 mM glutamic acid), *E. coli* was observed to produce OA at a concentration of 30 μM over 24 hours, a 96% increase compared to levels measured at 12 hours (1.2 μM). Our ongoing work focuses on quantifying OA production in *E. coli* under the influence of PD-relevant pharmacological agents, including L-DOPA, benserazide, and NSD-1015. Additionally, we are evaluating the neuroprotective potential of OA-enriched *E. coli* supernatants using in vitro cellular models of PD. This research seeks to uncover a novel gut microbiota-mediated mechanism of neuroprotection, offering promising insights into the development of probiotic-based interventions that target the gut-brain axis for managing PD.

Disclosures: S. Sharma: None. **A. Alachkar:** None.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.13/E45

Topic: C.03. Parkinson's Disease

Support: SFI 19/FFP/6666
Departmental internal support

Title: Investigating the neuroprotective potential of small molecule regulators of the BMP-Smad pathway in in vitro models of relevance to Parkinson's Disease.

Authors: *R. BEVANS[1], A. M. SULLIVAN[2], G. O'KEEFFE[1], L. COLLINS[1];
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Abstract: Recent interest in neurotrophic factor therapy (NTF) has focused on delivering NTF genes or recombinant proteins to the midbrain for the treatment of Parkinson's Disease (PD). Despite initial in vivo success, all trials have failed to meet their primary endpoints. Consequently, there is growing interest in identifying alternative strategies to protect dopaminergic (DA) neurons from degeneration. A significant challenge with NTFs is that they require direct administration to the brain due to being rapidly metabolised in vivo and an inability to cross the blood-brain barrier (BBB) in adequate doses. One strategy is to identify small molecules or biologics that can cross the BBB and selectively activate downstream targets of specific NTFs. The BMP-Smad signaling pathway is known for its neuroprotective effects on midbrain DA (mDA) neurons.We investigated whether novel small molecule activators of BMP-Smad signalling could protect against PD-related insults in vitro. SH-SY5Y cells and embryonic day (E) 14 ventral mesencephalon (VM) cultures were treated with varying doses of two small molecules. Cells were also treated with the neurotoxin 6-hydroxydopamine (6-OHDA) or transfected with plasmids overexpressing alpha-synuclein (αSyn). Small molecule treatment increased neurite length and protected against 6-OHDA and αSyn-induced insults. A BMP reporter assay revealed that both small molecules upregulated BMP- Smad-dependent transcription in SH-SY5Y cells.These results indicate that novel small molecules enhance BMP-Smad-dependent transcription, exerting a neuroprotective effect against PD-related insults in vitro. This finding warrants further in vivo testing.

Disclosures: R. Bevans: None. **A.M. Sullivan:** None. **G. O'Keeffe:** None. **L. Collins:** None.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.14/E46

Topic: C.03. Parkinson's Disease

Support: The Borealis Foundation

Title: Impact of a DNA aptamer on alpha-synuclein aggregation in a cell model of Parkinson's disease

Authors: *K. C. HARRIS[1], B. UNDERWOOD[1], D. KNIGHT[2], M. C. DEROSA[2], M. R. HOLAHAN[1];
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Abstract: Parkinson's disease (PD) is characterized by the pathogenic accumulation of misfolded alpha-synuclein (aSyn), which propagates between cells, precipitating the progressive loss of nigral dopamine neurons and the manifestation of motor symptoms. Thus, the inhibition of aSyn aggregation represents a promising target for novel interventional treatments of PD. Aptamers are single-stranded DNA or RNA oligonucleotides that bind to a target molecule with high specificity and affinity and represent an innovative alternative to antibody treatments. The current study examined the therapeutic impact of a DNA aptamer (a-syn-1), which binds to monomeric aSyn to inhibit fibrillization, in an in-vitro model of PD. Using differentiated SH-SY5Y cells treated with aSyn preformed fibrils (PFFs), we first examined the impact of the a-syn-1 aptamer on aggregation following differing schedules of administration: co-administration with pathology and after PFF-mediated seeding had occurred. To facilitate passage through lipid barriers, such as the blood-brain barrier, we then added a transferrin receptor aptamer to a-syn-1, forming the a-syn-1 chimera, and explored its impact on aSyn aggregation. Our results demonstrate that administration of the a-syn-1 aptamer significantly reduced aSyn aggregation, both when delivered concomitantly with aSyn PFFs and subsequent to the development of pathological aggregates. Further, the a-syn-1 chimera failed to inhibit aSyn aggregation, suggesting the structural and functional properties of a-syn-1 were compromised by the addition of the transferrin receptor aptamer. Collectively, these findings emphasize the preventative and therapeutic potential of the a-syn-1 aptamer in targeting aSyn pathogenesis to slow or prevent the progression of PD and underscore the necessity for carrier molecules that preserve the structural integrity of the aptamer.

Disclosures: K.C. Harris: None. **B. Underwood:** None. **D. Knight:** None. **M.C. DeRosa:** None. **M.R. Holahan:** None.

Poster

PSTR438: Developing Parkinson's Disease Therapeutic Strategies Using Cellular Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.15/E47

Topic: C.03. Parkinson's Disease

Title: Exploring the role of Cyclosporine A in protecting against α-synuclein-mediated neurotoxicity in in vitro and in vivo models of Parkinson's disease.

Authors: *A. BIR[1], S. SINGH[2], U. GANGULY[4], A. GHOSH[5], S. CHAKRABARTI[6], S. CHAKRABARTI[3];
[1]Biochem., Dr. B.C. Roy MultiSpeciality Med. research Centre, Indian Inst. of Technol. Kharagpur, Kharagpur, India; [2]Biochem., [3]MM Univ. of Med. Sci. and Research, MMDU, Mullana, Haryana, India, Haryana, India; [4]DBT Wellcome Trust India Alliance, Hyderabad, India; [5]Biochem., IIT Kharagpur,India, Kharagpur, India; [6]Inst. of Med. Sciences, Banaras Hindu University, Varanasi, India., Varanasi, India

Abstract: Mitochondrial dysfunction and α-synuclein accumulation are pivotal features of Parkinson's disease (PD), yet the mechanistic connection between them remains ambiguous (1). The mitochondrial permeability transition pore (mPTP) has been identified as a potential integrator of neurodegenerative stress signals (2). To characterise the role of mPTP in PD related neurodegeneration, we previously demonstrated that proteasomal inhibition in SH-SY5Y cells induced α-synuclein accumulation, which led to mitochondrial membrane depolarization and loss of ATP synthesis through mPTP activation(3). These effects were reversed by cyclosporine A (CsA), a selective mPTP inhibitor (3). Separately, we also showed that rotenone, a mitochondrial complex I inhibitor, caused neurodegeneration and mitochondrial dysfunction in both SH-SY5Y cells and rat brains, which were partially ameliorated by CsA (4). However, it remains unclear whether rotenone-induced neurotoxicity is mediated through α-synuclein-dependent mPTP activation. Here, we sought to explain this mechanistic relationship using both cellular and animal models of PD. To establish the causal role of α-synuclein, we showed that siRNA-mediated knockdown of α-synuclein was able to abolish rotenone induced mitochondrial depolarization, ATP depletion, ROS generation, and cell death in SHSY5Y cells. Moreover, CsA prevented rotenone-induced mitochondrial dysfunction and cell death without affecting α-synuclein accumulation. In a parallel model, adult Wistar rats were administered rotenone (1.5 mg/kg/day, intraperitoneal) for 8 days, resulting in classical Parkinsonian motor deficits and behavioural alterations along with marked dopaminergic neuronal loss in the substantia nigra, confirmed by tyrosine hydroxylase (TH) immunostaining. Mitochondria isolated from midbrain showed reduced membrane potential, impaired ATP production, and increased ROS production. Neuroinflammatory changes, including microglial activation and elevated IL-6 levels, were also evident. CsA significantly preserved motor function, dopaminergic neuron integrity, and mitochondrial bioenergetics, while also reducing inflammatory markers in rotenone-treated rats. Notably, CsA did not prevent α-synuclein accumulation, supporting the role of α-synuclein-mPTP interaction in mediating neurotoxicity. Together, these findings emphasize the vital role of mPTP inhibition in neuroprotection in PD. The results also suggest that CsA induced mitigation of PD pathology supports the idea that α-synuclein mediated PD toxicity arises from functional interaction with mPTP rather than from α-synuclein burden alone.

Disclosures: A. Bir: None. **S. Singh:** None. **U. Ganguly:** None. **A. Ghosh:** None. **S. Chakrabarti:** None. **S. Chakrabarti:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.01/E48

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: NRF RS-2023-00209580

Title: Association of choroid plexus volume with brain atrophy and glucose metabolism in multiple system atrophy

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Abstract: Background:The choroid plexus (CP) is a highly vascularized structure critical for cerebrospinal fluid (CSF) production and brain waste clearance via the glymphatic system. While previous studies have reported CP volume (CPV) enlargement in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), structural changes in the CP in multiple system atrophy (MSA) remain poorly understood. We aimed to investigate CPV in MSA and explore its associations with disease severity, brain atrophy, and glucose metabolism.
Methods:We retrospectively analyzed 87 patients with clinically established or probable MSA and 84 age-matched healthy controls who underwent 3T brain MRI and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). Volumetric analyses were conducted using FastSurfer for automated segmentation of CPV, intracranial volume (ICV), lateral ventricle volume (LVV), hippocampal volume, and white matter hyperintensity volume (WMHV). Multivariate linear regression analyses were performed to assess the relationship between CPV and clinical severity (Unified MSA Rating Scale; UMSARS), regional brain atrophy, and FDG uptake, adjusting for age, sex, symptom duration, and LVV.
Results:CPV was significantly smaller in MSA patients compared to controls (1.00 ± 0.27 vs. 1.30 ± 0.26, $P < 0.001$). In contrast to findings in AD and PD, this CP atrophy was consistently observed in both MSA-C and MSA-P subtypes. CPV showed no significant association with UMSARS scores. However, smaller CPV was significantly correlated with more severe regional brain atrophy, particularly in the cerebellar hemispheres and midline vermis, and with reduced glucose metabolism in the brainstem, cerebellum, thalamus, and ventral diencephalon. These associations were more robust in patients with the cerebellar subtype of MSA. No significant correlations were found between CPV and basal ganglia structures or FDG uptake in those regions.
Conclusion:This study demonstrates that CP atrophy is a characteristic neuroimaging feature of MSA and contrasts with the CP enlargement observed in other neurodegenerative conditions. Although unrelated to motor symptom severity, CPV was strongly linked to imaging markers of neurodegeneration, suggesting its potential utility as a structural biomarker reflecting disease burden in MSA. These findings highlight the choroid plexus as a novel site of structural involvement in MSA and underscore its relevance in disease pathophysiology.

Disclosures: S. Jeong: None. **S. Chung:** None. **P. Lee:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.02/E49

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: NIH Grant R01NS086778

Title: Droj2 and nedd4 modulate toxicity in a drosophila model of dentatorubral-pallidoluysian atrophy

Authors: *T. R. KULA, M. V. PRIFTI, S. V. TODI;
Wayne State Univ., Detroit, MI

Abstract: Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare and age related neurodegenerative disease. A polyglutamine (polyQ) disease caused by CAG nucleotide triplet repeat expansions in the transcriptional co-repressor ATN1 gene, DRPLA is characterized by progressive ataxia, dementia and epilepsy. To model DRPLA, we developed transgenic *Drosophila* lines expressing full-length human ATN1 with normal (Q7) or pathogenic (Q88) polyQ tracts. Pathogenic ATN1 impaired fly motility, lifespan, and tissue integrity. Using this model, we conducted a targeted genetic screen to identify potential interactors involved in protein quality control of the pathogenic ATN1 protein. Among various hits, knockdown of DroJ2, orthologous to human heat shock protein family member DNAJA1, improved degeneration. In another case, both overexpression and knockdown of the highly conserved E3 ligase NEDD4 improved degeneration. We are currently investigating the role of DroJ2 and NEDD4 in depth in our DRPLA fly model and will be presenting our physiological and biochemical results at this Society for Neuroscience meeting.

Disclosures: T.R. Kula: None. **M.V. Prifti:** None. **S.V. Todi:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.03/E50

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: NIH Grant R01NS086778

Title: Insights into the Biology of DRPLA from a New Cell Model

Authors: *J. P. RAUSCH[1], M. POURHADI[2], O. NUGA[3], S. V. TODI[2];
[1]Pharmacol., Wayne State Univ., East china, MI; [2]Pharmacol., Wayne State Univ., Detroit, MI; [3]Pharmacol., Wayne State Univ., Royal oak, MI

Abstract: Insights into the Biology of DRPLA from a New Cell Model Julia P. Rausch, Mandana Pourhadi, Oluwademilade Nuga, Sokol V. Todi Wayne State University Department of Pharmacology May 14th, 2025 The polyglutamine family of diseases is rooted in the abnormal repetition of a CAG triplet repeat that translates into the polyQ tract of the causative protein. Dentatorubral-pallidoluysian atrophy (DRPLA) is a member of this family of diseases; it is a rare autosomal dominant neurodegenerative disorder caused by the CAG expansion in *ATROPHIN-1*,

which encodes the protein Atrophin-1. The severity of DRPLA and its symptoms vary based on the number of CAG repeats in the polyQ tract, with 35-47 CAG repeats yielding incomplete penetrance to possibly asymptomatic, and 48-93 CAG repeats yielding complete penetrance. The symptoms for DRPLA tend to vary with age of onset, with the main symptoms being ataxia, cognitive impairment, choreoathetosis, myoclonus, and seizures. We recently generated stable HEK-293T cells expressing full-length human Atrophin-1 protein with a normal or pathogenic repeat at levels similar to the endogenous protein. This is the first step towards a complete series of stable cell lines expressing each polyQ disease protein to conduct parallel unbiased studies to investigate commonalities and differences in this family. Using this cell model, we conducted RNA-sequencing examinations that have revealed "usual suspects" and unexpected pathways impacted by the presence of pathogenic *versus* wild-type Atrophin-1 protein. We will continue to explore and validate our data in cells and *Drosophila* models of DRPLA and will present our results at this SfN meeting.

Disclosures: J.P. Rausch: None. **M. Pourhadi:** None. **O. Nuga:** None. **S.V. Todi:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

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Program #/Poster #: PSTR439.04/E51

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: R01 NS086778/NS/NINDS NIH HHS/United States
Deans Diversity Fellowship Wayne State University

Title: A Drosophila Platform for DRPLA: Linking Disease Phenotypes to Protein Quality Control Pathways

Authors: *M. V. PRIFTI, R. DULAY, N. PATEL, T. KULA, W.-L. TSOU, K. RICHARDSON, S. V. TODI;
Pharmacol., Wayne State Univ., Detroit, MI

Abstract: Dentatorubral-pallidoluysian Atrophy (DRPLA) is a rare, autosomal dominant, neurodegenerative disorder which manifests symptoms of ataxia, dementia and epilepsy with varying degrees of severity depending on age of onset. DRPLA, a member of the polyglutamine (polyQ) family of diseases, is characterized by an abnormal repeat expansion of CAG triplet report in protein-coding region of the gene *ATN1*. The resulting protein, Atrophin-1 functions in part as a transcriptional co-repressor. Similarly to other polyQ diseases, when the polyQ of ATN1 is expanded to a pathogenic length of 48 to 93, it forms aggregates which may in part contribute to overall neuronal toxicity and cell death. We recently generated transgenic *Drosophila melanogaster* lines that express full-length, human ATN1 with a normal (Q7) or pathogenic (Q88) repeat. We find that expression of both wild-type and pathogenic ATN1 is toxic in the fly with varying severity, depending on the tissue where it is expressed; the

pathogenic form its consistently more toxic than the wild-type version. Additional studies utilizing genetic eye screens highlight various members of the protein quality control pathway and immune pathway as important regulators of the toxicity of ATN1 in flies in a manner that does not always correlate with protein levels. Collectively, our data present *Drosophila* as an excellent model organism for this incurable neurodegenerative disorder and indicate key protein quality control members as potential targets for therapeutic development for DRPLA.

Disclosures: M.V. Prifti: None. **R. Dulay:** None. **N. Patel:** None. **T. Kula:** None. **W. Tsou:** None. **K. Richardson:** None. **S.V. Todi:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

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Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: The National Natural Science Foundation of China 32470564
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Title: A Knock-in Pig Modelof ATXN3 Recapitulates Neurodegenerationand Motor Deficits in SCA3 Disease

Authors: *C. LI[1,2], Y. LIN[1,2], J. SONG[1], Z. TU[1], S. YANG[1], X. LI[1], S.-H. LI[1], S. YAN[1]; [1]Guangdong-Hongkong-Macau Inst. of CNS Regeneration, Jinan Univ., Guangzhou, China; [2]State Key Lab. of Bioactive Molecules and Druggability Assessment, Guangdong Basic Res. Ctr. of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, Guangdong Provincial Key Lab. of Non-human Primate Research, Gu, Guangzhou, China

Abstract: Spinocerebellar ataxia type 3 (SCA3), the most prevalent autosomal dominant inherited ataxia globally, is caused by CAG repeat expansions in the ATXN3 gene, leading to abnormal polyglutamine(polyQ) tract elongation. Pathologically, the disease is characterized by cerebellar Purkinje cell degeneration, neuronal loss, and subsequent neurodegeneration. Utilizing CRISPR/Cas9-mediated genome editing and somatic cell nuclear transfer, we generated a porcine model with endogenous expression of full-length mutant ataxin-3 protein, mimicking the genetic etiology of SCA3. Through breeding, we established stable F1 and F2 generations of knock-in pigs. Phenotypic analyses revealed heritable motor dysfunction and gait abnormalities in F0 and F1 pigs, closely recapitulating human SCA3 symptoms. Notably, histopathological examinations demonstrated progressive Purkinje cell degeneration, synaptic damage, myelin disruption, and aggregate deposition in the cerebellum, brainstem, and spinal cord of SCA3 knock-in pigs, mirroring the neuropathology observed in SCA3 patients. This study establishes

the first large mammalian model demonstrating that endogenously expressed mutant ataxin-3 drives SCA3-specific neurodegeneration, highlighting the critical value of large animal models for elucidating disease mechanisms and developing therapeutic strategies.

Disclosures: C. Li: None. **Y. Lin:** None. **J. Song:** None. **Z. Tu:** None. **S. Yang:** None. **X. Li:** None. **S. Li:** None. **S. Yan:** None.

Poster

PSTR439: Ataxias and Dystonias

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Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: German Federal Ministry of Education and Research (BMBF, E-Rare project SCA-CYP, grant no. 01GM1803)
European commission (EUROSCA, LSHM-CT-2004-503304)
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Title: A gene therapy approach targeting the cholesterol metabolism in Spinocerebellar Ataxia Type 3 (SCA3)

Authors: J. JUNG[1], F. PIGUET[2], ***T. SCHMIDT**[1];
[1]Univ. Tuebingen, Med. Genet., Tuebingen, Germany; [2]Inst. du Cerveau et de la Moelle (ICM), Paris, France

Abstract: Cholesterol plays a critical role in the physiology of neurons, from development through to adulthood and it is required to maintain synaptic activity between neurons. Defects in brain cholesterol metabolism have been shown to contribute to several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). Brain cholesterol is synthesized almost exclusively within the brain itself and an excess cholesterol may be detrimental to neurons. However, the brain is incapable of eliminating cholesterol due to its inability to cross the blood-brain barrier. To be eliminated from the brain, cholesterol must first be converted into 24S-hydroxycholesterol (24S-OH-Chol) by the enzyme Cholesterol 24-hydroxylase (CYP46A1). 24S-hydroxycholesterol can then cross the blood-brain barrier. In this study, we present a gene therapy approach that targets cholesterol metabolism by overexpressing CYP46A1 in a model of Spinocerebellar Ataxia Type 3 (SCA3), also known as Machado-Joseph disease (MJD). SCA3/MJD is the most prevalent autosomal dominant spinocerebellar ataxia worldwide. It is caused by an expansion of a CAG repeat in the *ATXN3* gene, which leads to a polyglutamine expansion in the encoded Ataxin-3 protein. SCA3/MJD thus belongs to the group of polyglutamine (PolyQ) diseases. A defining feature of SCA3 and other polyglutamine diseases is the formation of neuronal intranuclear inclusion bodies, as well as neurodegeneration in characteristic brain regions. Currently, there is no approved treatment

strategy available for SCA3MJD patients. Following the demonstration of disturbances in cholesterol metabolism in a transgenic mouse model of SCA3/MJD, we adopted a gene therapy-based approach. We then studied the efficacy of this treatment on SCA3/MJD-associated symptoms in our mouse model. Interestingly, we observed differences in the response to the treatment between male and female mice. Furthermore, we demonstrate in SCA3/MJD patients that genetic modifications within the cholesterol pathway may contribute to the disease. We believe that our results will improve our understanding of the pathogenic processes underlying SCA3/MJD and represent a significant contribution to the development of effective therapeutic interventions for this condition.

Disclosures: J. Jung: None. **F. Piguet:** None. **T. Schmidt:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

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Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: Minnesota Office of Higher Education David J. Tomassoni ALS Research Grant Program
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Regenerative Medicine Minnesota

Title: Bulk RNA sequencing reveals a distinct transcriptomic signature in microglial ATXN1$^{146Q/2Q}$ knockout mice

Authors: *G. J. FUCHS, A. SELIMOVIC, E. PARNERKAR, M. CVETANOVIC; Neurosci., Univ. of Minnesota Med. Sch., Minneapolis, MN

Abstract: Spinocerebellar ataxia type 1 (SCA1) is characterized by deficits in muscle movement, balance, and cognition. SCA1 is caused by the expansion of CAG repeats within the coding region of the *ATXN1* gene, expressed constitutively throughout the central nervous system, leading to degeneration primarily in the cerebellum. Despite the observation of microgliosis early in the course of SCA1, neither the function of microglial *ATXN1* nor its role in disease pathology are well understood. Bulk RNA sequencing was performed on the cerebella of congenic *LYVE1*-cre crossed with cre-dependent conditional f-*ATXN1*$^{146Q/2Q}$ (microglial *ATXN1* KO), f-*ATXN1*$^{146Q/2Q}$ (disease), and WT (control) mice at approximately 9 months of age. Identified differentially expressed genes (DEGs) with respect to genotype were subjected to functional enrichment, network visualization, and pathway analysis. We identified a transcriptomic signature in microglial *ATXN1* KO mice that was not only smaller in the number of DEGs, but functionally distinct from that of disease mice. Additionally, IBA1 staining

suggests that cerebellar microglia may be morphologically different with respect to key measures of activation, such as soma volume and process ramification, in microglial *ATXN1* KO and disease mice, although additional analysis is ongoing to increase statistical power and determine if this trend rises to the level of statistical significance.

Disclosures: G.J. Fuchs: None. **A. Selimovic:** None. **E. Parnerkar:** None. **M. Cvetanovic:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

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Program #/Poster #: PSTR439.08/E55

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: National Institute of Health award (1R21NS136962 to M.C.)
National Ataxia Foundation Grant to E. L.

Title: Sca1 effect on motor network in freely moving animals

Authors: *E. LABRADA, M. CVETANOVIC;
Univ. of Minnesota, Minneapolis, MN

Abstract: Spinocerebellar Ataxia type 1 (SCA1) is a neurodegenerative disease characterized by progressive motor impairment and severe degeneration of cerebellar cells. While research has traditionally focused on cerebellar dysfunction, recent studies reveal broader brain impacts, including the striatum and cortex. This study aims to deepen understanding of SCA1's effect on motor network function in freely moving animals, addressing the limited knowledge of how SCA1 affects motor functions and cognition during free movement. This gap hinders effective treatment development for SCA1, which currently has no known therapies and significantly reduces quality of life. We will explore functional changes in the motor cortex (M2) and the Deep Cerebellar Nuclei (DCN) during late-stage disease progression using a knock-in mouse model, employing fiber photometry to record neuronal calcium activity in healthy and SCA1-affected mice during behavioral and motor tests.

Disclosures: E. Labrada: None. **M. Cvetanovic:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.09/E56

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: HI16C2210
HI21C1795

Title: Administration of hMSCs in SCA2 mice

Authors: *G.-B. LEE[1], S. KIM[1,2], U. JUNG[3], S. KIM, PHD[1,2];
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Abstract: Spinocerebellar ataxia type 2 (SCA2) is a neurodegenerative disorder caused by defects in the ataxin-2 (ATXN2) protein and a CAG trinucleotide repeat expansion in its coding gene, Atxn2. Although the mechanism of mesenchymal stem cells (MSCs) administration has not yet been fully elucidated, clinical studies suggest that MSCs have the potential to stimulate the expression of neurotrophins and suppress neuroinflammation in various forms of ataxia. This study aims to verify the neuroprotective effects of MSCs in vivo using a transgenic mouse model of SCA2 and elucidate the underlying therapeutic mechanisms. In this study, human bone marrow-derived MSCs (hMSCs) were injected into the cisterna magna of transgenic mice. Administration of hMSCs at 26 weeks of age led to significant improvement in motor dysfunction and sustained preservation of Purkinje cells in SCA2 mice that persisted up to 24 weeks post-injection. Reduced neuroinflammation and amelioration of SCA2 phenotypes at both behavioral and physiological levels were confirmed. Collectively, these findings suggest hMSC administration facilitates intrinsic protective processes and suppresses glia-mediated inflammatory pathways, offering a promising therapeutic strategy for SCA2.

Disclosures: G. Lee: None. **S. Kim:** None. **U. Jung:** None. **S. Kim, PhD:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.10/E57

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: AMED Graint 23ek0109648
AMED Graint 23bm1423020
JSPS Grant 24K10664

Title: Generation and Characterization of Induced Pluripotent Stem Cell-Derived Sensory Neurons from CANVAS Patients

Authors: *H. DOI[1], R. MORISHITA[2], H. NAKAMURA[2], R. ABE[2], Y. GOTO[2], T. WADA[2], H. KOMIYA[2], M. OKUBO[2], S. HASHIGUCHI[2], K. TAKAHASHI[2], E. KOSHIMIZU[3], S.

MIYATAKE[3], N. MATSUMOTO[3], S. MORIMOTO[4], H. OKANO[4], F. TANAKA[2];
[2]Neurol. and Stroke Med., [3]Human Genet., [1]Yokohama City Univ. Sch. of Med., Yokohama, Japan; [4]Keio Univ. Regenerative Med. Res. Ctr., Kawasaki, Japan

Abstract: Motivation: Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) is a late-onset, autosomal recessive neurodegenerative disorder caused by biallelic expansions of the intronic pentanucleotide repeats, AAGGG (AAGGG-Exp) and/or ACAGG (ACAGG-Exp), in *RFC1*. The underlying pathogenic mechanisms of CANVAS remain largely unknown. In this study, we generated human induced pluripotent stem cell (iPSC)-derived sensory neurons from CANVAS patients to investigate disease pathogenesis. Methods: iPSC lines were established from CANVAS patients harboring biallelic AAGGG-Exp (n = 3) and ACAGG-Exp (n = 3), as well as from age-matched healthy controls (n = 3). iPSCs were differentiated into sensory neurons via PiggyBac system-mediated expression of NGN2 and BRN3A. Pathogenic repeat expansions were confirmed using long-read DNA sequencing. Apoptotic cell death was evaluated by immunostaining for cleaved caspase-3. RNA foci formation was assessed by combined immunofluorescence and fluorescence in situ hybridization (FISH). Bulk RNA sequencing was performed on day 22 post-differentiation. Results: Expanded *RFC1* repeat lengths were stably maintained throughout iPSC generation and serial passaging. Differentiation yielded NeuN- and ISL1-positive sensory neurons with comparable efficiency across all lines. The proportion of cleaved caspase-3-positive cells did not significantly differ between CANVAS-derived and control neurons. Notably, RNA foci were observed exclusively in ACAGG-Exp neurons, but not in AAGGG-Exp neurons. RNA sequencing revealed widespread splicing abnormalities in CANVAS iPSC-derived sensory neurons, suggesting dysregulated RNA processing. Conclusion: We successfully established an iPSC-derived sensory neuron model from CANVAS patients, in which pathogenic repeat expansions were stably maintained. This model provides a valuable platform for elucidating disease mechanisms. Our findings suggest that RNA splicing dysregulation may play a role in the pathogenesis of CANVAS, particularly in ACAGG-Exp cases.

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Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.11/E58

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: RS-2024-00408736
HI21C1795

Title: Therapeutic potential of AAV-based gene therapy in cerebellar ataxia

Authors: *H. EO[1], U. JUNG[3], S. KIM[2], S. KIM, PHD[2];
[2]Kyungpook Natl. Univ., Daegu, Korea, Republic of, [1]Kyungpook Natl. Univ., Daegu, Korea, Republic of; [3]Pukyong Natl. Univ., Busan, Korea, Republic of

Abstract: Cerebellar ataxia (CA) is a progressive neurodegenerative disorder characterized by impaired motor coordination and balance, due to progressive loss of cerebellar neurons. Currently, no effective treatments are available. Previous studies have suggested that downregulation of mammalian target of rapamycin complex 1 (mTORC1) signaling contributes to disease progression in spinocerebellar ataxia type 2 (SCA2). In this study, we investigated whether restoring mTORC1 activity through Ras homolog enriched in brain [Rheb(S16H)], a constitutively active mTORC1 activator, could confer neuroprotection and mitigate motor deficits in a transgenic mouse model of SCA2. Targeted upregulation of Rheb(S16H) via adeno-associated virus serotype 1 (AAV1)-mediated delivery to the cerebellum resulted in robust expression in calbindin-D28K-positive Purkinje cells, leading to enhanced mTORC1 signaling and increased levels of neurotrophic factors. These molecular changes were associated with significant improvements in motor function, reduced abnormal behaviors, and enhanced survival of Purkinje cells compared to untreated SCA2 mice. Collectively, our findings demonstrate that Rheb(S16H)-mediated mTORC1 activation restores cerebellar function and provides neuroprotection, highlighting its potential as a therapeutic strategy for hereditary CA. This study was published in *Acta Pharmacologica Sinica*.

Disclosures: H. Eo: None. **U. Jung:** None. **S. Kim:** None. **S. Kim, PhD:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.12/F1

Topic: C.06. Neuromuscular Diseases

Title: Ethosuximide ameliorates clinical and pathological phenotypes in a mouse model of SCA42

Authors: *S. HASHIGUCHI[1], H. DOI[1], M. OKUBO[1], R. ABE[1], M. KUNII[1], Y. NAKAMURA[2], M. SHIMUTA[3], T. ISHIKAWA[3], F. TANAKA[1];
[1]Neurol. and Stroke Med., Yokohama City Univ. Sch. of Med., Yokohama, Japan; [2]Dept. of Pharmacol., [3]Neurosci., The Jikei Univ. Sch. of Med., Tokyo, Japan

Abstract: Spinocerebellar ataxia 42 (SCA42) is an autosomal dominant neurological disorder caused by the c.5144G>A (p.Arg1715His) variant in *CACNA1G*, which encodes the T-type

voltage-gated calcium channel Cav3.1. We previously established a mouse model of SCA42 by introducing the c.5168G> A (p.Arg1723His) variant into *Cacna1g*, which corresponds to the human variant identified in SCA42 patients, and demonstrated that this variant directly caused progressive ataxia and Purkinje cell degeneration. This variant is located in the voltage sensor domain of Cav3.1, and has been shown to alter the electrophysiological properties of Cav3.1 in both Purkinje cells and the inferior olive nucleus. However, the mechanisms by which these electrophysiological alterations lead to progressive ataxia and Purkinje cell loss remain unclear. To evaluate whether pharmacological modulation of Cav3.1 affects ataxic symptoms, neuronal dysfunction, and neurodegeneration, we performed behavioral, pathological, and electrophysiological analyses in wild type and SCA42 model mice treated with ethosuximide (ETX), a T-type voltage-gated calcium channel blocker. Compared to wild-type mice, ETX-treated heterozygous knock-in (hetero KI) mice exhibited significantly improved ataxic phenotypes between 36 and 50 weeks of age, along with reduced Purkinje cell loss at 50 weeks, as observed in sagittal cerebellar slice. Electrophysiological analysis of Cav3.1 using HEK293T cells revealed that ETX restores the abnormal shift in the activation curve of the variant Cav3.1. Furthermore we conducted RNA sequencing on cerebellar RNA from 10- and 50-week-old SCA42 model mice. Principal component analysis revealed genotype-dependent clustering based on expression patterns of differentially expressed genes. Hierarchical clustering further identified a subset of genes with consistent expression changes in both hetero KI and homo KI mice. Gene Ontology analysis of differentially expressed genes in 10-week-old homo KI mice revealed many neurodegeneration-related genes among the upregulated genes, while downregulation of genes involved in the calcium signaling and PI3K-Akt signaling pathways. Using the knock-in mouse model of SCA42, we demonstrated that ETX suppresses Purkinje cell degeneration and improves ataxic symptoms by modulating the voltage dependence of the variant Cav3.1. These findings suggest that ETX is a promising candidate for disease-modifying therapy in SCA42.

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Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

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Program #/Poster #: PSTR439.13/F2

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: FA212
Solid Biosciences

Title: Efficacy and safety of a novel AAV FXN gene therapy (SGT-212) for the treatment of Friedreich's ataxia

Authors: *G. PAVLATH[1], J. MARSHALL[1], J. LEE[1], M. HARMELINK[1], G. ROY CHOUDHURY[2], H. BORN[2], J. HORDEAUX[2], J. WILSON[2], G. BROOKS[1], J. HANRAHAN[1],

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Abstract: Introduction: Friedreich's ataxia (FA), the most common form of hereditary ataxia, is an autosomal recessive neurodegenerative disorder caused by variants in the frataxin (*FXN)* gene, which encodes a mitochondrial protein essential for iron-sulfur cluster biosynthesis and cellular energy production. FA is a multi-system disorder marked by progressive cerebellar ataxia, sensory neuropathy, and cardiomyopathy, the latter being the primary cause of mortality. **Hypothesis**: AAV-mediated gene replacement therapy can safely restore *FXN* expression in disease-relevant tissues and modify the course of FA. **Approach**: An AAVhu68-based gene therapy expressing human FXN under a ubiquitous promoter (SGT-212) was developed. To achieve broad tissue targeting, SGT-212 was administered using a dual route of administration via dual intravenous (IV) and intraparenchymal dentate nucleus (IDN) infusions. Efficacy was evaluated in conditional *Fxn* knockout mouse models targeting the nervous system (nKO) and heart (cKO), while long-term safety and biodistribution were assessed in non-human primates (NHPs). **Results:** In *Fxn* nKO mice, a single IV administration resulted in dose-dependent improvements in lifespan, sensorimotor function (as measured by Neuroscore and RotaRod), and increased FXN+ cells in dorsal root ganglia (DRG). In *Fxn* cKO mice, IV administration led to dose-dependent improvements in cardiac function (via echocardiography), prolonged survival, and restored FXN protein expression in cardiac tissue. In NHPs, dual IV/IDN administration was well tolerated for up to 12 months. No adverse findings were observed across multiple dose levels. Robust FXN expression was observed in key FA target tissues, including DRG, dentate nuclei, and myocardium. **Conclusions:** These nonclinical studies demonstrate that a one-time administration of SGT-212 can restore FXN expression in disease-relevant tissues, improve neurologic and cardiac phenotypes in mouse models, and is well tolerated in NHPs. These findings support advancement to a Phase 1b clinical trial using combined IV/IDN administration.

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Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.14/F3

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: NIH R35NS116883

Title: Electrophysiological and behavioral responses to semantic prediction violations in cerebellar degeneration

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Abstract: Although neuroimaging and neuropsychological evidence implicate the cerebellum in language, the functional contribution of the cerebellum to language is poorly understood. One prominent hypothesis posits that the cerebellum facilitates predictions related to the current discourse, similar to how it is hypothesized in the motor domain to providing internal models that anticipate the sensory consequences of movement. At odds with this hypothesis, individuals with cerebellar degeneration (CD) and controls show a similar reaction time benefit on a semantic verification task when the final word is highly predictable. However, real-world communication often involves dealing with semantic mismatches due to misinterpretation or noise. For conversation to remain fluid, we must be able to not only detect when predictions fail, but also rapidly revise the context. Given the cerebellum's central role in error correction, we hypothesized that CD may impair the ability to adjust internal models when predictions are violated. To test this, we conducted three experiments. In Experiment 1 (n=17 CD, 17 controls), participants performed a semantic verification task (meaningful or meaningless) in which for meaningful sentences, the final word was either predictable or unlikely; thus, for the latter, verification required revising an internal model of the discourse. Patients were efficient in rejecting meaningless endings but showed a larger reaction time cost to accept unlikely, yet

plausible endings, indicating impaired flexibility in switching semantic models. Further evidence of semantic inflexibility was observed in Experiment 2 (n=17 CD, 17 controls), with the CD group showing persistent priming from a predictable word in a lexical decision task, even when the completed sentence rendered that word irrelevant. EEG recordings were obtained in Experiment 3 while participants read sentences. Preliminary results (n=7 CD, 6 controls) show a prolonged and diffuse N400 in CD patients and reduced frontal post-N400 positivity for unlikely, yet plausible sentences. Together, these findings suggest that the generation of semantic predictions is intact in individuals with CD. However, these individuals exhibit an impairment in the corrective processes required to update or reorient an internal model when semantic predictions are violated.

Disclosures: A. Chirino-Pérez: None. **A. Lebel:** None. **F. Li:** None. **R. Ivry:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

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Program #/Poster #: PSTR439.15/F4

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

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R21DC021557

Title: Personalized functionally guided rTMS of motor impairments in focal dystonia

Authors: *L. B. HINKLEY[1], S. GUPTA[2], G. BATTISTELLA[4], K. SIMONYAN[5], J. M. BARKMEIER-KRAEMER[6], J. F. HOUDE[3], S. S. NAGARAJAN[7];
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Abstract: Neuromodulation strategies for focal dystonia (including laryngeal dystonia; LD) that stimulate a single target through repetitive transcranial magnetic stimulation (rTMS) have proven difficult to implement, with high variability in patient responsiveness. This variability is likely due to heterogeneity across patients in the underlying pathophysiology of the sensorimotor circuit. Here, we adopt a more personalized approach using case-control analyses of resting-state fMRI data to functionally identify rTMS sites to treat speech deficits in LD (n=10) on a single-

subject basis. MRI data (3.0T GE MR750; Waukesha, WI) was collected from participants using a standardized HCP protocol for both T1-weighted and resting-state fMRI images. Functional connectivity maps were generated through the CONN toolbox (www.conn-toolbox.org) by placing seeds in the caudate/putamen regions of the AAL atlas and then compared to a healthy control (n=84) normal distribution using case-control statistics (Hinkley et al., 2022). Functional targets (FT) were defined as a region of the premotor-parietal network showing the greatest change in connectivity from the null distribution in the fMRI analyses. Neuronavigated rTMS was delivered to the FT (1200 pulses @ 90% RMT) using a NBS 4.3 system (Nexstim Oy; Finland) using either an excitation (10Hz) protocol when the FT was underconnected or inhibition (1hz) protocol when the FT was overconnected. Participants also underwent a spatial control (SC) condition where the same parameters were applied to a region that showed no significant difference in case-control statistics, and a frequency control (FC) where the excitatory or inhibitory protocol was flipped over the functional target. Outcome measures were assessed using both subjective VAS scales and a mobile tool for speech quality (Phonalyze; Cognizn) during both sustained vowels and connected speech. Following FT stimulation, we observe a significant reduction in vocal breaks and increase in speech quality (CPPs) during sustained vowel production ($p<0.05$). For connected speech (CAPE-V), dysphonic measures (AVQI) were significantly reduced ($p<0.05$) following stimulation of FT. No significant benefits were observed in any speech measures following either SC or FC stimulation conditions. Overall, improvements in speech quality were observed in LD when targets were selected from resting-state fMRI data. This observation is consistent with emerging findings in other disorders that demonstrate better outcomes when rTMS targets are informed by baseline neuroimaging data and additionally provides a framework for more personalized approaches to neuromodulation.

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Poster

PSTR439: Ataxias and Dystonias

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Program #/Poster #: PSTR439.16/F5

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Title: Striatal Gnal Knockout Disregulates Striatal Output and Cholinergic Signaling in a Mouse Model of GNAL-Linked Dystonia

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Abstract: Gnal mutations in humans are causal for adult-onset dystonia, a disorder which is characterized by involuntary muscle clenching and twisting. Using a floxed mouse line with

stereotaxic injections of adeno-associated virus containing cre-recombinase, we have previously created a new mouse model of Gnal-linked dystonia. Given that Gnal encodes the alpha subunit of the heterotrimeric Galpha olf G-protein, it could affect signaling in the direct pathway, indirect pathway, and in striatal cholinergic interneurons. We investigated changes in striatal output using axonal fiber photometry with GCaMP8 axon and electrophysiology recordings. We additionally investigated changes in striatal cholinergic signaling using striatal fiber photometry with an acetylcholine sensor and through ex-vivo electrophysiology recordings. Overall, we found that striatal Gnal Knockout dysregulates striatal output and upregulates cholinergic signaling in the striatum. These findings have implications for treatment of Gnal-linked dystonia which we further investigated using targeted pharmacological compounds. Overall, our results fit with existing literature suggesting disrupted basal ganglia signaling in dystonia, and suggest that targeting this dysregulation as a promising therapeutic strategy for managing dystonia symptoms.

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Poster

PSTR439: Ataxias and Dystonias

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Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: NSFC Grant 2021YFA0805200
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Title: Mutant THAP11 causes cerebellar neurodegeneration and triggers TREM2-mediated microglial activation in mouse models of SCA51

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Abstract: Spinocerebellar ataxia type 51 (SCA51) is a polyglutamine (polyQ) disease caused by abnormal CAG trinucleotide repeat expansion in exon 1 of the *THAP11* gene. First reported in 2023, the neurodegenerative mechanism of SCA51 remains unclear. This study aims to elucidate the pathogenic mechanism of mutant THAP11. We found that THAP11 expression in the brain is subject to developmental regulation, showing enrichment in the cerebellum. Knocking down endogenous THAP11 in adult mice does not affect neuronal survival. In contrast, injection of adeno-associated virus (AAV) expressing mutant THAP11 with 47Q into the cerebellum of wild-type mice results in pronounced protein aggregation, Purkinje cell degeneration, and motor deficits, indicating the central role of gain-of-function mechanisms in SCA51 pathogenesis. Furthermore, we observed activated microglia expressing TREM2 in the cerebellum of the

injected mice. The loss of TREM2 alleviates the neurodegeneration induced by mutant THAP11, highlighting the role of TREM2-mediated microglial activation in SCA51 neuropathology. We have established knock-in mouse models of SCA51 and are currently analyzing their behavioral performance and neuropathology.

Disclosures: E. Ruan: None. **S. Yang:** None.

Poster

PSTR439: Ataxias and Dystonias

Location: SDCC Halls B-H

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Program #/Poster #: PSTR439.18/F7

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Title: Neurofeedback training using a brain-machine-interface for task-specific focal hand dystonia: A pilot study of 28 cases

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Abstract: Brain-Machine-Interface (BMI) technologies are systems that acquire brain signals through electrophysiological methods, such as EEG, and apply real-time analysis using artificial intelligence algorithms to provide feedback on the user's current brain state. In the medical field, BMIs are emerging as novel tools in neurorehabilitation by enabling real-time modulation of neural activity and facilitating functional recovery in post-stroke upper extremity weakness. Additionally, BMIs are increasingly being explored for therapeutic applications in movement disorders, including task-specific focal dystonia (TSFD). In this exploratory study, we evaluated the efficacy of BMI-based neurofeedback training (NFT) in patients with upper-limb TSFD. During each session, EEG and EMG signals—from the extensor digitorum communis and flexor digitorum superficialis—were recorded and analyzed. EEG was recorded from scalp electrodes placed over the sensorimotor cortex contralateral to the symptomatic hand. We quantified power spectral density (PSD), aperiodic 1/f components, and cortico-muscular coherence before and after the intervention. Symptom severity was recorded using multiple camera angles synchronized with EEG-EMG acquisition and evaluated with standardized clinical rating scales. Participants have been undergoing NFT sessions since October 2024. As of June 2025, 28 patients have been enrolled, and the study remains ongoing. Following the intervention, 14 participants demonstrated clear clinical improvement, and 10 reported subjective improvement. Visual Analogue Scale (VAS) scores decreased from 6.00 ± 2.57 to 5.04 ± 2.56. Fahn-Marsden Dystonia Rating Scale scores improved from 4.75 ± 2.43 to 3.89 ± 1.79 for the Movement subscale, and from 1.14 ± 1.56 to 1.00 ± 1.44 for the Disability subscale. Arm Dystonia Disability Scale scores increased from $71.63 \pm 13.19\%$ to $75.46 \pm 11.91\%$. No adverse events were reported. These findings suggest that BMI-based NFT may serve as a promising non-invasive approach for modulating motor symptoms in TSFD. We will present associated EEG

biomarkers and clinical outcomes in the context of neuroplasticity and motor control mechanisms.

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Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.01/F8

Topic: C.06. Neuromuscular Diseases

Title: Targeting p38 alpha MAPK signaling modulates axonopathy in the mutant SOD1G93A mouse model of amyotrophic lateral sclerosis

Authors: *L. NORIEGA[1], V. OCCHIEPPO[1], M. PRIEGO[1], M. GANZORIG[1], P. BOTTU[1], U. BHATTACHARYYA[1], T. A. HATZIPETROS[2], G. A. MORFINI[1];
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Abstract: Axonal pathology is an early and fundamental pathological feature in both familial and sporadic forms of amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease characterized by severe motor deficits. However, the precise molecular mechanisms underlying this pathological process are still not fully understood. Exploiting a unique *ex vivo* axonal preparation, our work revealed inhibition of fast axonal transport (FAT), a major cellular process sustaining axonal health, as a common effect elicited by several familial ALS (fALS)-related proteins, including mutant forms of superoxide dismutase 1 (mSOD1). Remarkably, we found that this toxic effect was mediated by p38 MAPKs, downstream components of a phosphorelay pathway referred to as the p38 MAPK module. Our experiments in isolated axons, confirmed in the SOD1G93A mouse model, further showed that mSOD1 proteins specifically activate p38alpha, the main isoform of the p38 MAPK family predominantly expressed in neurons. The crucial role of FAT on axonal homeostasis prompted us to address potential contributions of p38alpha to mSOD1-induced axonal degeneration in vivo. Specifically, we used a genetic approach to achieve ubiquitous attenuation of p38α signaling in transgenic SOD1G93A mice, a well-established model that faithfully recapitulates the ALS axonal pathology phenotype. Remarkably, our data shows that ubiquitous attenuation of p38α signaling prevents or delays the pathogenic mechanisms driving axonopathy in SOD1G93A mice. Furthermore, we identified upstream MAP2Ks mediating p38alpha activation in this model. Collectively, our findings demonstrate a role of p38α mSOD1-induced axonopathy, highlighting this kinase as a promising pharmacological target for therapeutic intervention in ALS.

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Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

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Title: Alleviation of mutant TDP-43-mediated neuropathology in monkeys by inducible stem cells

Authors: *X. SONG[1], S.-H. LI[2], S. YAN[2], X.-J. LI[2];
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Abstract: Abnormal cytoplasmic accumulation of TAR DNA-binding protein (TDP-43) is a common pathological feature of amyotrophic lateral sclerosis (ALS) and various neurodegenerative diseases. Since non-human primate models can better recapitulate this neuropathology than rodents, we used a monkey model to evaluate the therapeutic potential of stem cells for TDP-43-mediated neuropathology. We established a cynomolgus monkey model by expressing mutant TDP-43 (M337V) in the monkey striatum through AAV injection. This model exhibited motor dysfunction and abnormal cytoplasmic TDP-43 accumulation. Using multi-gene modified stem cells (NILB-hiPSCs) that can be induced to differentiate in vivo with doxycycline treatment, we found that transplanted NILB-hiPSCs improved the limb movements of the TDP-43-injected monkeys, differentiated into mature neurons, and were integrated with neural circuit activity in the monkey brain. Furthermore, NILB-hiPSC therapy reduced reactive gliosis and diminished the abnormal cytoplasmic localization of mutant TDP-43. These results highlight the potential of in vivo inducible stem cells for the treatment of neurodegenerative diseases.

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Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

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Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01 NS095969
DOD Grant AL230138

Title: A mechanism based AAV gene therapy approach for Amyotrophic Lateral Sclerosis

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Abstract: Abstract Recent human studies strongly support the view that the loss of splicing repression by an RNA binding protein, termed TDP-43, underlies the pathogenesis of amyotrophic lateral sclerosis (ALS), a neurodegenerative disorder currently without any disease modifying therapy. To address this unmet need, we employed a blood-brain-barrier crossing AAV (AAV-PHP.eB) gene therapeutic approach to complement the loss of TDP-43 splicing repression by delivering intravenously a splicing repressor (termed CTR) to adult central neurons, including spinal motor neurons. We demonstrate in a mouse model of motor neuron disease (*ChAT-Cre;Tardbp*$^{f/f}$ mice) mimicking presymptomatic loss of TDP-43 occurring in ALS, that such a mechanism-based therapy when delivered during early symptomatic stage of disease attenuates motor neuron loss and muscle atrophy, consequently extending its lifespan. Corroborating these findings in *ChAT-Cre;Tardbp*$^{f/f}$ mice, AAV expressing CTR (AAV-PHP.eB-CTR) prevented inclusion of cryptic exons in >70% of motor neurons and markedly improved muscle strength. Notably, no overt phenotype is observed in aged control mice transduced with AAV-PHP.eB-CTR. Together, these results validate an AAV therapeutic strategy designed to complement the loss of splicing repression by TDP-43 and thus for ALS provide an unprecedented opportunity towards clinical testing of this mechanism-based gene therapy.

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Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

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Program #/Poster #: PSTR440.04/F11

Topic: C.06. Neuromuscular Diseases

Title: Treatment with a cell-penetrating antibody targeting pTDP43 reduces intraneuronal pathology in a mouse model of ALS

Authors: *I. D. GALLAGER, L. W. LI, K. THOMAS, A. TRUMBLE, G. ZHANG, H. PRILL, K. LEE, J. SALMANS, E. GOLDBACH, A. PORAT, B. M. CAMPBELL, R. P. BRENDZA, P. J. DOLAN, T. NIJJAR, S. J. TAM, W. ZAGO;
Prothena Biosci. Inc., Brisbane, CA

Abstract: Amyotrophic lateral sclerosis (ALS) is a disease affecting approximately 32,000 people in the US annually[1], with an average post-diagnosis life expectancy of 3 years[2]. Due to the aggressive and fatal nature of ALS, the development of therapies towards attenuating or reversing pathology and symptomology is paramount. Transactive response DNA/RNA binding protein 43 (TDP43) plays essential roles in transcription, translation, RNA splicing, mRNA transport and is regulated by cytoplasmic transport. In ALS, TDP43 hyper-phosphorylation, ubiquitination, fragmentation and transportation from the nucleus promotes TDP43 aggregation and the formation of pathologic intracellular cytoplasmic inclusions[3]. These perturbations lead to RNA dysregulation and loss of TDP43 nuclear function and axonal transport which contribute to cellular dysfunction and concurrent neurotoxic events[4]. To test directly targeting and clearing pathologic intracellular inclusions of aggregated TDP43, we used cell penetrating technology in our CYTOPE® Platform and an anti-pS409/410-TDP43 antibody to develop a pTDP43-Cytope capable of cellular uptake and release into the cytoplasm. Initial in vitro studies demonstrated that pTDP43-Cytope localized to the cytoplasm and reduced pTDP43 cytoplasmic inclusions when applied to HEK293 cells overexpressing hTDP43. Subsequently, we investigated whether the pTDP43-Cytope could clear intracellular pathology in vivo using the rNLS8 (NEFH-hTDP-43ΔNLS) transgenic mouse model of ALS. This model expresses human TDP43 lacking the nuclear localization sequence under the control of an inducible tetracycline promoter and develops extensive TDP43 and pTDP43 neuronal pathology in the brain. Intravenous administration of pTDP43-Cytope treatment resulted in colocalization of pTDP43-Cytope with pTDP43 intraneuronal pathology in rNLS8 mice. Furthermore, we observed significant reduction of aggregated pTDP43 pathology in the brain following a dosing regimen over 4 weeks. These findings support further investigation of pTDP43-Cytope as a potential interventional therapy in ALS and the utility of the CYTOPE Platform for targeting cytosolic drug delivery.

Disclosures: I.D. Gallager: A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **L.W. Li:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **K. Thomas:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **A. Trumble:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **G. Zhang:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **H. Prill:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **K. Lee:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **J. Salmans:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **E. Goldbach:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **A. Porat:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **B.M. Campbell:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **R.P. Brendza:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **P.J. Dolan:** A. Employment/Salary (full or part-time): Prothena Biosciences, Inc. **T. Nijjar:** A.

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Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

Location: SDCC Halls B-H

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Program #/Poster #: PSTR440.05/F12

Topic: C.06. Neuromuscular Diseases

Title: Modulating TDP-43 aggregation directly and indirectly in C.elegans

Authors: *E. ELSHALIA[1], N. STILLMAN[1], M. E. SPAETH HERDA[2], A. G. WEAVER[2], D. A. LINSEMAN[2], S. KUMAR[1], S. HOROWITZ[1];
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Abstract: TDP-43 misfolds and aggregates in multiple diseases, currently with no therapeutic interventions. Here, we tested two different approaches via *C.elegans* expressing TDP-43 protein in motor neurons using either direct and indirect mechanisms to modulate TDP-43 aggregation. To directly inhibit TDP-43 aggregation, we tested two Oligopyridylamide (OP) ligands that were shown to directly bind TDP-43 and prevent its aggregation *in vitro*. Treating the worms with these OPs prevented TDP-43 aggregation and the development of neurological symptoms. In addition to aggregating, TDP-43 is also known to bind a nucleic acid secondary structure known as G-quadruplex (G4) structure, which has been shown previously to be a powerful modulator of protein aggregation. To indirectly modulate TDP-43 aggregation through G4s, we administered 5-aminolevulinic acid (5-ALA), a precursor to protoporphyrin IX (PPIX) that binds G4s. This G4-targeting treatment ameliorated TDP-43 aggregation as well as neurodegenerative symptoms in *C.elegans*. To further specify TDP-43 targeting via G4 structures, we administered PPIX that is ligated to a PROTAC group to target G4-TDP-43 complex for degradation. Our experiments showed that PPIX-PROTAC decreased the neurological symptoms in *C.elegans*. These results show that both direct and indirect aggregation prevention are possible avenues to pursue for TDP-43 lead therapeutics.

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Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.06/F13

Topic: C.06. Neuromuscular Diseases

Support: NRF Grant RS-2025-00560220
KDDF Grant RS-2025-02182973

Title: Zcs1, a lysosomal activator, improves survival and attenuates TDP-43 pathology in G93A-SOD1 mouse model of Amyotrophic Lateral Sclerosis.

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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive motor neuron degeneration. Although approximately 10% of cases are familial, associated with mutations in genes such as *C9orf72*, *SOD1*, and *TARDBP*, pathological accumulation of TDP-43 protein is observed in ~97% of all patients. Despite this common pathology, no effective treatment currently halts disease progression. Based on the recognition of ALS as a proteinopathy involving abnormal accumulation of TDP-43 and SOD1, we aimed to develop a lysosomal activator capable of restoring autophagy flux and lysosomal function. ZCS1 is a synthetic pentapeptide identified through a screening platform for compounds that reverse Bafilomycin A1-induced blockade of autophagy. Rhodamine-labeled ZCS1 was shown to enter cells via endocytosis, which was prevented by the endocytosis inhibitor methyl-β-cyclodextrin. ZCS1 possesses a zinc-binding motif that increases intra-lysosomal zinc levels, enhances lysosomal acidification, and promotes TFEB-dependent lysosomal biogenesis. In cellular models, ZCS1 enhanced cathepsin B and D activity and reduced insoluble TDP-43 aggregates even under conditions of autophagy inhibition. In vivo efficacy was evaluated in G93A-SOD1 transgenic ALS mice. In the first experiment, ZCS1 was administered daily by subcutaneous injection (40 mg/kg) beginning at 16 weeks of age, a time point when the mice began to exhibit reduced body weight relative to wild-type controls. This treatment led to improved motor performance and extended survival by approximately 20 days. In the second experiment, treatment was initiated at 18 weeks of age—approximately two weeks later—after the onset of motor dysfunction. Despite the more advanced disease stage and inter-individual variability, ZCS1 nevertheless modestly extended survival by ~9 days. Furthermore, ZCS1 significantly reduced serum neurofilament light chain levels at 150 days, a biomarker of neuronal damage. Histological analysis of the lumbar spinal cord revealed reduced accumulation of total and phosphorylated TDP-43 and preserved motor neuron integrity in ZCS1-treated animals. These findings demonstrate that ZCS1 restores autophagy-lysosomal function and mitigates key pathological features of ALS, supporting its potential as a therapeutic candidate for further development.

Disclosures: Y. Kim: A. Employment/Salary (full or part-time): Zincure Corp. **H. Lee:** A. Employment/Salary (full or part-time): Zincure Corp. **K. Kim:** A. Employment/Salary (full or part-time): Zincure Corp..

Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

Location: SDCC Halls B-H

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Program #/Poster #: PSTR440.07/F14

Topic: C.06. Neuromuscular Diseases

Support: NIH-R21 NS123761

Title: Translational Optogenetics in ALS: Preserving Swallowing Function via Hypoglossal Neuromodulation in SOD1 Mice

Authors: *A. BASAK[1], C. DRAGO[2], S. KINGTON[2], K. HOELSCHER[2], C. SCHELLMAN[2], G. EASON[2], G. OTI[3], E. MASKROD[2], K. L. OSMAN[2], N. L. NICHOLS[3], I. OZDEN[1], T. E. LEVER[2];
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Abstract: Dysphagia is a life-threatening symptom of Amyotrophic Lateral Sclerosis (ALS) that contributes significantly to malnutrition, dehydration, and aspiration pneumonia, increasing mortality rate by eightfold. Its onset in ALS coincides with tongue weakness and atrophy resulting from degeneration of hypoglossal lower motor units (XII MUs), which provide the sole motor innervation to the tongue. Despite its clinical impact, currently no therapies exist to directly target or preserve these critical motor units.We hypothesize that optogenetics can serve as a targeted gene therapy approach to slow XII MU degeneration and tongue atrophy by promoting neuronal repair and nerve terminal proliferation. We utilized a translational mouse model of ALS (*SOD1-G93A*) showing clinicopathological symptoms of dysphagia to develop our experimental therapeutic approach. Our pilot study gave promising results, where we injected adeno associated virus (AAV) mediated excitatory opsin Channelrhodopsin2 (ChR2) into the hypoglossal nucleus (HGN) to directly stimulate and record neural activity via an implanted optrode. Here, we are adapting this approach into a minimally invasive method with greater feasibility for translation to ALS clinical trials. We injected AAV mediated ChR2 into the tongue (midline into the base and blade; 10-15 µL per site) of *SOD1* (n=6) and wild-type (n=8) mice to retrogradely transfect XII MUs. Approximately 3 weeks post-injections, optogenetic stimulation (opto-stim) of the tongue surface under anesthesia (either ketamine-xylazine or isoflurane) resulted in tongue contractions visible via strain gauge recordings. Cryosection histology of the brainstem and tongue showed opsin expression in the HGN and tracts as well as the tongue myofibers. Of note, tongue injections were administered after clinical disease onset, when *SOD1* mice presumably had axonal transport deficits, a hallmark feature of ALS. We are currently refining strategies to improve opsin expression in XII MUs to enhance the efficacy and precision of opto-stim evoked tongue contractions. Post optimization, we will evaluate the therapeutic effects of targeted opto-stim in awake, freely behaving mice during voluntary licking from a light-emitting spout versus at rest via a light-emitting patch implanted subcutaneously under the tongue. This preclinical investigation is designed to assess whether selective activation of XII MUs can mitigate neurodegeneration, preserve bulbar motor function,

and extend survival, thereby establishing the translational potential of this approach for dysphagia therapy in ALS.

Disclosures: A. Basak: None. **C. Drago:** None. **S. Kington:** None. **K. Hoelscher:** None. **C. Schellman:** None. **G. Eason:** None. **G. Oti:** None. **E. Maskrod:** None. **K.L. Osman:** None. **N.L. Nichols:** None. **I. Ozden:** None. **T.E. Lever:** None.

Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

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Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R35 NS122140

Title: Effect of muscle-specific androgen receptor silencing in symptomatic SBMA mice

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Abstract: Spinal and bulbar muscular atrophy (SBMA) is a rare, late-onset X-linked neuromuscular disease caused by a CAG-polyglutamine (polyQ) expansion in the androgen receptor (AR) gene, resulting in nuclear aggregation of mutant AR protein and progressive muscle atrophy. Gene therapy strategies aimed at reducing AR expression are promising for treating SBMA, but it is unknown whether they remain effective after symptom onset. We previously showed that muscle-specific excision of the mutant AR gene beginning at ~embryonic day 12 completely removed the gene from skeletal muscle and fully prevented disease phenotypes in SBMA mice. However, it remains unclear whether therapeutic benefit can still be achieved at symptomatic stages, when nuclear aggregates are already established. To address this, we bred SBMA mice expressing floxed mutant AR with $Myf6^{CE/WT}$ mice (SBMA;$Myf6^{CE/WT}$), allowing tamoxifen-inducible, muscle-specific gene excision. Mice were treated with tamoxifen (i.p.) once daily for five consecutive days at 21 weeks of age and monitored for 10 weeks. Successful recombination was confirmed by tdTomato reporter activation in skeletal muscle. Despite effective mutant AR gene excision, some polyQ-AR aggregates persisted in myonuclei of SBMA;$Myf6^{CE/WT}$ mice after 10 weeks. Nonetheless, SBMA;$Myf6^{CE/WT}$ mice showed drastically improved grip strength ($p < 0.001$) and increased body weight ($p < 0.0001$) ($n = 6$-13 per group) over the 10 week period. Histological analysis revealed selective improvements in fast-twitch muscles, including an increased proportion of Type IIB fibers in the plantaris, which is the most strongly affected fiber type in SBMA. Additional increases in fiber cross-sectional area were observed in the gastrocnemius. These findings suggest that mid-symptomatic excision of the mutant AR gene can partially restore

muscle function and selectively ameliorate fast-twitch fiber pathology, independent of aggregate clearance, highlighting the potential for gene silencing therapies in SBMA even after disease onset.

Disclosures: D. Garg: None. **A. Gromova:** None. **A. La spada:** None.

Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

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Program #/Poster #: PSTR440.09/F16

Topic: C.06. Neuromuscular Diseases

Support: NIH NIA R01AG061447
NIH NIA 3R01AG061447-03S1

Title: Intranasal Dantrolene Nanoparticles for Treatment of Amyotrophic Lateral Sclerosis as a Disease-Modifying Drug

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Abstract: This study investigates the therapeutic potential of intranasally administered dantrolene, a ryanodine receptor antagonist, in SOD1G93A transgenic mouse models of amyotrophic lateral sclerosis (ALS). C57BL/6SJLF1 non-transgenic control mice and SOD1G93A ALS transgenic mice were divided into three different groups: no treatment, intranasal dantrolene nanoparticles (IN-DAN) (5mg/kg daily, from day 90 to 120), or intranasal vehicle. Body weight and motor function were monitored weekly, and survival was recorded daily throughout 30 day-treatment period. Afterwards, neurological scoring was conducted, and motor coordination and muscle strength were assessed with balance beam, rotarod, and grip force tests, respectively. Spinal cord degeneration was then evaluated by quantifying neurofilament light chain levels and measuring spinal cord weight. Compared to non-transgenic control mice, SOD1G93 ALS mice exhibited elevated neurological scores, reflecting significant neurological impairments. Treatment with IN-DAN attenuated this decline, reducing neurological scores by 90% ($P<0.0001$). On the beam balance test, ALS mice were also impaired in motor coordination and balance, exhibiting significantly increased crossing times and numbers of foot slips. IN-DAN treatment significantly improved performance comparatively, reducing foot slips by 84% ($P<0.0001$) and crossing time by 78% ($P<0.0001$) on 12mm-wide beams; these effects were not observed in the IN-VEH group. Moreover, IN-DAN treatment reversed the progressive body weight loss observed in ALS mice, while the vehicle treatment had minimal effect. Muscle strength, determined with grip force as a proxy, was noticeably diminished in ALS mice. However, IN-DAN treatment strongly conserved muscle strength, preventing the

decline by 213% (P<0.0001), with no impact observed in the vehicle group. Further, intranasal dantrolene treatment reversed the reduction in spinal cord weight observed in ALS mice, a result not achieved with the vehicle control. Analysis of survival revealed that only 67% of untreated or vehicle-treated ALS mice survived during the 30-day treatment period (up to 120 days of age). IN-DAN-treated ALS mice, however, demonstrated a significantly improved survival rate of 89%. Intranasal dantrolene nanoparticles significantly improved the neurological and motor function, muscle strength and survival outcomes in SOD1G93A ALS mice. This treatment effectively reversed spinal cord and body weight loss. This study support the potential of intranasal dantrolene nanoparticle treatment as a feasible, non-invasive, and effective disease-modifying strategy for ALS treatment.

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Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

Location: SDCC Halls B-H

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Program #/Poster #: PSTR440.10/G1

Topic: C.06. Neuromuscular Diseases

Support: US Dept of Veterans Affairs Grant I21RX005155
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Neurodegenerative Disease Research Inc Grant

Title: Therapeutic targeting of carboxyl-terminal modulator protein in amyotrophic lateral sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by impaired neuromuscular connections, muscle atrophy, and paralysis. Currently, there are no effective therapies or cures for ALS. The complex nature of the disease and the lengthy diagnostic process make developing meaningful treatments challenging. Muscle atrophy is a key feature of ALS progress, marked by reduced anabolic Akt signaling and increased atrogene expression after denervation. Our previous studies indicate that levels of the carboxyl-terminal modulator protein (CTMP) increase in skeletal muscle following ALS, nerve injury, and in response to TNF-α treatment. CTMP is recognized as an antagonist of Akt signaling, and our work has linked CTMP to the downregulation of Akt/mammalian target of rapamycin (mTOR)

signaling, promoting muscle breakdown in various models of muscle atrophy. Furthermore, increased activity of Akt and mTOR signaling is known to provide neuroprotection and support neuronal regeneration in models of disease and neurotrauma. Based on our research and that of others, we hypothesize that CTMP's ability to inhibit Akt signaling may help sustain functional neuromuscular connections, leading to delayed functional decline and extended lifespan in a commonly used mouse model of ALS. To test this, we developed a stable novel peptide that blocks CTMP's ability to bind to and inhibit Akt phosphorylation and activation, resulting in increased downstream anabolic signaling and cellular survival. We administered our CTMP-antagonist peptide (CAP) systemically near the onset of disease (starting at 70 days of age) and continued daily treatment. This approach significantly delayed the progression of neuromuscular dysfunction in the mutant superoxide dismutase 1 (SOD1G93A) mouse model of ALS compared to vehicle-treated control mice ($p < 0.05$). Additionally, the peptide significantly extended the lifespan of the SOD1G93A ALS mice compared to those treated with the vehicle ($p < 0.05$). These results suggest that our novel peptide-based approach to inhibit CTMP may offer a promising therapeutic option for improving functional outcomes and survival in ALS.

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Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

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Topic: C.06. Neuromuscular Diseases

Support: NIH-NINDS K08NS121519

Title: Modulating Cathepsin Expression to Enhance TDP-43 Proteostasis and Neuronal Viability in ALS Models

Authors: *T. ANTEE[1,2], Z. LIAU[2], P. J. SAMPOGNARO[2];
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Abstract: Amyotrophic lateral sclerosis (ALS), is a devastating neurodegenerative disease causing progressive motor neuron loss, paralysis, and death. A central pathological hallmark in most ALS is the aggregation and cytoplasmic mislocalization of TDP-43, a nuclear RNA-binding protein vital for RNA metabolism. Emerging evidence indicates lysosomal proteases, particularly cathepsin B (CTSB), cathepsin D (CTSD), and asparagine endopeptidase (AEP), are significantly involved in TDP-43 degradation and the maintenance of cellular proteostasis. In this study, we employed CRISPR interference (CRISPRi) and activation (CRISPRa) to precisely modulate CTSB, CTSD, and AEP expression. Modulations were performed in iPSC-derived cortical neurons (iNeurons) and motor neurons (iMNs) with wild-type (WT) TDP-43 or a Q331K

mutant variant. Using these engineered neuronal lines in 2D cultures, we systematically assessed TDP-43 protein levels and neuronal viability. Preliminary findings demonstrate specific cathepsin modulations significantly impact neuronal health and TDP-43 regulation. Upregulating CTSD expression substantially enhances cell viability while concurrently reducing steady-state levels of WT TDP-43 in iNeurons. Similarly, AEP activation also resulted in decreased TDP-43 levels. Conversely, inhibiting CTSD or AEP led to a marked reduction in neuronal survival. CTSB, on the other hand, exhibited a more modest response. In motor neurons, AEP modulation was particularly pronounced: inhibition diminished viability, while upregulation improved survival. To further investigate these mechanisms, we are actively studying these CRISPR-modulated lines in 3D brain organoid models. These involve co-culturing cortical or motor neurons (with activated or inhibited cathepsin expression) with astrocytes for 30-60 days. The primary objectives for utilizing these organoids are to replicate the in vivo neural microenvironment, facilitate prolonged neuronal culture for observing disease-relevant changes, and elucidate glial cell roles in ALS pathology. In these 3D systems, we will assess TDP-43 aggregation and clearance via biochemical assays and advanced high-resolution imaging techniques. This research aims to generate comprehensive, cell-type-specific, quantitative data on the roles of CTSB, CTSD, and AEP in TDP-43 proteostasis across both 2D and 3D neuronal systems. The overarching goal is to validate lysosomal cathepsins as viable therapeutic targets for enhancing TDP-43 clearance and promoting neuronal survival, offering a promising new avenue for treating ALS.

Disclosures: T. Antee: None. **Z. Liau:** None. **P.J. Sampognaro:** None.

Poster

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Program #/Poster #: PSTR440.12/G3

Topic: C.06. Neuromuscular Diseases

Title: Investigating the effects of edaravone on neuronal function in human motor neurons from a patient with ALS

Authors: *A. TOYCHIEV, S. MIKURIYA, T. SHIRAKAWA, M. TAMURA;
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by pathological aggregation and mislocalization of the TAR DNA-binding protein 43 (TDP-43), leading to impaired neuronal function and progressive neuronal degeneration. This study investigated the effects of edaravone, an FDA-approved ALS treatment, on the function of neurons derived from induced pluripotent stem cells (iPSCs) from both a healthy individual and an ALS patient with the TDP-43 A382T mutation. To enhance neuronal maturation, iPSC-derived neurons were co-cultured with astrocytes, and neuronal activity was measured using

multi-electrode arrays. Significant differences in neuronal activity were observed between ALS patient-derived neurons and healthy controls. Specifically, ALS neurons exhibited reduced numbers of active electrodes but an elevated overall firing rate. Furthermore, ALS-derived neurons showed increased bursting activity, characterized by more frequent bursts, shorter burst durations, shorter interburst intervals, and increased spikes per burst compared to healthy neurons. In response to electrical stimulation (100 ms pulses with 25 mV increments), ALS neurons exhibited an initial robust response that rapidly plateaued, whereas healthy neurons demonstrated a more sustained activity pattern. These findings suggest that the TDP-43 mutation impairs neuronal network dynamics, diminishing their capacity to respond effectively to stimulation. The therapeutic potential of edaravone was further evaluated by treating iPSC-derived neurons at week 5 with 100 μM edaravone. Edaravone significantly reduced firing rates and network burst activity in both healthy and ALS-derived neurons, indicating enhanced neuronal stability and function. Additionally, edaravone treatment resulted in an improved and sustained neuronal response to electrical stimulation in both groups. Limitations include that while iPSC-derived neurons are a valuable model system, they may not fully capture the multicellular interactions and systemic influences present in the human nervous system. As these findings are based on iPSC-derived neurons from a single donor, further validation across multiple patient-derived lines will be important to assess reproducibility. Collectively, these results demonstrate that edaravone improves neuronal network activity in ALS patient-derived neurons harboring the TDP-43 A382T mutation. These findings support the therapeutic potential of edaravone in ameliorating neuronal dysfunction associated with TDP-43 pathology in ALS.

Disclosures: **A. Toychiev:** A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma America. **S. Mikuriya:** A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma America. **T. Shirakawa:** A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma America. **M. Tamura:** A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma America.

Poster

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Topic: C.06. Neuromuscular Diseases

Support: Mitsubishi Tanabe Pharma America
Mitsubishi Tanabe Pharma Corporation

Title: E3 ligase LRSAM1 as a novel regulator of TDP-43 pathophysiology in amyotrophic lateral sclerosis

Authors: ***T. SHIRAKAWA**[1], S. MIKURIYA[1], Y. INOUE[2], K. MURASAKI[2], F. SALINAS[1], M. TAMURA[1];

[1]NeuroDiscovery Lab., Mitsubishi Tanabe Pharma America, Inc, Cambridge, MA; [2]Discovery Technol. Laboratories, Res. Div., Mitsubishi Tanabe Pharma Corp., Fujisawa, Japan

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by motor neuron degeneration, prominently involving abnormal cytoplasmic aggregation and mislocalization of TAR DNA-binding protein 43 (TDP-43). Although clearance mechanisms such as the ubiquitin-proteasome system (UPS) and autophagy are crucial for managing cytoplasmic TDP-43, factors precisely governing its aggregation and degradation remain incompletely understood.

Here we show that the E3 ubiquitin ligase LRSAM1, capable of activating both UPS and autophagy pathways, plays a previously unrecognized role in regulating TDP-43 dynamics during ALS progression. Immunohistochemical analyses of postmortem human spinal cord revealed strong colocalization of LRSAM1 with diffuse cytoplasmic TDP-43 but limited association with dense aggregates, suggesting LRSAM1 acts predominantly at early, reversible stages of TDP-43 mislocalization. Using induced pluripotent stem cell neurons (iPSNs) from patients with ALS, we found that LRSAM1 depletion worsened pathological features, including TDP-43 cytoplasmic mislocalization, phosphorylation, and impaired RNA processing of STMN2. In contrast, enhancing LRSAM1 expression reduced TDP-43-related abnormalities triggered by cellular stress in ALS iPSNs but had limited impact on control iPSNs. Through computational and biochemical studies, we determined that LRSAM1 directly interacts with and facilitates the degradation of TDP-43 C-terminal fragments prone to aggregation, particularly through binding to its RNA recognition motif 2. Additionally, manipulating LRSAM1 expression influenced neurite outgrowth, highlighting its neuroprotective potential in ALS conditions.

Our findings identify LRSAM1 as a key regulator that selectively targets aggregation-prone TDP-43 fragments, highlighting its critical role in managing pathological events in ALS. Modulating LRSAM1 function thus represents a potential therapeutic strategy to reduce TDP-43 pathological mislocalization and associated neurodegeneration.

Disclosures: T. Shirakawa: A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma America, Inc. **S. Mikuriya:** A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma America, Inc. **Y. Inoue:** A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma Corporation. **K. Murasaki:** A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma Corporation. **F. Salinas:** A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma America, Inc. **M. Tamura:** A. Employment/Salary (full or part-time): Mitsubishi Tanabe Pharma America, Inc.

Poster

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Support: NIH Grant 1RF1NS127407
Target ALS Foundation BB-2024-C1-L3

Title: Investigating the Role of LINE-1 in Innate Immune Activation and Neurodegeneration in ALS

Authors: *S. CHEN[1], C. MARQUES[1], B. WAINGER[2];
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Abstract: The long interspersed nuclear element 1 (LINE-1) class of retrotransposons, comprising around 17% of the human genome, is the only autonomously active transposable element (TE) in humans. It propagates via a "copy-and-paste" mechanism facilitated by its two encoded proteins ORF1p and ORF2p. Normally silenced in somatic cells, LINE-1 can become reactivated under cellular stress, promoting genomic instability, altered gene expression, and innate immune responses. LINE-1 and other retrotransposons are increasingly implicated in neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) where up to 20% of patients exhibit elevated TE expression. ALS is a fatal disorder marked by progressive loss of layer 5 cortical pyramidal motor neurons (L5-CPNs) and spinal motor neurons. About 10% of cases are familial (fALS)—most commonly due to a hexanucleotide repeat expansion in the **C9orf72** gene (C9-ALS)— while the majority are sporadic (sALS) with unclear molecular drivers. Previous studies have reported elevated LINE-1 activation in C9-ALS. We recently reported robust **STING** (stimulator of interferon genes) pathway activation in L5-CPNs from postmortem ALS patients across a range of fALS mutations. Given the ability of LINE-1 expression to activate immune responses, we investigate its role in driving enhanced STING signaling in ALS-affected neurons. Immunohistochemistry on postmortem primary motor cortices showed elevated ORF1p protein levels in L5-CPNs of C9-ALS patients (n=8) compared to non-neurological controls (n=9). To examine the subtype-specificity of LINE-1 expression, we are currently comparing ORF1p expression in fALS (FUS, TARDBP, KIF5A mutations) and sALS cases. Preliminary immunostaining reveals co-localization of ORF1p and STING in C9-ALS neurons, supporting a mechanistic link between LINE-1 de-repression and STING-mediated innate immune signaling. To further establish this relationship in a human neuronal model, we are evaluating ORF1p expression in human iPSC-derived cortical neurons from C9-ALS patients, where we previously observed STING activation. ORF1p overexpression in healthy control iPSC-derived cortical neurons was sufficient to induce a significant increase in STING pathway activation. Together, these findings support a model in which LINE-1-mediated STING activation contributes to ALS pathogenesis, and highlight ORF1p as a candidate for future investigation, both as a therapeutic target and biomarker.

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Poster

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Support: VA Merit grant BX005585 (to SD)
SCORCH grant U01 DA053630
VA Sequencing Collaborations United for Research and Epidemiology (seqCURE), James J. Peters VA Medical Center, Bronx, NY.

Title: Cell-type-specific transcriptomic dysregulation in standard and long-duration sporadic amyotrophic lateral sclerosis

Authors: *J. LI[1], A. KOZLENKOV[2], J. JUNG[2], T. D. STEIN[3], E. A. MUKAMEL[4], S. DRACHEVA[5];
[1]Cognitive Sci., UC San Diego, La Jolla, CA; [2]Dept. of Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Boston VA Med. Ctr., Boston, MA; [4]Cognitive Sci., Univ. of California San Diego, La Jolla, CA; [5]Dept. Psychiat, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that manifests in the progressive loss of motor neurons in the brain and spinal cord, resulting in muscle weakness, paralysis, and ultimately death from respiratory failure. ALS symptoms and severity vary among individuals due to the interplay of genetic predisposition and environmental exposures. Approximately 90% of all ALS cases occur without a family history and are considered sporadic (sALS). Cases of familial disease (fALS) include those associated with the hexanucleotide repeat expansion in the first intron of the gene C9orf72 (C9). ALS is known to have a higher incidence in U.S. military veterans than in the general population and is considered a service-connected condition. In addition, although ALS typically leads to death within 3 to 5 years after initial symptom onset, approximately 10% of patients develop long-duration ALS and live significantly longer (>10 years after symptom onset). However, the cell-type-specific molecular alterations driving these differences are still largely unknown.
We analyzed autopsied motor cortex specimens from 25 sALS cases with standard duration of the disease, 26 long-duration sALS subjects, and 25 control subjects from the Department of Veterans Affairs Biorepository Brain Bank. We performed single-nucleus RNA sequencing (snRNA-seq) with these samples, yielding high-quality transcriptome profiles in 546,748 nuclei. We detected differential expression across the diagnosis groups in the 14 major classes of neurons and glia, and the expression fold-changes were correlated with those reported in our previous study of fALS cases associated with C9. Using latent factor analysis, we discovered multicellular regulatory programs associated with the subtypes of sALS. We identified cryptic exons (CEs) predominantly in excitatory neurons and found fewer occurrences of CEs in long-duration sALS samples, correlated with less severe TDP-43 pathology. In addition, we validated these results with Nanopore long-read RNA sequencing of the same samples.
In summary, our study presents a comprehensive characterization of gene expression alterations in standard and long-duration sALS at single-cell resolution. Our findings provide insights into novel biological pathways relevant to the pathology and prognosis of the disease.

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Poster

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Topic: C.06. Neuromuscular Diseases

Title: Sigma-1 Receptor-Enriched Cisterns is Reduced in Lower Motor Neurons Independent of TDP-43 Pathology in ALS

Authors: *G. YUNISOVA[1], A. MENG, *[2], K. ONG, *[3], J. HUANG[2], T. KRISHNAN[2], A. HERMANN[2], R. SMITH[4], V. KO, **[2], J. M. RAVITS, **[5];
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Abstract: *These authors contributed equally to this work. ** Co-corresponding authors. Sigma-1 receptor (S1R)-enriched subsurface cisterns (SSCs) are specialized endoplasmic reticulum structures at postsynaptic membrane of motor neurons (MNs). SSCs are preferentially localized to neurons targeted by cholinergic synapses, also known as *C-boutons,* which contribute to the maintenance of neuronal viability. Their relevance in amyotrophic lateral sclerosis (ALS) where TDP-43 pathology is the most central mechanism is gaining attention but is unknown. In this study, our aim is to characterize S1R-enriched SSCs and to correlate to TDP-43 pathology. We performed dual immunofluorescence (IF) staining for TDP-43 and S1R on the hypoglossal nucleus in the medulla (n=6), lumbar spinal cord (LSC, n=4) and motor cortex (n=6) from postmortem tissue of sporadic ALS cases and age matched controls (n=4). The number of SSCs was quantified in individual MNs and compared across neurons classified by their TDP-43 phenotype. The TDP-43 phenotype of MNs was classified as normal nuclear, nuclear clearance and/or cytoplasmic mis-localization. We examined upper and lower MNs and various clinical phenotypes. Interestingly, S1R-enriched SSCs were only seen in lower MNs and not seen in upper MNs. In lower MNs, a significant reduction in the number of SSCs per cell was observed both in the medulla ($p<0.001$) and LSC ($p<0.0001$) in ALS. 63 of 195 neurons (32%) in the medulla showed TDP-43 pathology. 35 of 114 neurons (31%) in LSC showed TDP-43 pathology. No cells with TDP-43 pathology were found in control group. The reduction was observed in neurons with TDP-43 pathology in medulla ($p<0.03$) and LSC ($p<0.0003$) in the ALS group, and also observed in neurons with normal TDP-43 phenotype in medulla ($p<0.001$) and LSC ($p<0.03$). Within the ALS group, no significant difference in SSC count per cell was observed between neurons exhibiting TDP-43 pathology and those without. There were no differences in the nervous systems with different clinical phenotypes.We report for the first time fewer S1R-enriched post-synaptic SSCs in lower MNs of ALS patients independent of TDP-43

pathology, suggesting a broader structural vulnerability. These findings suggest important interplay between the cholinergic interneurons and lower MNs in ALS pathogenesis, support the significance of synaptic architecture in ALS biology and complexity of lower MNs.

Disclosures: G. Yunisova: None. **A. Meng:** None. **K. Ong:** None. **J. Huang:** None. **T. Krishnan:** None. **A. Hermann:** None. **R. Smith:** None. **V. Ko:** None. **J.M. Ravits:** None.

Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.17/G8

Topic: C.06. Neuromuscular Diseases

Title: Leveraging ultra-sensitive multiplex Simoa assays validated for blood for enhanced characterization of ALS pathology and differentiation from AD

Authors: D. CARACINO[1], B. COOPER[1], *C. SHIRLEY[1], J. HERRERA[1], K. MALYAVANTHAM[1], B. BERTRAN RECASENS[2], P. ORTIZ-ROMERO[3], M. SUÁREZ CALVET[3], M. RUBIO PEREZ[2];
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Abstract: Objective: Neurodegenerative diseases such as ALS and AD involve complex disruptions in cellular homeostasis, particularly in proteostasis. While tissue studies provide mechanistic insights, fluid biomarkers offer an *in vivo* view of disease biology. Ultrasensitive Simoa immunoassays enable detection of low-abundance neurodegenerative markers in blood and CSF. This study aimed to evaluate the performance of Simoa assays for blood biomarkers in distinguishing ALS from AD cases. **Methods:** Serum and plasma samples from 110 ALS patients and 20 AD controls were analyzed using Simoa single and multiplex assays:NFL, Neurology 4-Plex D (BD-Tau, NfL, GFAP, UCH-L1). Wilcoxon rank sum and Spearman's rank correlation tests were performed for group comparisons. **Results:** ALS patients (median age: 65), AD controls (median age: 75) with similar sex distribution were included in the study. NFL concentrations were markedly higher in ALS across both matrices: plasma NFL median levels were 59 pg/mL in ALS vs 13 pg/mL in AD, and serum median levels were 83 pg/mL vs 20 pg/mL respectively ($p<0.001$). GFAP levels were significantly lower in ALS: plasma GFAP median being 90 pg/mL (ALS) vs 156 pg/mL (AD), serum GFAP 105 pg/mL vs 221 pg/mL ($p<0.001$) respectively. BD-Tau and showed no significant differences ($p>0.05$). All biomarkers showed strong plasma-serum correlations ($R \geq 0.8$, $p<0.001$). **Conclusions:** Simoa-based assays reliably quantified NFL and GFAP in ALS and AD patients. Significantly elevated NFL in ALS reflects neuroaxonal injury,. Strong serum-plasma correlations support flexible matrix use, though optimized thresholds may be needed. Given diagnostic challenges in ALS, these blood-

based biomarkers could offer a minimally invasive, scalable tool for earlier detection and differentiation from other neurodegenerative conditions.

Disclosures: **D. Caracino:** A. Employment/Salary (full or part-time): Quanterix. **B. Cooper:** A. Employment/Salary (full or part-time): Quanterix. **C. Shirley:** A. Employment/Salary (full or part-time): Quanterix. **J. Herrera:** A. Employment/Salary (full or part-time): Quanterix. **K. Malyavantham:** A. Employment/Salary (full or part-time): Quanterix. **B. Bertran Recasens:** None. **P. Ortiz-Romero:** None. **M. Suárez Calvet:** None. **M. Rubio Perez:** None.

Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.18/G9

Topic: C.06. Neuromuscular Diseases

Support: 3/1/2/174/Neuro/2021-NCD-I

Title: Multi-omics integration of nmr-based metabolomics and microbiome profiling reveals gut-brain metabolic alterations in als

Authors: *P. GAUTAM[1], R. YADAV[2], C. SINGH[3], A. PATHAK[1];
[1]Neurol., Inst. of Med. Sciences, Banaras Hindu Univ., Varanasi, India; [2]Dept. of Biochem., [3]Biochem., Inst. of Science, Banaras Hindu Univ., Varanasi, India

Abstract: Title: Multi-Omics Integration of NMR-Based Metabolomics and Microbiome Profiling Reveals Gut-Brain Metabolic Alterations in ALS Author: [1]Priyanka Gautam, [2]Rahul Yadav, [2]Chandan Singh, [1]Abhishek Pathak Affiliation: [1]Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India - 221005 [2]Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India - 221005 Conflict of Interest: No conflict of interest Amyotrophic Lateral Sclerosis (ALS) is a progressive and fatal neurodegenerative disorder marked by motor neuron degeneration, with limited treatment options and a lack of reliable biomarkers for early diagnosis and disease monitoring. Although genetic predisposition plays a role, the majority of ALS cases are sporadic, implicating unidentified environmental and metabolic triggers. Metabolomics, situated at the intersection of genetic and environmental influences, including dietary patterns mediated by gut microbiota offers a powerful tool for elucidating disease mechanisms and identifying clinically relevant biomarkers. In this study, we performed integrative multi-biofluid analyses to investigate metabolic and microbial signatures associated with ALS. Serum metabolite profiling was carried out along with shotgun metagenomic sequencing of stool samples and high-resolution proton nuclear magnetic resonance (^{1}H NMR)-based metabolomics of the same. Subsequently, urine samples were examined to validate whether gut-associated metabolites were systemically represented. Distinct metabolomic alterations were observed in ALS compared to healthy

controls, including dysregulated levels of pyruvate, histidine, glutamine, isoleucine, leucine, creatinine, choline, imidazole, and arginine, alongside short-chain fatty acids (SCFAs), branched-chain amino acids (BCAAs), carbohydrates, and aromatic compounds. O-PLS-DA analysis confirmed a clear separation between ALS and control samples, reflecting disease-specific metabolic signatures. Shotgun metagenomics identified significant shifts in gut microbial composition, with higher abundance of *Bifidobacterium, Lactobacillus*, and *Enterococcus* in ALS, while *Lactiplantibacillus* and *Klebsiella* were enriched in controls. Integrated multi-omic analysis revealed strong correlations between microbial dysbiosis and host metabolic perturbations, with similar metabolite patterns mirrored in urine, suggesting systemic involvement. These findings highlight the critical interplay between gut microbiota and host metabolism in ALS, providing a foundation for developing non-invasive biomarkers.

Disclosures: P. Gautam: None. **R. Yadav:** None. **C. Singh:** None. **A. Pathak:** None.

Poster

PSTR440: ALS and Motor Neuron Disease: Human Studies and Preclinical Therapy Development

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.19/G10

Topic: C.06. Neuromuscular Diseases

Title: Elucidating the role of Bone Morphogenetic Protein Signaling in Hereditary Spastic Paraplegia Neurons type 3A

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Abstract: Hereditary spastic paraplegia (HSP) is a rare neurological disorder characterized by the degeneration of cortical motor neuron axons. Spastic paraplegia type 3A (SPG3A) is an autosomal dominant form of HSP caused by mutations in the *ATL1* gene that codes for atlastin 1 protein. Studies showed that atlastin 1 knockdown led to increased bone morphogenetic protein (BMP) signaling and axonal abnormalities. Moreover, BMP signaling blocks ESC differentiation, further impairing neurogenesis and contributing to the progression of SPG3A. Herein, we have used SPG3A patient induced pluripotent stem cell (iPSC)-derived neurons to investigate how the BMP signaling is altered in SPG3A and whether targeting BMP signaling can mitigate the degeneration of SPG3A neurons. Patient-specific stem cells were differentiated into cortical projection neurons using lab established protocol, which led to efficient generation of CTIP2-positive neurons. Increased expression of BMP genes and proteins was observed in SPG3A neurons, hypothesized to result from disruptions in BMP receptor trafficking. Given atlastin-1's role in endoplasmic reticulum morphology, our findings suggest that ATL1 mutations disrupt ER structure, potentially impacting endosome function and contributing to altered BMP

receptor trafficking**.** Finally, to examine the protective effects of targeting the BMP signaling, control and SPG3A neurons were treated with a BMP inhibitor for 1-week. The treatment of BMP inhibitor significantly mitigated the increased apoptosis and pNFH levels in SPG3A neurons. Taken together, our data suggests that BMP signaling is dysregulated in SPG3A patient-derived neurons and that targeting BMP signaling serves as a potential approach to mitigate the pathological changes in SPG3A. Further studies will explore how dysregulated BMP signaling contributes to disease phenotypes in SPG3A patient-derived neurons.

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Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.01/G11

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

Support: NIH Grant NS132533
AFOSR Grant FA9550-18-1-0051
DURIP grant 13107771
DURIP grant FA9550-23-1-0627

Title: Excitotoxic stress converts endoplasmic reticulum-associated F-actin into stabilized filaments

Authors: *B. CALABRESE, M. A. GRUBER, S. PARKS, B. QUAN, Y.-W. SHERPA, C. SCHIAVON, U. MANOR, S. L. HALPAIN;
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Abstract: Cellular pro-survival cascades are activated in response to acute neuronal stress, yet the coordination among such cascades is poorly understood. Interference with these natural cellular responses is detrimental to neuronal survival during ischemia or other acute stressors. In the somatodendritic compartment, pro-survival responses include changes in the morphology of the endoplasmic reticulum (ER) and induction of the unfolded protein response, as well as a rapid reorganization of actin filaments that we term “actinification” (Calabrese et al., 2022). Actinification is characterized by the rapid accumulation of filamentous actin (F-actin) throughout the soma and dendritic arbor, with concomitant depolymerization of F-actin in dendritic spines. Actinification is mediated by inverted formin 2, which associates with the ER membrane via a specific splice variant. Here, using an ER-targeted actin nanobody as a probe for ER-associated F-actin (“ER-actin”), we investigated the potential coordination of ER and cytoskeletal responses to stress. Under basal conditions, ER-actin is present in a gradient, i.e. concentrated in soma and proximal dendrites, but nearly undetectable in the distal dendritic arbor. This contrasts with the ER membrane itself, which extends throughout the entire dendritic

arbor. During actinification, filaments accumulate in the dendrites out to all the dendrite tips. Surprisingly, ER-actin remains barely detectable in distal dendrites. Moreover, although at rest the ER-actin is dynamic and readily disassembles during monomer sequestration by latrunculinA (LatA), during actinification ER-actin becomes highly resistant to LatA. This stabilization was not observed when ER stress was triggered in a manner that does not induce actinification. Together, these data suggest that actinification converts ER-adjacent filaments into a stabilized state.

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Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.02/G12

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

Support: JST SPRING PMJSP2126
the Study of the Health Effects of Heavy Metals Organized by the Ministry of the Environment, Japan

Title: Characterization of novel brain lesions underlying methylmercury-induced neuropsychiatric symptoms

Authors: *R. MIKI[1], Y. IIJIMA[1], H. ITO[1], R. NOMURA[1], T. IWAWAKI[2], M. FUJIMURA[3], T. UEHARA[1];
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Abstract: Minamata disease is a neurodegenerative disorder caused by severe methylmercury (MeHg) poisoning, which primarily affects neurons in the cerebellum and cerebral cortex. These lesions are associated with symptoms such as ataxia and sensory loss. In addition to motor and sensory deficits, clinical observations of Minamata disease include psychiatric symptoms such as personality changes and depression. However, the underlying pathophysiological mechanisms for these psychiatric symptoms remain poorly understood. In this study, to elucidate the pathophysiological mechanisms of psychiatric symptoms by MeHg poisoning, we examined MeHg-induced neuronal damage in brain regions associated with affective and cognitive functions in a mouse model. C57BL/6NJcl mice (n=6) were given drinking water containing MeHg (final concentration 30 ppm) ad libitum for 8 weeks to establish a model of MeHg poisoning. Using TUNEL staining to specifically detect apoptotic cells, we screened for damaged areas in the limbic system and diencephalon, which are involved in emotion and

cognitive processing. In the newly identified loci of damage, we assessed neuronal loss by immunostaining for NeuN, a neuron-specific marker. We then quantified GABAergic neurons by immunostaining for GAD65/67, and glutamatergic presynaptic terminals by immunostaining for VGLUT2. MeHg exposure led to an increase in TUNEL-positive cells and a decrease in NeuN-positive neurons in five brain regions implicated in psychiatric functions: the anterior cingulate cortex (ACC), nucleus accumbens (NAc), central nucleus of the amygdala (CeA), basolateral amygdala (BLA), and mediodorsal thalamic nucleus (MD) - key areas for emotion, motivation, and cognition. In these same regions, we observed a marked reduction in GAD65/67-positive cells. Although VGLUT2-positive terminals were also reduced, the extent of the reduction was less pronounced than that of GAD65/67-positive cells. These findings suggest that preferential disruption of GABAergic signaling relative to glutamatergic transmission in these brain regions may underlie the psychiatric manifestations of Minamata disease. We are currently analyzing how MeHg exposure affects behavioral abnormalities, such as anxiety-like behaviors, using this model.

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Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.04/G14

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

Support: Support from Alabama College of Osteopathic Medicine (ACOM) Dothan, AL 36303

Title: Cadmium chloride-mediated histopathological changes correlate with downregulation in the expression of nuclear factor-erythroid 2-related factor-2 (Nrf2) and vascular endothelial barrier antigen in the developing rat hippocampal formation: An immunofluorescent investigation.

Authors: *M. O. IBIWOYE;
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Abstract: Background Cadmium is a heavy metal found in association with zinc, lead, and copper ores as natural components of the earth's crust and its harmful effect is well known. The adverse health impact of cadmium is well known and its association with multi-organ damage throughout the body has been well documented. The metal has been detected in at least 1,014 of the 1,669 most hazardous sites identified and designated as National Priorities List (NPL) by the Environmental Protection Agency (EPA), indicating the public health significance of cadmium as an environmental pollutant (ASTDR, 2017; Environ. Int, 2018, 113: 259-268; Hum. Expt. Toxicol, 2018, 37(3): 321-328). Cadmium pollutes the environment via diverse anthropogenic

activities including rechargeable batteries production, smelting, electroplating, phosphate fertilizers production, and high-volume waste incineration. Cadmium enters the air, soil, and water through soil erosion, wildfires, and volcanic eruptions. Studies have established that maternal exposure during pregnancy results in children manifesting growth retardation, memory disorders and other cognitive disabilities. The mechanism of cadmium neurotoxicity is not completely understood, but the metal appears to exert its toxicity via reactive oxidants stress-induced morphological and functional perturbation of blood-brain barrier (BBB) structures. A rat BBB-specific marker has been previously identified and characterized by Sternberger and Sternberger. Nrf2 has been postulated to play a key role in the cellular antioxidant defense mechanisms against adverse consequences of oxidant exposure such as cadmium, and loss of Nrf-2 is known to contribute to redox imbalance and poor outcomes, particularly in cadmium-induced kidney injury. **Methods** We applied a standard two-step immunofluorescent protocol to detect and characterize the expression of Nrf2 and EBA within the hippocampus in paraformaldehyde-fixed coronal brain sections of normal and cadmium-exposed six-week-old albino rats (n=10). **Results** We detected a reduced expression of Nrf2 and EBA in all regions of the hippocampal formation in Cd-exposed animals compared to normal controls. Sections from experimental animals exhibited neuronal loss, degeneration, and disorganization in all *Cornu Ammonis* regions of the hippocampus especially in segments CA3 and CA4. **Conclusion** This preliminary investigation supports the hypothesis that cadmium exposure-mediated Nrf-2 downregulation may contribute to the cadmium-induced neurotoxicity observed in the developing rodent model system.

Disclosures: M.O. Ibiwoye: None.

Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.05/G15

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

Support: Astellas Foundation for Research on Metabolic Disorders
JSPS KAKENHI, 24K09795, 24KK0181, 24H00678

Title: Nitric oxide induces neural cell death related transcriptional changes in human iPSC derived excitatory neurons

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Dept. of Medicinal Pharmacology, Grad. Sch. of Medicine, Dentistry, and Pharmaceut. Sci., Okayama Univ., Okayama, Japan

Abstract: Nitric oxide (NO) participates in various biological processes, including cellular proliferation, apoptosis, and neurotransmission, primarily through protein S-nitrosylation, which is a reversible post-translational modification like protein phosphorylation. Excessive NO

production has been implicated in the pathogenesis of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease via aberrant S-nitrosylation. While numerous studies have explored NO-induced cell death mechanisms in mouse primary neurons or human neuroblastoma cell lines, investigations using human iPSC-derived neuronal cells remain limited. In this study, we aimed to elucidate transcriptional pathways activated by NO in human neurons. We employed human iPSCs (Elixirgen Scientific) and differentiated them into excitatory neurons. To enable transcriptome analysis from limited RNA quantities, we utilized Ramda-seq-based amplification and library preparation. First, we characterized transcriptional differences between undifferentiated iPSCs and iPSC-derived excitatory neurons. Principal component analysis revealed a clear separation between the two cell types. Differential gene expression analysis (fold change ≥ 2.0; adjusted $p < 0.05$) identified 2,371 significantly upregulated and 2,305 downregulated genes in differentiated neurons. Gene ontology (GO) analysis of upregulated genes revealed enrichment in pathways such as axon guidance and glutamatergic synapse formation, confirming successful neuronal differentiation. To investigate the effects of NO, we treated the iPSC-derived excitatory neurons with an NO donor for 48 hours and extracted total RNA. Transcriptome analysis identified 225 upregulated and 193 downregulated genes in response to NO treatment. GO analysis of upregulated genes indicated enrichment in processes including the positive regulation of the extrinsic apoptotic signaling pathway. In conclusion, our data suggested that NO treatment induces apoptosis-related transcriptional responses in human iPSC-derived excitatory neurons. Ongoing analyses aim to identify key mediators and molecular targets involved in NO-induced neuronal cell death.

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Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.06/G16

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

Support: This work is supported by MUR, PRIN-PNRR2022 CODE NUMBER: P2022AA47Y- CUP D53D23021910001

Title: Polylactic acid (PLA) bioplastic nanoparticles induce neurotoxic effects by negatively affecting NGF-induced PC12 cell differentiation and causing C6 cell activation

Authors: *A. SANTORO[1], M. MARINO[1], R. D'AURIA[1], M. LOMBARDI[1], M. LULLO[1], E. P. LAMPARELLI[1], G. DELLA PORTA[1], R. MECCARIELLO[2], A. VIGGIANO[1];
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Abstract: Plastic contamination (PLASTAMINATION) is the main human-caused change worldwide. In recent years, the need has increased to switch from fossil-derived plastics to bio-

based and biodegradable alternatives such as polylactic acid (PLA). As it degrades, this polymer can release micro (MPs, 1-1000 μm) and nano (NPs, 1-1000 nm) -plastics faster than conventional counterparts raising concerns about its risk for human health. Given the ability of conventional MPs/NPs to induce multisystemic alterations and cause oxidative stress, inflammation and neuronal disruption, we aimed to investigate PLA NPs-induced toxicity in the central nervous system (CNS) by using two different in vitro models: the rat adrenal pheochromocytoma PC12 cells and the rat C6 glioma cell line. Both cell types were treated with PLA NPs (170 ± 64 nm) loaded with rhodamine at concentrations of 100 and 300 μg/mL from 24 to 72 hs. Cell uptake, cell cycle distribution during nerve growth factor (NGF)-induced PC12 cell differentiation, and the potential mechanism of action have been explored. Flow cytometric and immunofluorescence analyses revealed that both PC12 and C6 cells efficiently internalize PLA NPs, localizing around the nucleus and within the cytoplasm. The uptake reached 100% at highest concentration starting from 24 hs of treatment. Once internalized, PLA NPs induce an S-phase cell cycle increase in differentiating PC12 cells and after 7-days exposure, PLA NPs significantly reduce the number and the length of neurites. Expression analysis of the extracellular-signal-regulated kinases (ERK) and protein kinase B (pAKT) indicate a reduction in proteins' activation corroborating that PC12 cell differentiation is hindered by PLA NPs. Moreover, in PC12 cells, an increase in both the pro-inflammatory cytokine CINC-1 and Reactive Oxygen Species (ROS) production have been observed. Similarly, in C6 cells PLA NPs treatment significantly enhances the expression of pAKT, glial fibrillary acidic protein (GFAP) and ROS production thus suggesting an activation status. Untargeted metabolomic analysis in C6 cells supported these results showing a significant alteration in redox homeostasis, and in dicarboxylic acid metabolism and nitrogen metabolism as well. Overall, our findings show that PLA degradation products can effectively cross cell membranes with potential toxic effects on CNS functions.

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Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.07/H1

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

Support: NSF BRC-BIO Grant 2217826
OWU Theory-to-Practice Grant
OWU Summer Science Research Program

Title: Novel resilience to lead toxicity in urban wall lizards (Podarcis muralis)

Authors: *E. G. FOSTER[1], E. R. HOLT[1], M. D. HORN[1], C. A. VADNIE[2], A. R. GUNDERSON[3], E. J. GANGLOFF[1];
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Abstract: The heavy metal lead (Pb) poses a serious threat to human and animal health, with effects including impairments in neurodevelopment. Lead pollution affects many organisms living in urban environments, such as the introduced common wall lizards (*Podarcis muralis*) abundant in Cincinnati, Ohio, USA. We characterized blood lead levels in these lizards (N = 71) and revealed that many (67.6%) exhibited blood lead levels above the threshold considered "safe" for humans, with a select few (9.86%) tolerating levels that exceeded the acute lethal limit for humans. Behavioral tests of running endurance and balance capabilities in male lizards (N = 43; N = 41) also lent support to the hypothesis that lizards may have a unique resilience to lead toxicity; blood lead level was not significantly associated with impaired performance on ecologically relevant tasks. Lizards possess a widespread capacity for adult neurogenesis that has the potential to reverse neurotoxin-induced damage (Austin et al., 2023, *Developmental Dynamics*). We hypothesized that following consumption of lead, wall lizards would exhibit higher rates of neurogenesis in the medial cortex—the homolog of the mammalian hippocampus—in order to mitigate lead-induced neuronal damage. To test this, we developed a lead administration technique for use on lizards in captivity and found that wall lizards can tolerate blood lead levels ten times greater than those observed in the field without exhibiting any symptoms of lead poisoning. Lizards (N = 36) were divided into nine treatment groups based on lead dosage (distilled water, 10 mg Pb/kg body weight, 50 mg Pb/kg body weight) and time of sacrifice following the dosing period (5 days, 15 days, 30 days). In the future, we plan to quantify neuronal proliferation and cell death in these lizards using immunohistochemistry with BrdU and TUNEL stains and fluorescent microscopy. We expect to find associations between blood lead level and neuronal death and proliferation that support the role of adult neurogenesis in repairing lead-induced neuronal damage over time. These unique investigations in urban wall lizards will inform studies of neurodegeneration and regenerative mechanisms across species.

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Poster

PSTR441: Neuroprotection and Neurotoxicity

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.08/H2

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

Support: NIH Grant 5R25GM060507

Title: Docosahexaenoic acid inhibition of palmitic acid-induced lipotoxicity involves regulation of autophagy and endoplasmic reticulum dynamics

Authors: *F. ZAMORA[1], V. DINH[2], J.-W. LIU[3], M. DE LEON[4];
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Abstract: Elevated saturated fatty acids cause lipotoxicity (LTx), which is a feature of metabolic disorders such as diabetes or obesity that are often linked with neuropathic pain (NP). We previously demonstrated that palmitic acid-induced LTx (PA-LTx) in Schwann cells (SCs) involves ER stress, calcium [Ca^{2+}] depletion, mitochondrial membrane depolarization, and apoptotic cell death. However, co-treatment of SCs with [Ca^{2+}] chelator BAPTA-AM or polyunsaturated fatty acid docosahexaenoic acid (DHA), inhibits the deleterious effects of PA-LTx. *In vivo*, a DHA-enriched diet promotes an anti-inflammatory metabolomic profile and significantly attenuates NP. Given that autophagy dysfunction in neurons and glial cells is implicated in NP pathology, the present study aims to examine how PA-LTx and DHA regulate autophagic processes in immortalized SCs (ISCs). PA-LTx was induced by exposing ISC cultures to 300 μM PA: 150 μM bovine serum albumin for up to 24 or 48HR. Co-treatment with 50 μM DHA was used to inhibit LTx, and Chloroquine (CQ) served as positive control autophagic flux inhibition. To monitor autophagic flux, we used Western blot to measure LC3-II and p62/SQSTM1 protein levels, and confocal microscopy to assess autophagosome-autolysosome dynamics of RFP-GFP-LC3-expressing cells. ER stress genes, CHOP and ATF4, were measured using RT-qPCR, and cell viability was assessed by WST-1 assay. Lastly, ER [Ca^{2+}] concentrations were measured using a Fluo-4 NW Calcium assay. As previously reported, PA exposure caused significant loss of ISC viability, whereas co-treatment with DHA fully rescued cells from PA-LTx. Although CQ alone did not alter cell viability, its addition to PA exacerbated cell death. Also, CQ diminished DHA's sustained protection against PA-LTx at 48HR, suggesting proper autophagic flux is needed for cell survival. At 24HR, PA significantly increased LC3-II and p62 levels, as well as the GFP/RFP ratio compared to control, consistent with impaired autophagic flux. In contrast, DHA co-treatment normalized these markers, suggesting restoration of autophagic clearance. PA also significantly upregulated CHOP and ATF4 expression, and triggered early ER [Ca^{2+}] depletion, while DHA co-treatment inhibited this ER stress response. Overall, these findings suggest that prolonged PA exposure causes ER stress and impairs autophagic flux in ISCs, contributing to cell death. However, DHA's protection involves restoring proper autophagic clearance, likely through reducing ER stress and calcium dysregulation. These findings align with DHA's ability to promote glial cell function and reduce NP, with autophagy emerging as key therapeutic target.

Disclosures: F. Zamora: None. **V. Dinh:** None. **J. Liu:** None. **M. De Leon:** None.

Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.09/Web Only

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

Title: Planaria Dugesia japonica as a model organism for measuring the toxicity of environmentally relevant concentrations of Per- and poly-fluoroalkyl substances (PFAS)

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Abstract: Per- and poly-fluoroalkyl substances (PFAS) are ubiquitous in the environment and have significant detrimental effects on physiology and behavior. Planaria have recently increased in popularity as a model for toxicology and regeneration research. These organisms possess a primitive centralized nervous system that is thought to be more similar to the vertebrate brain than to other invertebrate brains in terms of structure and function and possesses the same neuronal subpopulations and neurotransmitters as the mammalian brain. While other studies have investigated the behavioral effects of PFAS and PFOA on planaria, there is still limited research on these effects at environmentally relevant concentrations. This study investigates the effects of PFOA (perfluorooctane sulfonate) on acute toxicity, behavioral activity, and regeneration in Dugesia japonica. Results suggest that planaria are an effective toxicology model for measuring the effects of small, environmentally relevant concentrations of PFOA and potentially other environmental contaminants.

Disclosures: C. Rodeo: None. **J.A. Schroeder:** None.

Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.10/H3

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

Title: The novel antioxidant iron chaperone ATH434 suppresses heme-induced oxidative stress in glutamatergic HT22 neurons

Authors: *D. K. BAILEY[1], R. NIHLAWI[1], M. BRADBURY[2], D. KOSMAN[1];
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Abstract: ATH434, a small molecule therapeutic with *moderate* ferric and ferrous iron affinity, has recently been shown to possess endogenous antioxidant activity. In a menadione-induced oxidative stress model in HT22 neurons with mitochondrial superoxide production, ATH434 rescued deficits in mitochondrial membrane potential while deferiprone (DFP), a *strong* ferric iron chelator did not. ATH434 protected cells from menadione-induced lipid peroxidation similarly to the antioxidants α-tocopherol and Trolox. We have extended these findings to assess the neuroprotective effects of ATH434 in a model of heme-induced oxidative injury.
Heme is essential for oxygen transport and serves as a protein cofactor. However, in cases of intracranial hemorrhage, excess heme in the brain is neurotoxic, leading to inflammation and cell death. Injection of the oxidized form, hemin, is an intracranial hemorrhage model. In this study,

we used hemin to investigate the mechanisms of heme-induced oxidative stress in the glutamatergic HT22 neuronal cell model. We assessed the extent of hemin injury in our neuron model at two dose levels (2 and 10 μM). Hemin induced a time- and dose-dependent increase in ferrous iron released into cells as detected by FerroOrange (FO). Hemin also induced a time- and dose-dependent increase in lipid peroxidation measured by BODIPY. Pretreatment with HOi, an inhibitor of the heme degrading enzyme HMOX1, decreased the FO signal in response to hemin, confirming that breakdown of hemin is responsible for the increased intracellular iron.
We next investigated whether hemin-induced lipid peroxidation could be rescued by ATH434, and compared the results to those of DFP, α-tocopherol and Trolox. Cells were pre-treated for 1 h with each compound, then treated with hemin for an additional 6 h in the continued presence or absence of compound. Pretreatment with DFP did not rescue the increase in BODIPY signal from either dose of hemin. However, pretreatment with ATH434 partially prevented the lipid peroxidation from both hemin treatments as early as 2 h, similar to results with α-tocopherol and Trolox. Similar to our previous work, ATH434 alone increased the FO signal, reflecting an increase in the chaperoned labile iron pool. ATH434 in combination with hemin at 2 h increased the FO signal. Hemin-induced saturation of the labile iron pool was evident at 6 h. The dose-dependent susceptibility of neurons to hemin-induced lipid peroxidation support this as a cellular model for damage induced by intracranial hemorrhage or microbleeds. ATH434's novel iron chaperone and antioxidant activities show potential for neuroprotective therapeutic activity after neurovascular injury.

Disclosures: D.K. Bailey: F. Consulting Fees (e.g., advisory boards); Alterity Therapeutics. **R. Nihlawi:** None. **M. Bradbury:** A. Employment/Salary (full or part-time): Alterity Therapeutics. **D. Kosman:** 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.; Alterity Therapeutics.

Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.11/H4

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

Support: CONACyT for scholarship (No. 842645)
Proyectos VIEP 2025 ID: 00548

Title: Sodium phenylbutyrate mitigates oxidative stress, neuroinflammation, and hippocampal damage in a rat model of chronic hyperammonemia

Authors: *D. JUÁREZ SERRANO[1], J. MORAN PERALES[2], A. HANDAL[2], M. MUNOZ ARENAS[3], S. TREVINO MORA[4], I. CESAR ARTEAGA[3], O. VERA LÓPEZ[3], G. FLORES[4], A. DIAZ[4];
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Abstract: Hyperammonemia, commonly resulting from hepatic dysfunction, leads to neurotoxic effects mediated by elevated ammonia (NH_3) levels in the brain. These effects include oxidative stress, neuroinflammation, and altered cellular morphology in vulnerable regions such as the hippocampus. In this study, we evaluated the therapeutic potential of sodium phenylbutyrate (NaPB), an ammonia-scavenging agent approved for urea cycle disorders, in a rat model of chronic hyperammonemia induced by carbon tetrachloride (CCl_4). Twenty-four male Wistar rats, aged three months, were obtained from the Claude Bernard Vivarium at BUAP. They were randomly divided into 4 experimental groups. Group 1 (Control), Group 2 (CCl_4), Group 3 (NaPB) and Group 4 (NaPB + CCl_4). CCl_4 was prepared in a 1:1 ratio with corn oil, its administration was carried out for 10 weeks, intraperitoneally (i.p.) in the group (CCl_4). NaPB (20 mg/kg) was dissolved in 0.9% NaCl and administered i.p. for 10 weeks after CCl_4 induction in the (CCl_4 + NaPB) group. Biochemical assays and histological analyses were conducted to assess hippocampal redox balance, inflammatory markers, and tissue integrity. Results showed that CCl_4 administration significantly elevated hippocampal lipid peroxidation products, including malondialdehyde (MDA) and 4-hidroxi-2-nonenal (4-HNE), while reducing antioxidant enzyme activities (superoxide dismutase and catalase). NaPB treatment attenuated these effects, restoring antioxidant capacity and lowering oxidative biomarkers. Additionally, NaPB reduced the hippocampal expression of proinflammatory cytokines (IL-1β, IL-6, IL-17 and TNF-α) and improved levels of the anti-inflammatory cytokine (IL-10, IL-4, IL-1ra y TGF-β). Histological examination using hematoxylin and eosin staining revealed that NaPB preserved neuronal density and cytoarchitecture in hippocampal regions (CA1, CA3, and dentate gyrus), which were otherwise disrupted by hyperammonemia. Additionally, immunofluorescence analysis targeting GFAP demonstrated reduced astrocyte activation in NaPB-treated animals, indicating attenuated glial reactivity. NaPB not only clears NH_3 but also modulates oxidative stress and inflammation, helping preserve neuronal and glial integrity.

Disclosures: D. Juárez Serrano: None. **J. Moran Perales:** None. **A. Handal:** None. **M. Munoz Arenas:** None. **S. Trevino Mora:** None. **I. Cesar Arteaga:** None. **O. Vera López:** None. **G. Flores:** None. **A. Diaz:** None.

Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.12/H5

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

Title: Cytotoxic effect of Scutellaria baicalensis in C6 cells and neuroprotective effect of Scutellaria baicalensis against hydrogen peroxide-induced toxicity in NE-4C cells

Authors: S. NG, W. NGAI, T. YIP, C. WONG, H. TONG, R. SIN, *K. SUEN;
Sci., PLK Laws Fndn. Col., Hong Kong, China

Abstract: *Scutellaria baicalensis*, a traditional Chinese medicinal herb, is known for its flavonoid constituents, such as baicalein, which exhibit antioxidant and antiproliferative properties. This study investigates the cytotoxic and neuroprotective effects of *Scutellaria baicalensis* aqueous extract on C6 glioma and NE-4C neural stem cell lines under oxidative stress, a key feature of neurodegenerative diseases. C6 cells were treated with single dosage of *Scutellaria baicalensis* aqueous extract (0, 0.1, 1 and 10, μg/mL) for 24 hours while NE-4C cells were first treated with *Scutellaria baicalensis* extract (0, 0.1, 1 and 10, μg/mL) followed by hydrogen peroxide (H_2O_2) to induce oxidative stress. Cytotoxicity was assessed using the lactate dehydrogenase (LDH) assay. Single dosage of *Scutellaria baicalensis* aqueous extract induced moderate cytotoxicity in C6 cells, while showing minimal cytotoxicity in NE-4C cells, indicating low toxicity to neural stem cells, implying that *Scutellaria baicalensis* has potential anticancer effect. In combination treatments (i.e., pre-treatment of *Scutellaria baicalensis* aqueous extract for 24 hours followed by hydrogen peroxide), the extract reduced cytotoxicity induced by hydrogen peroxide in NE-4C cells, suggesting neuroprotection via antioxidant mechanisms. These findings highlight *Scutellaria baicalensis*'s potential for selective cytotoxicity against glioma cells and neuroprotection in neural stem cells, with implications for brain cancer and neurodegenerative disease therapies.

Disclosures: S. Ng: None. **W. Ngai:** None. **T. Yip:** None. **C. Wong:** None. **H. Tong:** None. **R. Sin:** None. **K. Suen:** None.

Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.13/H6

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

Title: Experimental and computational investigation of bromelain's neuroprotective mechanisms in a mouse model of MSG-induced neurotoxicity

Authors: *N. A. OMEIZA[1,2], J. CHIMEZIE[3], O. M. OGUNYEMI[4];
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Abstract: Monosodium glutamate (MSG), a widely consumed food additive, poses a growing public health concern due to its role in glutamate receptor-mediated excitotoxicity, which contributes to neurochemical imbalances and behavioral deficits. While bromelain, a proteolytic enzyme derived from *Ananas comosus* is known for its neuroprotective and anti-inflammatory properties, its activity against MSG-induced neurotoxicity remains largely unexplored. Herein, we combined behavioral, biochemical, and computational approaches to evaluate the

neuroprotective potential of bromelain in a mouse model of MSG-induced excitotoxicity. Bromelain treatment significantly improved locomotor activity, spatial memory performance, and depressive-like behaviors. Biochemically, bromelain restored antioxidant defense by increasing glutathione, catalase, and superoxide dismutase levels, while reducing malondialdehyde, nitrite, and pro-inflammatory cytokines (IL-6, TNF-α). Also, it exhibited notable anti-acetylcholinesterase and monoamine oxidase inhibitory activity, alongside upregulation of glutamate decarboxylase (GAD). Complementing the experimental findings, molecular docking simulations, which integrated AlphaFold3 protein structure modeling, revealed important molecular interactions of bromelain with key neurotransmitter-regulating enzymes, including acetylcholinesterase (AChE), monoamine oxidase (MAO), and GAD. These interactions suggest bromelain may attenuate excitotoxic and oxidative pathways at the molecular level. Altogether, our findings highlight bromelain's promising neuroprotective role against MSG-induced neurotoxicity via antioxidative, anti-inflammatory, and enzyme-targeted mechanisms. These results support its potential as a nutraceutical intervention for glutamate-mediated neurodegenerative disorders.

Disclosures: N.A. Omeiza: None. **J. Chimezie:** None. **O.M. Ogunyemi:** None.

Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.14/H7

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

Support: NIH-NINDS CounterACT program (U01 NS117284)

Title: The Brain's SOS, A Systems Approach to Neuroinflammation, Seizures, and Recovery post-soman Exposure

Authors: *N. MASSEY[1], S. SUNDARA VASANTHI[1], C. MEYER[1], N. RAO[1], C. WANG[2], S. S. KANNURPATTI[3], T. THIPPESWAMY[1];
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Abstract: Nerve agent exposure initiates a cascade of neurotoxic events, leading to persistent seizures, oxidative stress, neuroinflammation, and structural brain damage, culminating in long-term neurological deficits. In this study, we employed a systems approach to quantify the brain's distress signals ("SOS triad") following soman exposure and assess the efficacy of saracatinib, a Src kinase inhibitor, as a disease-modifier. Soman-exposed animals exhibited sustained seizure activity, oxidative stress, and neuroinflammation, resulting in structural and functional impairments in the amygdala, hippocampus, cortex, and thalamus. Functional MRI (fMRI) revealed significant reductions in connectivity in these regions, with histological analyses confirming increased microgliosis, astrogliosis, and inhibitory neuron loss. Saracatinib treatment

modulated seizure patterns, improved hippocampal functional connectivity, reduced oxidative stress markers, and decreased inflammatory responses. Structural MRI and histological assessments indicated neurodegeneration and amygdalar glial scarring in soman-treated animals. Behavioral deficits, including impaired novel object recognition, motor dysfunction, and altered fear extinction responses, correlated with fMRI changes and neuroinflammatory markers. Correlation analyses demonstrated that oxidative stress negatively impacted functional connectivity, while seizure activity correlated with functional damage. These findings highlight the progressive nature of soman-induced neurotoxicity and underscore the potential of targeting the SOS triad for therapeutic intervention. Saracatinib effectively disrupted the injury cascade, promoting recovery and preserving neural function. This study provides critical insights into the neurobiological mechanisms of soman-induced brain injury and suggests novel opportunities for neuroprotective strategies to mitigate long-term neurological sequelae.

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Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.15/H8

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

Title: Exploring Fucoxanthin's Role in Mitochondrial Protection during Excitotoxicity: Insights into F_1F_o ATP Synthase Regulation

Authors: *K. FERDOUS[1], K. WON[2], K. RAO[3], R. BLOCH[3], K. CROWE-WHITE[2], A. ELLIS[3], H.-A. PARK[4];
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Abstract: Excitotoxicity causes mitochondria-mediated neuronal death. Central to this process is opening of the mitochondrial permeability transition pore (mPTP), a non-selective channel in the inner mitochondrial membrane. The F_1F_o ATP synthase, a central enzyme complex that produces ATP, has previously been shown to form mPTP. During excitotoxicity, F_1F_o ATP synthase triggers the prolonged opening of the mPTP and impairs cellular energy metabolism, leading to neuronal death. Therefore, developing approaches to inhibit F_1F_o ATP synthase-mediated mPTP opening is a potential therapeutic strategy to prevent neuronal death. Fucoxanthin, a marine carotenoid in brown seaweed, has demonstrated neuroprotective properties in *in vitro* and *in vivo* models. We hypothesized that fucoxanthin exerts its mitochondrial protection during excitotoxicity by regulating F_1F_o ATP synthase. Rat primary hippocampal neurons were treated with fucoxanthin (100 nM), glutamate (20 μM), or their combination. After incubation, levels of F_1F_o ATP synthase subunits were quantified, and their localization was determined by immunoblotting and immunocytochemistry, respectively. The opening of the mPTP was assessed

by the calein-Co quenching technique. Mitochondrial membrane potential and cell death were assessed using tetramethylrhodamine methyl ester (TMRM) and propidium iodide (PI) probes, respectively. Fucoxanthin treatment prevented the decrease of β-subunit protein and the dissociation of the β and c-subunits of the F_1F_o ATP synthase during excitotoxicity. Additionally, treatment with fucoxanthin prevented glutamate-induced mPTP opening, consequent loss of mitochondrial membrane potential, and cell death. The results suggest that fucoxanthin has a capacity to regulate mPTP-mediated neuronal death during excitotoxicity. Further research is essential to clarify the mechanisms underlying fucoxanthin's mitochondrial uptake and how it modulates ATP synthase subunits to better understand its neuroprotective properties.

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Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.16/H9

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

Title: Differential Neuroprotection by Cannabinoids in Hippocampal verses Cortical Cultured Neurons

Authors: *L. K. FRIEDMAN[1,2], T. GREENBERG[1], M. P. SHAKARJIAN[1], R. J. ZEMAN[1,2]; [1]New York Med. Col., Valhalla, NY; [2]NeuroInfusions LLC, Valley Stream, NY

Abstract: Previously we reported that cannabidiol (CBD) with low concentrations of tetrahydrocanabinol (THC) protected the hippocampus from traumatic brain injury (TBI) which assisted in the recovery of vestibulomotor and cognitive functions. More recently, an optimal ratio of CBD to THC appeared critical as $CBD_{10:1}$ and $THC_{20:1}$ gave the most protection against injury whereas $THC_{100:1}$ gave the least. To determine whether the ratio of CBD:THC is critical for protection against glutamate pathogenicity associated with TBI and epilepsy, dissociated hippocampal and sister cortical cultures were pre-exposed to a single “hit” of glutamate for 15 min at 37° C followed by washout and post-treatment with medicinally available $CBD_{300:1}$ (10 μM) or $THC_{20:1}$ (1 μM) for 48 h. In cortical cultures, NeuN immunohistochemistry showed only 5.7 ± 1.8 % of neurons survived after the glutamate “hit” compared to 87.18 ± 8.8 % with $CBD_{300:1}$ post-treatment. High magnification revealed that the surviving population had healthy densities as control populations, and the number of apoptotic cells was reduced by approximately 80%. In contrast, neuroprotection of cortical neurons by $THC_{20:1}$ was not observed; the number of apoptotic cells exceeded glutamate only treated cultures by 33.33 ± 2.4%. In sister hippocampal cultures, both cannabinoids afforded neuroprotection, however, the number of survivors were significantly higher with the $CBD_{300:1}$ dominant extract (77.04 ± 6.4 % vs 48.46 ± 5.3% of untreated sister cultures, $p < 0.001$). While the density of hippocampal neurons was reduced after glutamate and $CBD_{300:1}$ or $THC_{20:1}$, the number of apoptotic cells that could be

counted following depletions were similar among all groups not being different from untreated cultures. Thus, a ratio with CBD dominance protected cortical neurons to a greater extent than hippocampal neurons and to a greater extent than THC dominant treatment. Differences in neuroprotection may be due to differential distributions of Ca^{+2} voltage gated channels, Ca^{+2} binding protein distributions and their affinity for CBD and THC dominant chemical compounds to inhibit their excitotoxic actions.

Disclosures: L.K. Friedman: None. **T. Greenberg:** None. **M.P. Shakarjian:** None. **R.J. Zeman:** None.

Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.17/H10

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

Title: A Human iPSC-Based Platform for Functional Toxicity Screening of CNS-Targeted RNA Therapeutics

Authors: *J. KOEPKE[1], B. SAMSON-COUTERIE[2], K.-C. PITSA[1], **S. JAIN**[1];
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Abstract: Human induced pluripotent stem cell (iPSC)-derived neural co-cultures provide a physiologically relevant and translationally predictive system for evaluating central nervous system (CNS) toxicity of antisense oligonucleotides (ASOs). As CNS-targeted RNA therapeutics advance in the clinic, safety assessment remains a key hurdle, particularly for identifying neurotoxic liabilities not detected in traditional models. Recent studies have linked ASO-induced neurotoxicity with suppression of calcium transients in vivo [Hagedorn et al., Nucleic Acid Ther., 2022], motivating the development of functional assays for early de-risking. We established a high-throughput 384-well calcium imaging assay using iPSC-derived neurons and astrocytes. Under vehicle-treated conditions, cultures showed robust and reproducible spontaneous calcium transients with a peak firing rate of 0.15-0.25 Hz, ΔF/F amplitudes of ~1.5-2, and oscillation scores ranging from 80-100%. Inter-well variability remained below 15%, enabling reliable and scalable screening. We evaluated 70 ASO candidates using this platform and stratified them into three categories based on calcium oscillation score suppression and recovery dynamics: (1) ASOs causing >60% suppression with no recovery, which correlated with severe in vivo CNS symptoms (e.g., seizures, tremors); (2) ASOs with partial recovery (20-30%) over 15 minutes, corresponding to milder behavioral effects; and (3) ASOs that retained normal calcium activity even at 100 μM, indicating minimal neurotoxicity. Overall, calcium scores showed ~80% concordance with in vivo rodent CNS toxicity readouts. Additionally, we applied the assay to support structure-activity relationship (SAR) optimization. Sequence engineering of a neurotoxic ASO improved its calcium oscillation score from <40% to ~80%, while retaining target knockdown potency. This iPSC-based functional neurotoxicity platform

enables sensitive, high-throughput screening of ASOs and provides a human-relevant approach to derisk RNA therapeutic development, improving translational confidence and safety profiling for CNS-targeted programs.

Disclosures: J. Koepke: A. Employment/Salary (full or part-time): Employment/Salary. **B. Samson-Couterie:** A. Employment/Salary (full or part-time): Employment/Salary. **K. Pitsa:** A. Employment/Salary (full or part-time): Employment/Salary. **S. Jain:** A. Employment/Salary (full or part-time): Employment/Salary.

Poster

PSTR441: Neuroprotection and Neurotoxicity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.18/H11

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

Title: A Human iPSC-based Neuroinflammation Model for Early Toxicity Screening via Morphological Profiling

Authors: M. BSIBSI, *M. ZANELLA, C. LOOMANS, L. GEERTS, S. KOSTENSE, L. BUTI, M. VLAMING;
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Abstract: Induced pluripotent stem cell (iPSC)-derived neuronal and glial monocultures have been used to model Central Nervous System (CNS) diseases. However, to better mimic the complex cellular microenvironment and intercellular communication involved in neuroinflammation and neurodegeneration, more physiologically relevant multicellular models are needed. We established a complex in vitro culture model existing of four iPSC-derived CNS cell types (glutamatergic neurons, astrocytes, oligodendrocytes, and microglia) implicated in neuroinflammatory disease processes. These complex in vitro cultures were exposed to functionally relevant stimuli including β-amyloid fibrils, lipopolysaccharide (LPS), and nigericin to induce neurotoxicity and neuroinflammation. Cell-specific markers and high-content imaging, paired with machine learning-based phenotypic analysis, enabled quantitative assessment of morphological and functional responses. β-amyloid-induced neurite degradation, glial morphological alterations and oligodendrocyte cell death are associated with neurofilament light chain (NfL) release in a dose-dependent manner. Nigericin exposure resulted in significant cytotoxicity and triggered NfL release in a dose-dependent manner. in contrast, LPS had minimal direct impact on neuronal viability but activated glial cells. Upon β-amyloid triggering, astrocytes displayed hypertrophic morphology in a dose-dependent manner, while microglia underwent a clear morphological transformation from a bipolar/resting state to a rounded and ultimately cluster-forming activated phenotype. —mimicking in vivo neuroinflammatory activation. Oligodendrocyte exhibited marked morphological heterogeneity, enabling identification of subpopulations with distinct differentiation and functional potential. In conclusion, these findings support the use of morphological phenotyping to distinguish OPC

subtypes and monitor glial responses under pathological conditions. This platform offers a scalable, relevant alternative for early neurotoxicity screening and mechanism-of-action studies. Furthermore, this complex multicellular model complements the Retrogenix® Cell Microarray Technology at Charles River, supporting on/off-target profiling with CNS- and BBB-specific libraries in a comprehensive drug discovery pipeline.

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Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR442.01/H12

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

Support: Innovation Fund Denmark 3129-00023B

Title: 3D imaging framework for spatiotemporal characterization of neuroinflammation in whole-brain

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Abstract: Neuroinflammation is a hallmark of numerous neurological diseases, yet its spatial and temporal complexity remains poorly understood due to limitations in current analytical approaches. To address this, we developed a 3D whole brain imaging framework, integrating light-sheet fluorescence microscopy (LSFM) of microglia markers detected by *in situ* hybridization (ISH) and immunohistochemistry (IHC), followed by AI-based image analysis. In this study, we applied this platform to characterize neuroinflammatory dynamics in the permanent middle cerebral artery occlusion (pMCAO) mouse model of ischemic stroke. Male C57BL/6JRj mice underwent pMCAO by ligation of the left MCA. Brains were collected at 1-, 7-, and 14-days post-infarct (dpi) following perfusion fixation. Microglial responses were assessed using ISH for hexosaminidase subunit beta (*Hexb*) and triggering receptor expressed on myeloid cells 2 (*Trem2*), and IHC for ionized calcium-binding adapter molecule 1 (IBA1). Vascular changes were evaluated by IHC for cluster of differentiation 31 (CD31) and smooth muscle 22 (SM22). Using 3D LSFM and image analysis, microglial and vascular changes were evaluated across 840 brain regions. Our findings indicate a dynamic neuroinflammatory response following stroke, propagating across the brain. At 1 dpi, *Hexb* expression modestly increased in the peri-infarct region and extended into adjacent white matter tracts, including the corpus

callosum and corticothalamic projections, while *Trem2* expression remained minimal. By 7 dpi, *Hexb* signal intensified in the infarct border zone and extended more broadly along white matter tracts, coinciding with the initial emergence of Trem2, which overlapped with Hexb. At 14 dpi, both markers were strongly upregulated, with *Trem2* colocalizing with high-intensity *Hexb* signal. The spatiotemporal expression patterns of *Hexb* closely paralleled IBA1 immunoreactivity, which showed progressive microglial activation extending from the infarct zone into ipsilateral and contralateral white matter regions, including the contralateral corpus callosum by 7 dpi and thalamus by 14 dpi. CD31 staining revealed early and progressive vascular remodelling in parallel with infarct evolution, while SM22 expression confirmed MCA occlusion. This study establishes a scalable 3D imaging platform for spatiotemporal analysis of neuroinflammation and validates a dual-marker ISH strategy for microglial profiling. Crucially, whole-brain imaging enabled us to characterize how focal stroke induces inflammatory responses in anatomically distant brain regions, providing new insights into the global impact of localized CNS injury.

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Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.02/H13

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

Title: Bead-based multiplex assay panels for quantifying neuroinflammation and tau phosphorylation biomarkers in neuroinflammation and neurodegenerative conditions

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Abstract: Neuroinflammation plays a pivotal role in the onset and progression of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Neuroinflammation is the response of central nervous system (CNS) cells such as astrocytes, microglia, and endothelial cells, to injury, infection, or pro-inflammatory stimuli. Inflammation of the brain weakens the blood-brain barrier (BBB) leading to increased inflammation signals in both CSF and serum plasma. When acute inflammation is not fully resolved or in recurring low-grade inflammation, microglia release cytokines including IL-1β, IL-6, and TNF-α, which stimulate kinases that drive tau phosphorylation. Tau hyperphosphorylation leads to microtubule destabilization, impaired axonal transport, synaptic dysfunction, and ultimately neuronal death. Both inflammatory mediators and phosphorylated tau contribute to synaptic loss, creating a vicious cycle that accelerates the progression of AD and PD. Targeting neuroinflammation has emerged as a promising therapeutic intervention in neurodegenerative disease. To address the critical need for sensitive and multiplexed biomarker quantification in neuroscience research, BioLegend has developed LEGENDplex™ bead-based multiplex assay panels. The LEGENDplex™ assay enables simultaneous quantification of key biomarkers involved in neuroinflammation and neurodegeneration, including phosphorylated tau isoforms (pTau217, pTau181, pTau262), markers of neuronal tissue damage (NSE, sCD163, sCD14), neuroinflammatory mediators (YKL-40, sTREM-2, VILIP-1, CCL2, sICAM-1, sVCAM-1), pro-inflammatory cytokines (TNF-α, IL-6, TGF-β1), and systemic inflammation markers (CRP, D-dimer, vWF). Designed for use with standard flow cytometers, these panels utilize highly specific antibodies to ensure assay specificity and have been validated in CSF, serum, and plasma samples from individuals diagnosed with AD or PD. Preliminary data demonstrate that levels of IL-6, YKL-40, sTREM-2, VILIP-1, and CCL2 were significantly elevated in serum samples from AD and PD patients compared to healthy controls. Notably, pTau217 was markedly increased in CSF samples from both AD and PD patients, whereas pTau181 and pTau262 were not detected. LEGENDplex™ panels provide reliable, convenient, and cost-effective tools for high-sensitivity biomarker quantification, disease monitoring, and mechanistic studies. By enabling comprehensive profiling of neuroinflammatory and neurodegenerative processes, these assays empower neuroscience researchers to accelerate translational discoveries and therapeutic development for CNS disorders.

Disclosures: A. Zhao: None. **T. Tran:** None. **M. Kort:** None. **J. Ni:** None.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

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Program #/Poster #: PSTR442.03/H14

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

Support: R43NS139845
R43AG082625
R44ES029898

Title: Damp-mediated neuroinflammation in neuroimmune organoids for drug discovery

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Abstract: Neuroinflammation has been increasingly implicated in a variety of neurological disorders, from disease onset to progression. As the resident immune cells of the CNS, glia play a critical role in the production and propagation of inflammatory mediators such as cytokines, chemokines, reactive oxygen species, and bioactive lipids. The study of the activation, resolution, and failure of resolution of neuroinflammation by glial cells is of significant interest to the field and elucidating this process will further our understanding of neurological disorders and potential therapeutics thereof. Human derived iPSCs have transformed our understanding of developmental biology and greatly enhanced our ability to investigate disease etiology. The use of these cells in CNS-related research has accelerated disease modeling and drug discovery while overcoming interspecies differences. However, monoculture and coculture systems fail to capture the complex heterogeneity and intercellular signaling that occurs in the brain microenvironment. Brain organoids overcome some of these obstacles as they contain multicellular constituents and microglia can be integrated and gain a homeostatic profile. We have developed an organoid system that eliminates much of the inherent variability in organoids by leveraging our proprietary synthetic hydrogel platform to form reproducible planar organoids containing responsive astrocytes and microglia. Herein, we describe neuroinflammatory disease modeling that has been implicated in propagating neurodegenerative disorders. Organoids were treated with a variety of Damage Associated Molecular Pattern (DAMP) molecules to activate DAMP receptors alone or in combination and analyzed for reactive oxygen species generation, microglial activation, down-stream damage to neurons and astrocytes through release of Neurofilament Light and GFAP, and confocal image analysis. DAMP-mediated neuroinflammation is a physiologically relevant alternative to traditional models employing LPS and can be used for screening efforts to modulate the progression of neurogenerative disorders affected by sterile rather than pathogen-induced inflammation. This complex multicellular organoid system offers higher recapitulation of the human brain model and can provide crucial and fundamental information on therapeutic development with high translational relevance.

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Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.04/H15

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

Title: High-throughput screening identifies novel inhibitors of complement activation in human astrocytes

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Abstract: Dysregulated activation of the complement cascade contributes to neuroinflammation and is increasingly implicated in the pathogenesis of neurodegenerative diseases. Astrocytes, key regulators of the neuroimmune environment, are both targets and active participants in complement-mediated responses. In this study, we conducted a high-throughput small-molecule screen to identify inhibitors of complement activation in primary human astrocytes.The goal was to identify compounds capable of attenuating complement activation without impairing cell viability. Complement component levels—most notably C3, C1q, and downstream effectors—were measured using a multiplex immunoassay. Several candidate compounds emerged that significantly reduced complement activation markers. These hits are currently undergoing secondary validation to assess their specificity, potency, and potential mechanisms of action. This work establishes a screening platform for identifying complement-modulating therapeutics and highlights astrocyte-centric models as effective tools for studying neuroinflammatory processes relevant to CNS diseases.

Disclosures: F. Pontarelli: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **F. Rapino:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **S. Ryan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **D. Ofengeim:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **T.R. Hammond:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.05/H16

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

Title: Multiplexed screening in hiPSC-derived microglia using an automated, high-throughput platform identifies potent NLRP3 pathway inhibitors

Authors: J. HENDERSON[1], N. IBARRA AIZPURUA[1], A. PEALL[1], R. ALVAREZ[2], R. KABECHE[4], A. SOMMER[4], G. S. SAHIN[2], ***S. HANSON**[3], T. HARDCASTLE[4], K.-D. CHOI[2], C. COOK[1];
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Abstract: Chronic neuroinflammation has been shown to increase neuronal stress and pyroptosis, playing a significant role in the pathophysiology and progression of neurodegenerative diseases, including Alzheimer's disease (AD). Toll-like receptor 4 (*TLR4*) and triggering receptor expressed on myeloid cells 2 (*TREM2*) are among the main receptors on microglia to mediate neuroinflammation, and loss-of-function mutations in the TREM2 protein (e.g. TREM2 R47H) have been genetically linked to increased risk of developing AD. The potent proinflammatory cytokines IL-1β and IL-18 are secreted in response to TREM2 or TLR4 signaling via downstream activation of the NLRP3 inflammasome. TREM2 or TLR4 activation results in the "priming" of microglia, leading to NFκB translocation and transcriptional upregulation of NLRP3 inflammasome components, pro-caspase 1 and pro-IL-1β. A further "activation" signal (e.g. K^+ efflux) in primed microglia results in NLRP3 inflammasome assembly, cleavage of caspase-1 and subsequent maturation and secretion of IL-1β and IL-18, contributing to neuroinflammation. In this study, we sought to identify inhibitory molecules that can prevent the activation of the NLRP3 inflammasome, and secretion of proinflammatory cytokines in response to TREM2 or TLR4 activation. We obtained wild-type and TREM2 R47H knock-in (KI) human iPSC-derived microglia from EditCo and BrainXell. We performed screening in a 384-well plate format, using Arctoris' Ulysses® high-throughput, automated platform. We screened 245 compounds from a human metabolite library, plus a known NLRP3 inhibitor MCC950, at 10 μM in technical triplicate and measured multiplexed Caspase-Glo 1 activity and IL-1β release following LPS + nigericin stimulation. We then stratified hits as on-target/upstream/downstream of NLRP3 by high content imaging for phospho-NFκB translocation following stimulation. We additionally characterized the functional consequences of TREM2 R47H in iPSC-derived microglia. We found that there was bait-specific impairment of phagocytosis in the hiPSC-derived TREM2 R47H KI microglia, but increased secretion of IL-6, IL-8 and CCL2 in response to both LPS and amyloid β_{42} (Aβ) oligomers. Hence, we further evaluated if NLRP3 inhibitor hits can rescue sensitivity to LPS + nigericin insult in TREM2 R47H microglia. In summary, we observed a strong correlation of hits and interpolated controls across orthogonal assays, demonstrating the reliability and reproducibility of our screening

platform. We identified 40 compounds that inhibited both IL-1β secretion and caspase-1 activation by 50% or more and further validated these hits using microglia, modelling AD.

Disclosures: J. Henderson: A. Employment/Salary (full or part-time): Arctoris, Ltd. **N. Ibarra Aizpurua:** A. Employment/Salary (full or part-time): Arctoris, Ltd. **A. Peall:** A. Employment/Salary (full or part-time): Arctoris, Ltd. **R. Alvarez:** A. Employment/Salary (full or part-time): BrainXell, Inc. **R. Kabeche:** A. Employment/Salary (full or part-time): EditCo Bio, Inc. **A. Sommer:** A. Employment/Salary (full or part-time): EditCo Bio, Inc. **G.S. Sahin:** A. Employment/Salary (full or part-time): BrainXell, Inc. **S. Hanson:** A. Employment/Salary (full or part-time): BrainXell Inc. **T. Hardcastle:** A. Employment/Salary (full or part-time): EditCo Bio, Inc. **K. Choi:** A. Employment/Salary (full or part-time): BrainXell, Inc. **C. Cook:** A. Employment/Salary (full or part-time): Arctoris, Ltd..

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.06/I1

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

Title: Development of a drug screening cascade to identify novel potent and selective NLRP3 inhibitors

Authors: D. TURNER[1], B. HALL[1], T. MODEBADZE[1], M. CORTIGIANI[2], H. HARB[2], L. ROBINSON[2], X. CORTES-LAVAUD[1], *S. GIACHETTI[1], T. PESNOT[2], **E. MALAVASI**[1]; [1]Concept Life Sci., Edinburgh, United Kingdom; [2]Concept Life Sci., Chapel en le Frith, United Kingdom

Abstract: Inflammasomes are large intracellular protein complexes that assemble in response to danger signals and function as key components of the innate immune system. Different types of inflammasomes respond to different activating stimuli but once assembled, they all activate Caspase-1, triggering the secretion of pro-inflammatory cytokines IL-1β and IL-18. Caspase-1 activation additionally results in the activation of pyroptosis, a lytic and inflammatory form of cell death. Inflammasome activation is essential for host defence, but its overactivation is implicated in a variety of inflammatory diseases. The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome responds to various damage- and pathogen-associated molecular patterns and is now an extensively validated therapeutic target for neurodegenerative diseases. Here, we aimed to validate a phenotypic drug screening cascade to identify new potent, selective and non-toxic NLRP3 inhibitors. To support the Hit identification to Lead optimisation stages of drug discovery, we developed a high-throughput assay using human THP1 cells. The cells were differentiated to macrophages by stimulation with PMA, followed by NLRP3 activation with Nigericin, in the presence or absence of reference controls or test substances. Cells were then simultaneously assayed by Caspase-1-Glo®, to assess target engagement, and LDH-Glo®, to quantify the phenotypic outcome, then fixed and stained for quantification of

endogenous ASC specks by High Content Imaging, to confirm the mechanism of action. In parallel, to test for any inherent compound toxicity, THP1-derived macrophages were treated with reference or test substances in the absence of nigericin and assayed by LDH-Glo®. To support the later stages of drug development, from Lead Optimization to candidate selection, we optimized the NLRP3 activation assay described above using primary human macrophages, with quantification of secreted levels of IL-1β as an additional functional readout. In addition, to confirm the NLRP3 selectivity of test compounds, we developed activation assays for NLRC4 and AIM2 inflammasomes (using primary human macrophages) and NLRP1 inflammasome (using primary human keratinocytes). Finally, to confirm the activity and lack of toxicity of clinical candidates in cell-based and 3D Central Nervous System models, we optimised the NLRP3 activation assay in human iPSC-derived microglia, as well as rodent organotypic brain slices. The assay validation data is presented and discussed here, along with the results of the evaluation of novel candidate NLRP3 inhibitors.

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Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.07/I2

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

Title: Hyp-102 mediates neuroprotection through regulation of NLRP3 inflammasome activity in BV-2 cells

Authors: *S. BAEK[1], H. KIM[2], J. IM[1];
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Abstract: Neuroinflammation, an innate immune response of the central nervous system to harmful stimuli such as pathogens or chronic mild stress, plays a pivotal role in the pathogenesis of neurodegenerative disorders, largely mediated by protein complexes called inflammasomes. The NLRP3 inflammasome, predominantly expressed in microglia, comprises the NLRP3 receptor protein, apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase-1. Activation of the NLRP3 inflammasome by DAMPs or PAMPs triggers the release of inflammatory cytokines, including IL-1β and IL-18, and induces pyroptosis—a form of

programmed cell death characterized by membrane pore formation and rupture. Despite extensive development and clinical evaluation of compounds, no candidates with both high efficacy and low toxicity have been identified for brain diseases. To address these differences, we aimed to develop an NLRP3 inflammasome inhibitor with negligible cytotoxicity, high metabolic/blood stability, notable blood-brain barrier permeability, and neuroprotective effects. Key findings from our development process include:We constructed a library of 462 compounds targeting NLRP3 inflammasome inhibition. Through bioassay screening, HYP-102 emerged as the most promising candidate. In THP-1 (human monocytic leukemia) and BV2 (murine microglial) cells with NLRP3 inflammasome activation (induced by LPS/nigericin or ATP), HYP-102 effectively suppressed IL-1β and caspase-1 production with minimal cytotoxicity. It significantly inhibited ASC oligomerization and gasdermin-D cleavage, key steps in pyroptosis. Additionally, HYP-102 reduced nitric oxide generation and proinflammatory cytokine secretion (e.g., TNF-α, IL-6) in LPS-stimulated BV2 cells, while downregulating inflammatory mediators such as iNOS and COX-2.This study demonstrates that HYP-102 attenuates NLRP3 inflammasome activation by reducing the expression of NLRP3, ASC, caspase-1, and IL-1β. These findings underscore its potential as a dual-action therapeutic agent with anti-inflammatory and neuroprotective properties, offering a promising strategy for treating neurodegenerative diseases.

Disclosures: S. Baek: A. Employment/Salary (full or part-time): Full time. **H. Kim:** A. Employment/Salary (full or part-time): Full time. **J. Im:** A. Employment/Salary (full or part-time): Full time.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.08/I3

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

Title: Investigating the role of NOGAR1 (NMDAR-Oxygen & Glucose-Associated Regulator 1) phosphorylation in inflammation during ischemic preconditioning

Authors: *J. BAE[1,2], X. RONG[1,2], V. L. DAWSON[3], T. M. DAWSON[4];
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Abstract: Background: Stroke is a major neurological disease and a global burden. The lack of effective stroke treatment calls for an exploration of disease-related cellular biology and therapeutic targets. A major cause of brain damage following stroke is inflammation. Microglia is a major area of investigation, due to its dual role of being pro-inflammatory and anti-inflammatory. With this dual function identified from previous studies, a better understanding of the microglial activation pathway can lead to potential therapeutic targets. **Innovation**: The

primary innovation of our study is the identification of a major regulator via decoding the fundamental pathways associated with oxygen & glucose and energy-demanding N-methyl-D-aspartate receptors (NMDAR)-dependent cognition, which likely plays a major role in neuroprotection during neuroinflammation. The newly discovered major regulator, NMDAR-Oxygen & Glucose-Associated Regulator 1 (NOGAR1), may act as a regulatory nexus in fundamental pathways for post-ischemic inflammation by influencing microglia activation. **Significance**: Microglial activation under low oxygen & glucose conditions, a consequence of NOGAR1 phosphorylation, can manage the neuroinflammatory process following ischemic stroke. Additionally, the human neuronal cell model used for this study was developed by our group and provides a genuine human model system for studying ischemic stroke-related phenotypes. **Aim**: Our primary aim was to examine the impacts of NOGAR1 phosphorylation on post-ischemic inflammation through changes in microglia activation during oxygen-glucose deprivation with preconditioning (OGD-PC). Our secondary aim was to investigate how NOGAR1 phosphorylation influences neuroinflammation and neuronal recovery in the MCAO stroke mouse model. **Results**: Our study shows that NOGAR1 phosphorylation downregulates pro-inflammatory markers such as IFN-γ, TNF-α, and inflammatory interleukins and upregulates anti-inflammatory markers such as IL-10 and FGF-β. NOGAR1 S614A, S615A mutations promoted mRNA expression of pro-inflammatory and interferon-stimulating genes. These same mutations displayed inflammatory microglial activation in the mouse model, identified with a ramified morphology and IFN-γ and CD68 inflammation markers. **Conclusion**: Loss of NOGAR1 phosphorylation is linked to increased pro-inflammatory and decreased anti-inflammatory factors, and activation of pro-inflammatory microglia. Further investigation of NOGAR1, which can regulate anti-inflammatory microglial activation as well, may lead to alternative therapeutic targets for inflammation following ischemic stroke.

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Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

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Program #/Poster #: PSTR442.09/I4

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

Title: Investigating NOD2 expression in the brain and its potential role in traumatic brain injury

Authors: *J. SMYTH[1], M. QUIROZ[4], J. E. EXLINE[2], M. VOLYANYUK[5], K. E. SCROGIN[6], E. FOECKING[3], G. E. TORRES[7];
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Abstract: Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) is an immune sensor that is activated by a bacterial metabolite known as muramyl dipeptide (MDP). When activated, NOD2 sets off a signaling cascade that activates the nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), and Caspase-1 pathways. These pathways promote the production of proinflammatory cytokines and induce an immune response. Interestingly, NOD2 has been implicated in systemic inflammatory conditions like Crohn's Disease and even studied as a potential target for the treatment of neurological disorders such as Alzheimer's disease, Parkinson's disease, and ischemic stroke. Still, little is known about the regional and cellular expression of NOD2 in brain tissue. Furthermore, NOD2 has not been investigated in models of acute neuroinflammation, such as in traumatic brain injury (TBI). Understanding where NOD2 is expressed in the brain and how its expression changes under neuroinflammatory conditions is crucial, as it can enhance our comprehension of NOD2's broader role, particularly in neurological disorders. Here, we examined the expression of NOD2 in three different brain regions that have been characterized in models of neuroinflammation: the hippocampus, striatum, and cortex. We explored NOD2 expression in wild type rats using RNAscope, a technique that combines in situ hybridization for NOD2 mRNA expression with immunofluorescence for protein marker detection. We explored colocalization of NOD2 with markers for microglia, astrocytes, and neurons to determine which cell types NOD2 is expressed in. NOD2 expression levels varied throughout the three brain regions and the cell types that we examined. We also examined the expression of NOD2 in the brain by RT-qPCR in a rat model of TBI. Using a controlled cortical impactor to induce a closed-head repetitive mild TBI, we examined NOD2 expression in the hippocampus at 1-, 3-, 7-, and 14-days post-injury (DPI). PCR analysis showed a downregulation of NOD2 at 14 DPI in the hippocampus. Interestingly, NOD2 was upregulated at 3 DPI in the somatosensory cortex, but expression returned to baseline by day 14. These results suggest that NOD2 is expressed in brain tissue and might represent a novel target in neuroinflammatory conditions such as TBI.

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Poster

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

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Timothy William Trout Chairmanship

Title: Microglial activation in response to oxidized lipids in Tmem135 mutant mice

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Abstract: Purpose Age-related retinal diseases, including age-related macular degeneration (AMD), are strongly linked to dysregulated lipid metabolism. However, the specific role of lipid abnormalities in the onset and progression of these diseases remains unclear. Transmembrane protein 135 (TMEM135) is a transmembrane protein known to be localized on peroxisomes and mitochondria and play an important role in the metabolism of polyunsaturated fatty acids. We previously identified a mouse strain harboring a mutation in *Tmem135* that displays signs of accelerated aging in the retina as well as pathologies observed in AMD including microglial activation. We hypothesize that lipid dysregulation, particularly the accumulation of oxidized lipids, drives microglial activation and contributes to AMD-like pathologies. In this study, we examined how a mutation in *Tmem135* impacts retinal lipid metabolism, microglial behavior, and retinal integrity. **Methods** We used mice homozygous for a mutation in the *Tmem135* gene, $Tmem135^{FUN025/FUN025}$, for all experiments. Eyes were collected for lipidomic profiling, RNA-sequence, electron microscopy, and immunofluorescence staining to assess subretinal microglia and oxidized lipids. Additional samples were used for western blot analysis. **Results** $Tmem135^{FUN025/FUN025}$ mice showed significant upregulation of lipids containing arachidonic acid (20:4) in the neural retina. Levels of 4-hydroxynonenal (4-HNE), a terminal product of lipid peroxidation, were also elevated in the neural retina but not in the retinal pigment epithelium (RPE) layer. Microglia were markedly increased in the subretinal space (between neural retina and RPE) and exhibited signs of activation. These activated microglia contained oxidized phosphatidylcholines (oxPCs), suggesting that they migrated toward the RPE and interacted with oxidized lipids. Ether-linked lipids were also upregulated in the neural retina, potentially as a compensatory response. Gene expression analysis revealed significant upregulation of triggering receptor expressed on myeloid cells 2 (*Trem2*), a receptor involved in lipid sensing and microglial activation. **Conclusion** Our findings suggest that the *Tmem135* mutation induces a selective accumulation of 20:4-containing lipids in the retina, leading to enhanced lipid oxidation and subsequent activated microglial engulfment. This study underscores the importance of lipid homeostasis in maintaining retinal health and highlights a potential mechanism by which oxidized lipids contribute to neuroinflammation via TREM2 signaling in AMD pathogenesis.

Disclosures: R. Hagimori: None. **P. Gogoi:** None. **S. Ikeda:** None. **K. Yamada:** None. **A. Ikeda:** None.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.11/I6

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

Support: AARG-21-846012

Title: Effects of PLCG2 deficiency on neuroinflammatory gene expression, lipid metabolism, and sickness behavior after LPS challenge

Authors: *E. GUTIERREZ KURI[1], K. F. BIENIEK[2], J. P. PALAVICINI[3], S. C. HOPP[4]; [1]Med. / Pharmacol., Univ. of Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX; [2]Biggs Inst. for Alzheimer's & Neurodegenerative Dis., Univ. of Texas Hlth. Sci. Center, San Antonio, San Antonio, TX; [3]Univ. of Texas Hlth. Sci. Ctr. At San A, San Antonio, TX; [4]Biggs Inst. for Alzheimer's and Neurodegenerative Dis., UT Hlth. San Antonio, San Antonio, TX

Abstract: PLCG2, a critical immune regulator, has emerged as a key factor in Alzheimer's disease, with genetic variants conferring both risk and protection. In the brain, PLCG2 is mainly expressed in microglia, influencing cellular functions including calcium signaling. We investigated PLCG2's role in neuroinflammation using constitutive and inducible knockout mouse models with LPS-induced acute inflammation.In the constitutive KO**,** LPS treatment induced >200 differentially expressed genes in the brain, altering pathways related to innate and adaptive immune responses, inflammatory signaling, and microglial function. KO mice exhibited a distinct gene signature in response to LPS, with upregulated genes associated with interleukin signaling, prostaglandin response, and interferon pathways. Interferon-responsive genes were upregulated in homozygote KO mice post-LPS treatment, a phenotype that has been linked to white matter pathology. Consistently, principal component analysis of myelin-enriched genes revealed LPS-treated homozygote KO samples clustering separately from other genotypes. Brain lipidomes where also assessed by targeted mass spectrometry. Behaviorally, LPS-treated KO mice displayed reduced locomotion in open field tests, correlating with expression of sickness behavior-related genes. These findings suggest PLCG2 deficiency enhances interferon responses, potentially driving behavioral changes and myelin pathology phenotypes. Inducible KO mice showed distinct behavior, with ongoing efforts focused on assessing their brain transcriptomes.

Disclosures: E. Gutierrez Kuri: None. **K.F. Bieniek:** None. **J.P. Palavicini:** None. **S.C. Hopp:** None.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.12/I7

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

Support: 2023000CB0030
2023100CB0060

Title: Nicotine Attenuates LPS-Induced Neuroinflammation via Modulation of Sphingolipid Metabolism

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Abstract: Neuroinflammation is a pathological hallmark of neurological disorders, where dysregulated sphingolipid (SPL) metabolism plays a critical role. Pro-inflammatory SPLs (e.g., ceramides and sphingosine) directly promote neuroinflammatory cascades by activating glial cells and amplifying cytokine production. Nicotine, a cholinergic agonist, exhibits immunomodulatory properties. In this study, we investigated nicotine's anti-neuroinflammatory effects through sphingolipid regulation. In vitro, BV2 microglial cells treated with LPS (250 ng/mL) ± nicotine (0.01 μM) for 24 h showed that nicotine co-treatment significantly reduced LPS-induced pro-inflammatory cytokine gene expression (*TNF-α, IL-6, IL-1β*) and protein secretion via qPCR/ELISA, concurrently attenuating LPS-driven upregulation of SPL-metabolizing enzyme genes (*Sptcl2*). Live-cell fluorescence imaging using TMRM and Bodipy 493/503 revealed nicotine preserved mitochondrial membrane potential and reduced lipid droplet accumulation. Lipidomics confirmed nicotine suppressed LPS-induced ceramide accumulation. In vivo, nicotine pretreatment (0.25 mg/kg/day s.c., 7 days) in C57BL/6J mice prior to dual LPS injections (0.5 mg/kg i.p.) significantly inhibited neuroinflammation, reducing pro-inflammatory cytokine gene expression (*TNF-α, IL-6, IL-1β*) in hippocampus, cortex, and striatum. Lipidomics and immunofluorescence demonstrated nicotine abrogated LPS-elevated ceramide levels and region-specific accumulation across these brain regions. Our findings establish that nicotine exerts potent anti-neuroinflammatory effects by normalizing sphingolipid metabolism and ceramide dysregulation, highlighting its therapeutic potential for targeting neuroinflammation through lipid metabolic pathways.

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Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR442.13/I8

Topic: B.09. Glial Mechanisms

Support: NIH Grant ES036241
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Title: Characterization of OGlcNAc modified YTHDF1 during microglial activation in neuroinflammatory models of neurodegenerative disease

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Abstract: Neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, dementia with Lewy bodies, and along with other mixed etiology dementia (MED)-related diseases, are associated with an abnormal accumulation of pathological α-synuclein (αSyn) in the brain. Pathological αSyn accumulates in Lewy bodies (LBs), which are known to activate microglia and drive chronic neuroinflammatory processes, ultimately contributing to progressive neuronal damage. Emerging evidence suggests that epitranscriptomic dysregulation, particularly involving N6-methyladenosine (m6A) mRNA modifications, may underpin pathogenesis of chronic neurodegenerative processes in Parkinson's Disease (PD). We have recently demonstrated METTL3 and YTHDF2 dysregulated during metal-induced neurotoxicity by driving proinflammatory transcript upregulation. Interestingly, YTHDF1, the key m6A-mRNA translation promoting reader, has been implicated in memory-related brain function and is dysregulated in MED-related diseases. To date, however, the mechanistic and functional implications of αSyn-induced m6A dysregulation have yet to be reported. In this study, we observed that YTHDF1 is downregulated in αSyn-induced microglial activation. Our functional studies indicate YTHDF1 may preferentially target certain proinflammatory mRNA transcripts such as TNFα, IL-6 and IL-1β—all linked to the neuroinflammatory process in PD. Interestingly, we found that YTHDF1 is differentially OGlcNAcylated in αSyn-induced microglial activation. To further characterize the OGlcNAcylation of YTHDF1, we have generated a site-specific antibody against *O*-YTHDF1^{S196} and detect differential abundance in cell culture and animal models of αSyn-induced neuroinflammation. Importantly, human post-mortem samples from healthy and DLB patients showed significant changes in the substantia nigra as determined by immunoblotting and fluorescent immunohistochemistry. Further studies revealed functional relevance of *O*-YTHDF1^{S196} in neuroinflammatory context. Overall, this work provides novel molecular insights into the m6A/YTHDF1-dependent regulatory mechanisms in microglia-driven chronic neuroinflammation in PD.

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Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.14/I9

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

Support: NIH S10OD030346
Coins For Alzheimer's Research Trust Grant

Title: Uncovering YTHDF1-m6A Recognition in Neuroinflammatory Responses

Authors: ***S. WANG**[1,2], M. PONNUSAMY[3], L. NGUYEN[3], O. PATEL[3], G. THINAKARAN[2]; [1]Univ. of south florida, Tampa, FL; [2]Byrd Alzheimer's Res. Inst., Tampa, FL; [3]Univ. of South Florida, Tampa, FL

Abstract: m^6A RNA methylation, the most abundant modification in eukaryotic mRNA plays essential roles in RNA metabolism, including processing, translation, and degradation. The precise regulation of m^6A is recognized as an additional layer of gene expression control. YTH domain family protein 1 (YTHDF1) is an m^6A reader that binds to m^6A-modified mRNA and promotes its translation in the cytoplasm. YTHDF1- m^6A modality of regulation promotes learning and memory in the central nervous system and responds to neuronal damage after traumatic brain injury by enhancing the translation of proteins involved in synaptic plasticity and immune responses. However, the systemic profile of YTHDF1 targets during immune responses in the brain is lacking, representing a significant gap in our understanding of the m^6A-mediated dynamic immune response. We investigated the role of YTHDF1 in the inflammatory response of the mouse brain following peripheral LPS administration using multi-omics approaches, which include bulk RNAseq, Digital Spatial Profiling, CUT&RUN m^6A-seq, and the assay of reverse transcription-based RBP binding site sequencing (ARTR-seq). We explored the YTHDF1-dependent methylated regions in the transcriptome associated with LPS-induced neuroinflammation in mouse. Interestingly, the acute inflammatory response to LPS was significantly exacerbated in *Ythdf1*$^{-/-}$ mice, as evidenced by robust induction of *Tnfa*, *Stat1*, *Stat2*, *Igtp*, *Cst7*, and *Spp1*. In contrast, the activation of subchronic neuroinflammation was reduced in *Ythdf1*$^{-/-}$ mice, as indicated by the expression levels of *Il10*, *Tnfa*, *Ccl22*, *Irf1*, *Ifitm3*, *Cst7*, *Ccl6*, *Spp1*, *Timp1*, and *Gfap*. These intriguing findings suggest that YTHDF1 limits neuroinflammatory activation during the acute phase but is necessary to sustain the subchronic phase.

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Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR442.15/I10

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

Support: NIAAA R15AA027909 to ESO
William Paterson University
Guest Researcher NIDA-IRP-NIH

Title: Unraveling immunomodulatory components of endocannabinoidome and mu opioid receptor systems

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Abstract: Marijuana (cannabis) is getting global medical and recreational approvals at the same time of the opioid epidemic. Opiates have been used for medical and recreational purposes for millennia. COVID-19 lockdown and isolation increased excessive alcohol drinking behavior, drug addiction and opioid overdose and deaths. Both opiates and cannabis are often co-abused, and their use increase the risk of opioid and cannabis use disorders (OUDs and CUDs), and dependency. Opioid and cannabinoid systems are complex, have endogenous ligands, and share many immunomodulating and pharmacological effects by activating opioid and cannabinoid receptors, respectively. CB2R cannabinoid receptor (CB2R), a component of the expanding endocannabinoid system (ECS) referred to as endocannabinoidome (eCBome) plays a key role in inflammasome signaling. Inflammation is increasingly implicated in many diseases, and mμ-opioid receptor (MOR) and CB2R have been linked to neuroinflammation. The hypothesis that changes in MOR and CB2R mediated behavioral and cytokine alterations are associated with their roles in inflammation was tested. Naïve male C57Bl/6J as wild type, MOR KO mice with deletion of MOR, DAT-*Cnr2* cKO mice with deletion of CB2R from dopamine neurons and CX3Cr1-*Cnr2* cKO mice with deletion of CB2R from microglia were used in the study. Behavioral analysis using wheel running activity (WRA) for five minutes, and tail-flick latencies for nociception with cut-off at twelve seconds were assessed in the animals. After the behavioral experiments animals were prepared for the proinflammatory cytokine assays. ELISA assay was used to investigate the level of cytokines and chemokines in the cerebellum and prefrontal cortical regions of the animals. MOR KO, DAT-*Cnr2,* and CX3Cr1-*Cnr2* mice displayed differential phenotypes with genotypic and brain region alterations of TNFα, IL-1α, IL-1β, IL-6, IFNγ, MCP-1 and CXCL10 in the cerebellum and prefrontal cortical regions of the animals. DAT-*Cnr2* cKO mice displayed hyper-psychomotor WRA responses while the CX3Cr1-*Cnr2* cKO were less sensitive to the tail-flick latencies compared with MOR KO DAT-*Cnr2* cKO and WT controls. The results indicated that deletion of MOR, and selective deletion of CB2Rs from either dopamine neurons or microglia had differentially modified motor activity and nociceptive responses, with genotypic, and brain region (cerebellum and prefrontal cortex) alterations of cytokines and chemokines. Modulation of components of the eCBome and opioid systems could thus offer immune regulation strategies in terms of therapeutic targets for disorders associated with inflammation in chronic pain conditions.

Disclosures: E.S. Onaivi: None.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.16/I11

Topic: B.09. Glial Mechanisms

Support: CIHR Grant FRN 180241
NIAAA Grant R37AA012446

Title: Prenatal tetrahydrocannabinol exposure results in regional differences in neuroinflammation in the rat hippocampus

Authors: *M. A. C. TILL[1,3], H. M. O. REID[1,3], A. HINDE[2], K. BALL[1], K. CONWAY[2], C. MURRAY[1], F. RAMNARAIGN[1], R. PRZY[1], B. JACOBY[1], K. R. BREIT[4,5,6], C. RODRIGUEZ[5], J. D. THOMAS[5], B. R. CHRISTIE[1,5,7,2];
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Abstract: This study aimed to investigate the effects of prenatal exposure to tetrahydrocannabinol (THC) on microglia morphology in the hippocampus of adult rats. Pregnant rats were exposed throughout gestation to either THC or a vehicle through a vapour inhalation chamber. One male and one female pup per litter were aged to PD 70 and used in the study. 24 rats were used for the analysis of microglia morphology and 20 were used for western blots. A circularity analysis and Sholl analysis were used to observe microglia morphology in the cornu ammonis (CA) and dentate gyrus (DG) regions of the hippocampus. The results of the circularity analysis showed that prenatal THC exposure resulted in decreased microglia circularity in both regions ($p<0.001$), compounded with sex ($p=0.007$) and dorsal/ventral effects ($p=0.005$). A Sholl analysis further supported the hypothesis, finding that microglia in the CA express a hyper-ramified phenotype ($p<0.001$). Western blots were then performed to evaluate levels of CD68, which is a lysosomal protein expressed by active microglia. The results found an increase in CD68 expression in the CA ($p<0.001$) and a decrease in the DG ($p<0.001$) of rats prenatally exposed to THC. This research suggests that microglia are responding to prenatal THC exposure in a region-specific manner, whereby those in the CA become hyper-ramified and express greater CD68, indicative of an altered neuroinflammatory state. On the contrary, microglia in the DG appear to have suppressed lysosomal activity, without affecting microglia surveillance. The DG has been previously shown to undergo adult neurogenesis, which may explain the differing results between regions of the hippocampus. Overall, this study shows that microglia can be altered long after insult in utero, yet before any obvious damage is seen. Regional differences in results point to diverse subpopulations of cells, even within the hippocampus.

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Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.17/I12

Topic: B.09. Glial Mechanisms

Title: Lipopolysaccharide-mediated activation of glia induces cell type specific upregulation of kappa opioid receptor

Authors: *A. G. WHITE, T. HAMAD, A. ZHANG, M. T. MANNERS;
Rowan Univ., Glassboro, NJ

Abstract: Chronic stress results in a pro-inflammatory response and can yield serious health consequences, including major depressive disorder (MDD) and substance use disorder (SUD). Given the high prevalence of chronic stress and the common comorbidity of MDD and SUD, understanding shared molecular factors underlying the development of these disorders may lead to improved therapeutics. The opioid system plays a crucial role in the behavioral stress response, and kappa opioid receptors (KORs) are dysregulated in patients with MDD and SUD. Furthermore, astrocytes and microglia are key inflammatory modulators of the central nervous system and respond to chronic stress. This study investigates the cellular expression of KORs in response to inflammation. Astrocytes and microglia were treated with lipopolysaccharide (LPS) for 4 or 24 hours to induce an inflammatory response. The data suggests that LPS treatment increases KOR expression in microglia 24 hours after treatment. In contrast, there is no change in KOR levels when astrocytes are treated with LPS. These findings indicate that upregulation of KOR in response to inflammation is cell type specific.

Disclosures: A.G. White: None. **T. Hamad:** None. **A. Zhang:** None. **M.T. Manners:** None.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.18/J1

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

Support: NIH grant R01AG076537

Title: Effects of Kidney Dysfunction on Cerebrovascular and Brain Immune Systems

Authors: *T. ANDREWS[1], T. KANEKIYO[2];
[1]Mayo Clin., Jacksonville, FL; [2]Neurosci., Mayo Clin. Jacksonville, Jacksonville, FL

Abstract: Background: Prevalence of *cognitive impairment* in chronic kidney disease (**CKD**) exceeds those of age-matched healthy controls. In CKD, uremic toxin exposure likely injures the neurovascular unit, contributing to brain disease pathogenesis. However, limited investigations demonstrate uremic toxin effects on neuroinflammation and the neurovascular unit processes in

CKD. **Methods**: To assess the effects of uremia on human induced pluripotent astrocytes, human immortalized microglia (HMC3), and human immortalized brain vascular endothelial cells (hCMEC/D3) in monoculture were incubated in 4mM of indoxyl sulfate or control for 4 hours. Endothelial cell activation and neuroinflammation were compared between groups. qPCR was conducted to evaluate gene of interest expression levels. **Results**: Overall, exposure to indoxyl sulfate disturbs astrocytic, microglial, and endothelial cell function compared to controls *in vitro*. Exposure to indoxyl sulfate in human induced pluripotent astrocytes led to an increase in mRNA coding for VEGF-A and trended towards an increase in mRNA coding for BAX ($p=0.06$). Similarly, human microglia had an increase in mRNA coding for IL-1β. Finally, human brain vascular endothelial cells had an increase in mRNA coding for E-selectin, IL-6, IL-1β, and TNF-α. **Conclusion**: Uremic toxin indoxyl sulfate induces neuroinflammation, apoptosis, and endothelial cell dysfunction *in vitro*. Elucidating the mechanisms by which uremic toxin accumulation in kidney dysfunction contributes to cognitive impairment could lead to successful development of targeted therapeutics

Disclosures: T. Andrews: None. **T. Kanekiyo:** None.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR442.19/J2

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

Support: NIH Grant 5R01NS123644
AHA Grant 25PRE1356745

Title: Chronic blood pressure variability drives microglial reactivity and neuroinflammation

Authors: *R. E. PATTERSON[1], K. XIE[1], P. J. O'HERRON[2], J. A. FILOSA[1];
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Abstract: Blood pressure variability (BPV) is increasingly recognized as a key contributor to cerebrovascular disease, cognitive decline, and dementia. While BPV-induced biomechanical forces, such as shear stress, directly impact the microcirculation, their role in neuroinflammatory responses remains incompletely understood. This study investigates whether chronic BPV promotes a pro-inflammatory microglial state, ultimately exacerbating vascular dysfunction and neuroinflammation. Using a novel murine model of BPV, we employed *in vivo* two-photon imaging, immunohistochemistry, and molecular approaches to assess microglial morphology, gene expression, and cytokine production. Male C57BL/6 and CX3CR1 mice received either saline (control) or pulsatile angiotensin II (18 μg/day) via a programmable pump over 20-30 days, with continuous cardiovascular monitoring via DSI telemetry. On treatment days 14 and 30 (pending), we performed 2P imaging to evaluate microglial responses to acute BP elevations. At the end of the treatment period, brain tissue was harvested for cytokine quantification and

immunohistochemical assessment of microglial structural changes. Following 14 days of treatment, *in vivo* imaging revealed that acute BP elevations were associated with increased microglial reactivity, as demonstrated by enhanced density of microglial processes. By day 25, brain tissue analysis showed elevated expression of pro-inflammatory cytokines ($P<0.05$) and reduced cortical microglial arborization (decreased # of junctions and endpoints, $P<0.02$), suggesting a transition to a pro-inflammatory phenotype. Ongoing investigations will determine whether the observed microglia decrease in arborization under chronic BPV reflects the terminal phase of dynamic microglial remodeling in response to sustained vascular stress and inflammation. Overall, these findings indicate that chronic BPV-induced vascular stress drives a pro-inflammatory microglial phenotype, potentially compromising cerebrovascular integrity and contributing to neurovascular dysfunction.

Disclosures: R.E. Patterson: None. **P.J. O'Herron:** None.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

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Program #/Poster #: PSTR442.20/J3

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

Support: NIH Grant 1P01AI073693

Title: Mechanisms of anti-NMDAR antibody-mediated neuronal pathology and mitigation by angiotensin II signaling inhibition

Authors: *K. CARROLL[1], M. MIZRACHI[3], S. SIMMONS[4], J. WINGARD[2], R. WEISSMAN-TSUKAMOTO[5], B. T. VOLPE[6], B. DIAMOND[7];
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Abstract: Cognitive impairment is a frequent manifestation of neuropsychiatric systemic lupus erythematosus (NPSLE), present in up to 80% of patients and leading to a diminished quality of life. We used a model of lupus-like cognitive impairment that is initiated when antibodies that cross-react with DNA and excitatory neuronal receptors penetrate the hippocampus, causing immediate self-limited excitotoxic death of hippocampal neurons, which is then followed by a significant loss of dendritic complexity in surviving neurons and impairment in spatial memory. This injury creates a maladaptive equilibrium that is sustained in mice for at least 1 year. We identified a feedforward loop of microglial activation and microglia-dependent synapse elimination dependent on neuronal secretion of high mobility group box 1 protein (HMGB1) which binds the receptor for advanced glycation end products (RAGE) and leads to microglial secretion of C1q, upregulation of interleukin-10 with consequent downregulation of leukocyte-

associated immunoglobulin-like receptor 1 (LAIR-1), an inhibitory receptor for C1q. While we previously showed that treatment with a centrally acting angiotensin-converting enzyme inhibitor restored a healthy equilibrium, microglial quiescence and intact spatial memory, we now show that a centrally acting angiotensin receptor blocker also is effective, confirming the angiotensin pathway as a mediator of neuronal damage. We have identified a mechanism by which neuroinflammation can be sustained in a feedforward process despite no intrinsic, genetically determined abnormality of neurons or microglia and no continuing external triggers for inflammation. The inhibition of angiotensin II/angiotensin receptor 1 signaling is able to halt the self-sustaining inflammatory cycle by lifting the suppression of LAIR-1, which enables microglia and neurons to return to a state of quiescence and a healthy homeostasis. This has the translational implication that there needs to be a direct manipulation of the cells in the CNS to modulate or abort the inflammatory process.

Disclosures: K. Carroll: None. **M. Mizrachi:** None. **S. Simmons:** None. **J. Wingard:** None. **R. Weissman-Tsukamoto:** None. **B.T. Volpe:** None. **B. Diamond:** None.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

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Program #/Poster #: PSTR442.21/J4

Topic: B.09. Glial Mechanisms

Support: NIH R21NS121959

Title: Testing for a role of interleukin-6 in hippocampal microglial reactivity following astrocytic mitochondrial DNA damage

Authors: A. MATARAZZO[1], A. CASE[2], R. SRINIVASAN[3], *M. RIMER[4];
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Abstract: We developed a novel adeno-associated virus (AAV) tool, Mito-PstI, which specifically targets the restriction enzyme PstI to astrocytic mitochondria, in a brain-region-specific manner. Using Mito-PstI on the dorsolateral striatum (DLS) and hippocampal dentate gyrus (HPC) of young adult mice, we reported that Mito-PstI depleted and deleted astrocytic mitochondrial DNA (mtDNA) *in vivo*, leading to brain-region-selective effects. Thus, Mito-PstI: (i) induced significant morphological changes to astrocytic mitochondria in DLS but not in HPC, (ii) led to alterations of astrocytic spontaneous Ca^{2+} influx events that were much more dramatic in DLS than HPC, and (iii) was associated with microglial reactivity in HPC but not in DLS (Ayala, Matarazzo et al., *Sci. Rep.*, 2024). Here, we have begun investigating a possible mechanism for the hippocampal astrocytic mtDNA-damage-induced microglial reactivity by evaluating a role for interleukin-6 (IL-6), a cytokine linked to increased hippocampal

inflammation in Alzheimer's Disease (AD).Eight-week-old male and female C57Bl/6 wild type (WT) mice received unilateral stereotaxic injections of Mito-PstI, Mito-GFP, or saline into the HPC dentate gyrus. Three weeks later, HPC tissue was harvested for quantitative PCR. Of the several neuroinflammatory markers tested, IL-6 mRNA expression was specifically upregulated in the Mito-PstI group (1.74-fold over saline controls, n=5-6 mice/treatment, P = 0.015). To assess if IL-6 was required for microglial activation, we repeated AAV injections in IL-6 knockout (KO) mice (n=3-5/treatment). After perfusion, HPC sections were analyzed by IBA-1 immunohistochemistry and confocal microscopy. Average microglial staining area/field of view in WT siblings injected with Mito-PstI (13,043±1314 μm²) was significantly higher than with Mito-GFP (5,380±475 μm², $P < 0.01$). In IL-6 KOs there was no difference between the two treatments (Mito-PstI 7,167±695 and Mito-GFP 7787±411 μm², $P > 0.05$). Downstream genes of the cGAS-STING pathway (*Isg15*, *Usp18*, *Cxcl10*) were not upregulated in WT Mito-PstI mice relative to control, pointing instead to toll-like receptor 9 (TLR9) as possible DNA damage sensor mediating IL-6 signaling. Further assessment of microglia activation and experiments in TLR9 KO mice are ongoing.These findings suggest that IL-6 is necessary for microglial activation induced by astrocytic mtDNA damage in HPC. Implications of our results for AD will be discussed.

Disclosures: A. Matarazzo: None. **A. Case:** None. **R. Srinivasan:** None. **M. Rimer:** None.

Poster

PSTR442: Neuroinflammation: Cell and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.22/J5

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

Support: NIH T32NS096050
NIH Grant R01ES034796
NIH K00 ES033033
NIMH R01 MH125956
NIH R01 DK110049
NIH R01 AG075820

Title: Mitochondrially transcribed double-stranded RNA mediates manganese-induced neuroinflammation

Authors: *H. MENDEZ-VAZQUEZ[1], A. GOKHALE[2], M. M. SAMPSON[3], F. RIVERA MOCTEZUMA[5], A. HARBUZARIU[1], A. SING[3], S. A. ZLATIC[4], M. PRAJAPATI[6], B. R. ROBERTS[1], T. BARTNIKAS[7], L. WOOD[8], S. A. SLOAN[3], V. FAUNDEZ[2], E. WERNER[1]; [2]Cell Biol., [3]Human Genet., [4]Dept of Cell Biol., [1]Emory Univ., Atlanta, GA; [5]Georgia Inst. of Techology, Atlanta, GA; [6]Ferris State Univ., Big Rapids, MI; [7]Brown Univ., Providence, RI; [8]Georgia Inst. of Technol., Atlanta, GA.

Abstract: Manganese is an essential trace element required for various physiological processes, but excessive manganese accumulation is neurotoxic. Manganese-exposed brain regions show astrogliosis, neuronal loss, and evidence of neuroinflammation, yet the underlying molecular mechanisms driving these outcomes are not well understood. We have identified a novel manganese-dependent mechanism linking mitochondrial dysfunction to neuroinflammation which precedes classical hallmarks of mitochondrial dysfunction like reactive oxygen species generation. We demonstrate that manganese exposure disrupts mitochondrial RNA processing, leading to the accumulation of complementary transcripts that form double-stranded RNAs (dsRNAs). Further, we observed that these dsRNAs migrate to the cytoplasm, where they activate cytosolic sensor pathways, triggering type I interferon responses and inflammatory cytokine production. Using single-cell RNA sequencing in 100-day human cerebral organoids, we found that manganese induces upregulation of interferon responses predominantly in mature astrocytes. Further, we observed manganese-induced inflammatory upregulation across multiple systems, including the brains of mice harboring mutations in the *SLC30A10* gene, which leads to manganese accumulation. These findings highlight a previously unrecognized role for mitochondrial dsRNAs in manganese-induced neuroinflammation and provide insights into the molecular basis of manganese-induced neuropathology. We propose that this mitochondrial dsRNA-induced inflammatory pathway has broad implications in for neurodegenerative diseases caused by environmental or genetic insults.

Disclosures: H. Mendez-Vazquez: None. **A. Gokhale:** None. **M.M. Sampson:** None. **F. Rivera Moctezuma:** None. **A. Harbuzariu:** None. **A. Sing:** None. **S.A. Zlatic:** None. **M. Prajapati:** None. **B.R. Roberts:** None. **T. Bartnikas:** None. **L. Wood:** None. **S.A. Sloan:** None. **V. Faundez:** None. **E. Werner:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.01/J6

Topic: D.02. Ischemia

Title: The Role of Histone Deacetylase Inhibitors in Neuroprotection and Cardioprotection following Neonatal Hypoxic-Ischemic Brain Injury

Authors: *B. GUNDI[1,2,3], X. ZHANG[1,2,3], Z. LUO[1,2,3], Z.-P. FENG[1,2], H.-S. SUN[1,2,3]; [2]Dept. of Physiol., [3]Dept. of Surgery, [1]Univ. of Toronto, Toronto, ON, Canada

Abstract: Stroke is a devastating disease marked by disrupted circulation of oxygenated blood to the brain. With the incidence of stroke in younger populations on the rise globally, hypoxic-ischemic brain injury (HIBI) becomes a major cause for neurological impairment, morbidity, and mortality in neonates. HIBI often leads to severe secondary complications, including post-HI myocardial injury. Despite the large scale impact of this disease, current treatments are proving insufficient to treat both the primary insult and its downstream effects. The existing gold

standard treatment, therapeutic hypothermia, is limited by its short therapeutic window and widespread adverse effects. As such, it is paramount that more impactful treatment options are explored. Histone deacetylase inhibitors (HDACi) have recently been investigated for their protective properties in cerebrovascular incidents, however their effects in neonatal HIBI remain unknown. As such, the aim of the present study is to examine the effect of histone deacetylase inhibitors in neuronal and cardiac outcomes following neonatal HIBI. Post-natal day 7 mice were randomly assigned to receive a single intraperitoneal injection of either drug treatment or vehicle of treatment 30 minutes prior to or following ischemic surgery. Histological assessments were performed, and short-term behavioural assessments were carried out at multiple timepoints following the procedure. Long-term behavioural testing, cardiac function evaluation, and mechanistic studies are ongoing. TTC staining revealed that both pre- and post-treatment with a histone deacetylase inhibitor significantly reduced corrected infarct volume by nearly 50% compared to vehicle. Drug pre-treatment also improved performance on geotaxis and cliff-avoidance behavioural tasks. Righting reflex and grip strength were also significantly improved in the drug pre-treatment group, relative to vehicle. Importantly, post-treatment groups showed similar behavioural and histological improvements.Ultimately, a histone deacetylase inhibitor as a pre- and post-treatment has been shown to improve neuronal damage and behavioural outcomes following neonatal HIBI, introducing a new potential therapeutic option for HIBI.

Disclosures: B. Gundi: None. **X. Zhang:** None. **Z. Luo:** None. **Z. Feng:** None. **H. Sun:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.02/J7

Topic: D.02. Ischemia

Support: 1R01NS117428-01A1
ANR-21-CE17-0019-01

Title: Short- and Long-term Neuroprotective Effect of a Novel Purine Derivative Drug in Severe Hypoxia Ischemia Related Brain Injury

Authors: *C. DISDIER[1], A. TSINTZOU[1], O. PULVÉRIC[2], X. CHEN[3], S. MERIAUX[2], F. BOUMEZBEUR[2], B. S. STONESTREET[3], R. POIRIER[4], A. MABONDZO[1];
[1]CEA, DMTS, SPI, Neurovascular Unit Res. & Therapeut. Innovation Laboratory, Paris-Saclay University, Paris Saclay Univ., Gif sur yvette, France; [2]Neurospin, Gif sur yvette, France; [3]Women & Infants Hosp. of Rhode Island, Providence, RI; [4]Paris-Saclay Neurosci. Institute, UMR 9197, CNR, orsay.

Abstract: Hypoxic-ischemic encephalopathy (HIE) is a major cause of morbidity and mortality in new-borns resulting in motor and cognitive impairment. Therapeutic hypothermia is the only approved treatment for HIE, but it is only partially effective. There are currently no

pharmacological agents available to treat HIE in newborns. Therefore, it is essential to develop alternative and/or adjunctive novel therapeutic agents to attenuate the sequela resulting from HIE. Inflammation, neurovascular unit (NVU) damage as well as mitochondrial dysfunctions are key contributors to the pathophysiology of HI-related brain injury that all represent exciting potential targets for therapeutic intervention. We sought to develop a novel pharmacological agent based on an innovative trisubstituted purine derivative, BRT_002, which potentially could target multiple biological systems and compartments within the central nervous system (CNS) and attenuate HI-related injury in the neonatal brain. We previously determined that BRT_002 improves neurovascular functions, mitochondrial function, and reduced neuroinflammation after neonatal moderate HI. In this study, the neuroprotective effect of BRT_002 has been assessed in a neonatal rat Rice Vannucci model of severe HI (8% oxygen for 150 min). Sham and HI exposed P7 rats received BRT_002 (30 mg/kg, immediately, 24, and 48 h after HI) or placebo. Three groups (sham, HI + placebo and HI + BRT_002) underwent motor tests (Righting Reflex (P7-P10), the Ambulation test (P8-P10), the Grid test (P14-P16), and the Wire test (P14-P16)) to evaluate early effects. The data highlighted a motor deficit due to HI with a sex-specific response and an improvement with the BRT_002 treatment. The long-term effect on memory of the BRT_002 was assessed by the Novel Object Recognition (NOR) test (P28-29). Results revealed memory impairment in the "HI + placebo" group and restoration with BRT_002 treatment in males. Finally, spatial learning was evaluated by the Morris Water Maze (MWM) (P28-P34) showing an HI-induced spatial learning impairment and a significant improvement with the treatment in both sexes. Finally, the animals underwent MRI scans to evaluate the extent of the brain injury with and without BRT_002 treatment. The findings confirm that BRT_002 provides short- and long-term neuroprotection against HI in neonate rats improving their motor and cognitive HI-induced deficits. In conclusion, the study presents encouraging preclinical findings that could potentially serve as a basis for phase I clinical trials.

Disclosures: C. Disdier: None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.03/J8

Topic: D.02. Ischemia

Support: Canadian Institutes of Health Research (CIHR) to ZPF (PJT-191824)
Heart and Stroke Foundation of Canada (HSFC) to HSS (G-23-0035032)

Title: Trpm7 kinase inhibition provides neuroprotection and attenuates neuroinflammation in neonatal hypoxic-ischemic brain injury

Authors: *X. ZHANG[1], Z. LUO[2], Z.-P. FENG[3], H.-S. SUN[2];
[1]Dept. of Physiology, Dept. of Surgery, Temerty Fac. of Medicine, Univ. of Toronto, Toronto, ON, Canada; [2]Dept. of Physiology, and Dept. of Surgery, Temerty Fac. of Medicine, Univ. of

Toronto., Toronto, ON, Canada; [3]Dept. of Physiology, Temerty Fac. of Medicine, Univ. of Toronto., Toronto, ON, Canada

Abstract: **Introduction:** Hypoxic-ischemic brain injury (HIBI) describes deleterious brain damage that occurs perinatally and causes significant neonatal mortality and disability worldwide, yet its therapeutics remain limited. Transient receptor potential melastatin 7 (TRPM7) is a unique channel-kinase containing a divalent cation channel and an atypical α-kinase domain, plays a critical role in ischemic and hypoxic brain damage. While its channel activity has been extensively studied, the kinase domain remains less understood in HIBI pathophysiology. **Objective:** To investigate whether TG100-115 (TG), a novel and potent pharmacological inhibitor against TRPM7 kinase, provides both short- and long-term neuroprotection against HIBI *in vivo*. **Materials and Methods:** An *in vivo* HIBI model was established in postnatal day 7 CD-1 mice. Brain injury was quantified using both histological and morphological measurements, and neurobehavioral assessments were performed to examine functional outcomes. The dose response of TG was tested. Western blot, immunohistochemistry, and confocal imaging were used to evaluate the potential mechanisms of the drug. **Results:** Among 3 effective doses, TG 2.5 mg/kg pre-HIBI treatment significantly reduced brain infarction. Post-treatments up to 3 (1, 2, and 3) hours after HIBI also decreased infarction, illustrating the therapeutic time window. Multiple treatment paradigms of TG preserved brain morphology and body weight following HIBI, and enhanced short-term behavioral performance in the cliff avoidance, geotaxis, righting reflex, and grip strength tests at 7 days post-injury. Long-term behavioral outcomes (accelerated rotarod, novel object recognition, and passive avoidance) were also improved, indicating TG's long-term neuroprotection against HIBI. Furthermore, TG treatments: (1) reduced HIBI-induced caspase-3 cleavage and apoptosis, preserving neuronal integrity; (2) downregulated the elevated TRPM7 expression in HIBI; and (3) inhibited microglial activation and NLRP3 inflammasome-mediated neuroinflammation in HIBI. **Conclusion:** TG shows neuroprotection and anti-inflammatory effects against HIBI.

Disclosures: X. Zhang: None. **Z. Luo:** None. **Z. Feng:** None. **H. Sun:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.04/J9

Topic: D.02. Ischemia

Support: NIH RO1EY033902-S1
NIH RO1EY033902

Title: Targeted therapeutic potential of functionally engineered extracellular vesicles overexpressing miR-22-3p.

Authors: *D. OGBU[1], S. ROTH[2];
[1]Univ. of Illinois at Chicago, Chicago, IL; [2]Anesthesiol., Univ. of Illinois, Chicago, IL

Abstract: Central retinal arterial occlusion (CRAO) induces retinal injury, ultimately leading to vision loss. Extracellular vesicles (EVs) derived from dental pulp stem cells are neuroprotective due to neural crest origins. Our past work shows that DPSC EVs reduce retinal ganglion cell dysfunction, which may be attributable to microRNA (miRNA/miR) within EVs and contribute to their potent neuroprotective and anti-inflammatory properties. We previously showed that inflammatory preconditioning of DPSC EVs resulted in EVs with enhanced anti-inflammatory properties. We profiled miRs within the EVs of inflammatory-preconditioned DPSCs and chose miR-22-3p as a leading candidate. MicroRNA-22-3p is well known for its anti-inflammatory and anti-apoptotic actions. Here, we characterize the neuroprotective potential of DPSC EVs overexpressing miR-22-3p, termed functionally engineered EVs (FEE-22). We hypothesize that DPSC EVs overexpressing miR-22-3p (FEE-22) will alleviate retinal injury after ischemia. To generate FEE-22, the DPSCs were transfected with a lentiviral system containing miR-22-3p and a GFP marker. Following stable selection with puromycin, we confirmed GFP in DPSCs and the selective overexpression of miR-22-3p in the EVs derived from these DPSCs using RT-qPCR. For an in vitro model, we exposed retinal R28 cells to hypoxia for 6 h, then incubated them with EVs for 18 h. Then, we performed RT-qPCR to measure pro-apoptotic genes. To measure the functional efficacy in vivo of FEE-22 vs. PBS (n=6 per group), we conducted electroretinography (ERG) in a rat model of retinal ischemia. We measured flicker response to assess photoreceptors and pattern ERG (PERGs) to determine the functional response of retinal ganglion cells (RGCs). ERGs were recorded at baseline, day 7, 14, and 28 days after ischemic insult. The left eye was a non-ischemic control, and the right was ischemic. A two-way ANOVA was used for statistical analysis. Next, we quantified RGC counts in flat mounts and examined Muller cells and microglial expression in cryosections. We successfully generated DPSCs overexpressing miR-22-3p at 14-fold vs native EVs. In R28 cells exposed to hypoxia, FEE-22 robustly decreased *Caspase3*, *Bax*, and *p53* mRNA levels. In the in vivo study, FEE-22 ischemic eyes trended towards an increased amplitude of flicker and pERG, which was not present in the PBS-treated eyes. In conclusion, FEE-22 ameliorated apoptotic markers on a molecular level, rescued retinal function, preserved RGC, and reduced Muller cell and microglial expression.
This project is funded by NIH RO1EY033902 (to Dr. Roth and Dr. Ravindran), NIH RO1EY033902-S1.

Disclosures: D. Ogbu: None. **S. Roth:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.05/J10

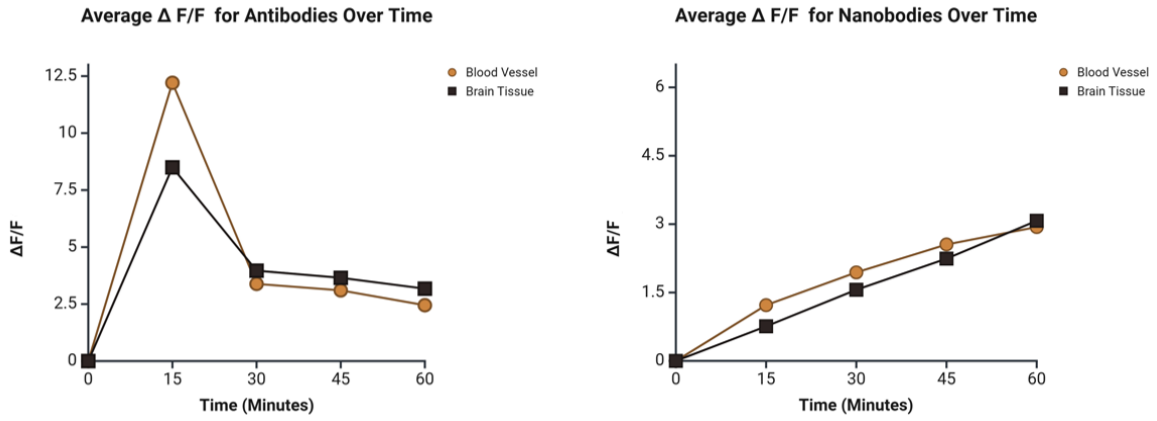
Topic: D.02. Ischemia

Support: NIH Grant 1R01EY030841
ARPA-H THEA

Title: Investigating Galectin-3 as a therapeutic target in retinal ischemia/reperfusion injury

Authors: *E. M. ESCH[1], J. BARRETO[2], B. SCHOLL[3];
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Abstract: Retinal ischemia/reperfusion (I/R) injury elicits an acute inflammatory response that contributes to retinal ganglion cell (RGC) damage and visual impairment. Galectin-3 (Gal-3), a β-galactoside-binding lectin expressed by activated microglia and macrophages, has been implicated in neuroinflammation following CNS injury but remains understudied in the retina. Our initial studies have validated a murine I/R injury model using transient intraocular pressure elevation, demonstrated increased expression of inflammatory markers and RGC death by Western blot and histological analysis, and confirmed CNS and retinal delivery of fluorescently labeled Gal-3-targeting antibodies and nanobodies following systemic injection. Future work will assess the therapeutic potential of Gal-3 modulation using Gal3 knockout mice, pharmacologic and biologic inhibition, and additional structural and functional readouts. This project aims to clarify Gal-3's role in retinal I/R pathology and explore its utility as a therapeutic target to preserve visual function after injury.



Disclosures: E.M. Esch: None. **J. Barreto:** None. **B. Scholl:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.06/J11

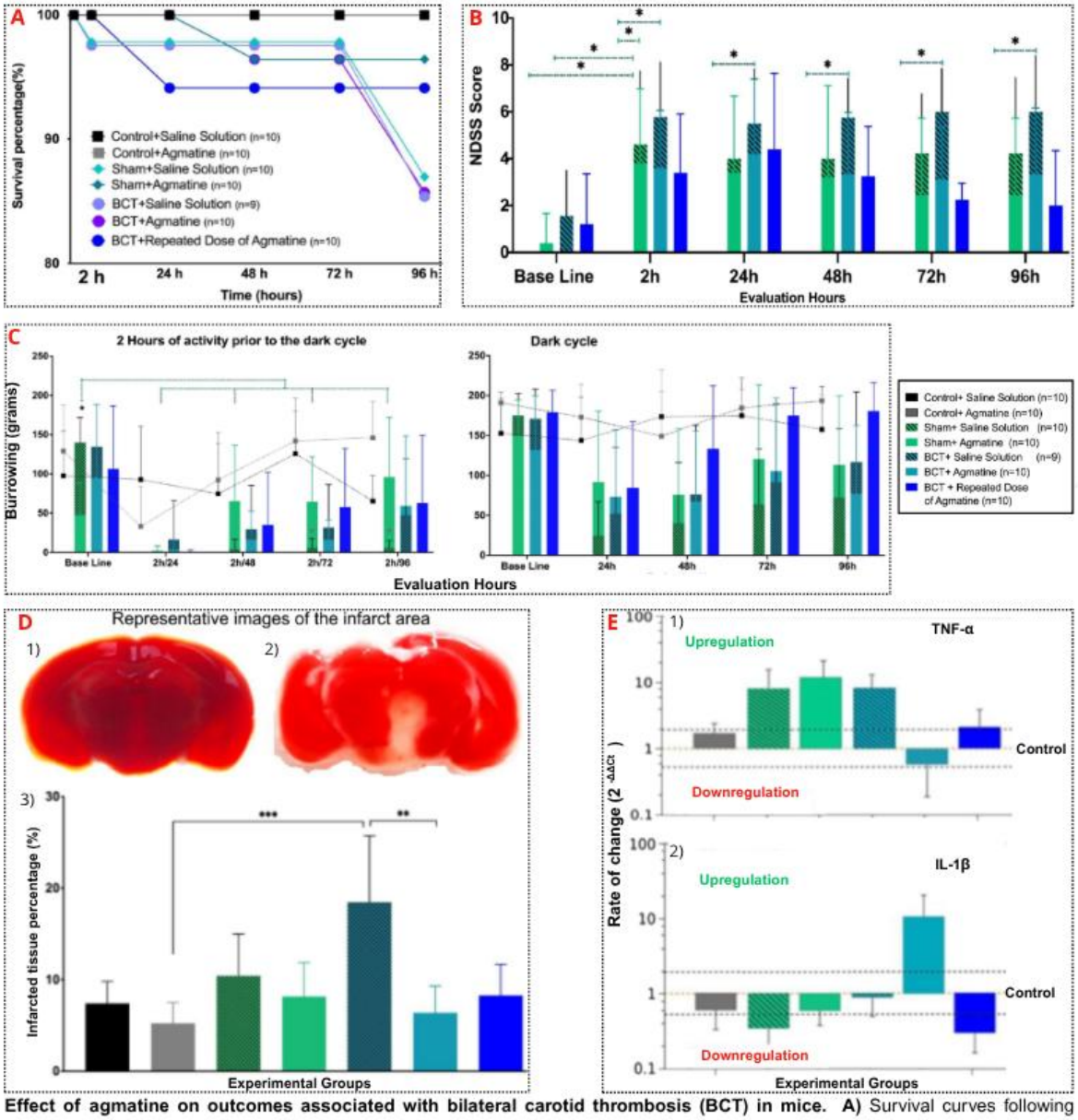
Topic: D.02. Ischemia

Support: PhD fellowship support (ID 913949)
This work was supported by Facultad de Medicina, Universidad Nacional Autónoma de México.

Title: Agmatine Mitigates Brain Damage in Recurrent Ischemic Stroke: A Preclinical Study

Authors: *M. MIRANDA-MOSQUEDA[1], C. GOMEZ[2];
[1]Pharmacol., UNAM, México, Mexico; [2]Pharmacol., Natl. Univ. Mexico, Mexico, Mexico

Abstract: OBJECTIVE To propose a pharmacological alternative with neuroprotective effects against recurrent cerebrovascular events, and potential as an adjuvant in functional recovery after ischemic damage. Stroke is a major global health issue, is the third leading cause of death ant the primary cause of disability in older adults. In 2019 it accounted for the loss of 143 million disability adjusted life years and generated a substantial hospital burden. The risk of acute stroke increases after a transient ischemic event; one in three individuals progresses with a half doing so within 12 months. Ischemic stroke wich accounts for 85% of cases, results from a transient or permanent reduction in cerebral blood flow due to thrombotic or embolic obstruction. This leads to irreversible cellular damage and activates several biochemical processes known as the ischemic cascade. Agmatine is a biogenic amine naturally found in various foods. Recent studies have described its benefits in treating central nervous system disorders, attributed to antiinflammatory actions (NFκB and metalloproteinases inhibition, proinflammatory cytokines reduction and eNOS increase) METHODS *Bilateral carotid thombosis (BCT)* thrombus formation was induced by topical application of $FeCl_3$ on both common carotid arteries, one per event, 32 days apart. *Burrowing test* assesment of nesting behavior, a task sensitive to hippocampal dysfunction. *NDSS test* Evaluation of neurobehavioral deficits using a scale analogous ti the NIHSS. *Infarct area quantification* Brain sections stained with 2,3,5-triphenyltetrazolium chloride (TTC), wich detects mitochondrial activity. *Quantification of proinflammatory cytokines (RT-qPCR)* mRNA expression of IL-1β and TNF-α. *Treatment* Agmatine (100 mg/kg) or saline administered 15 min after the second surgery in the BCT model. CONCLUSIONS Agmatine treatment enhances neurological recory and reduces tissue damage, supporting its potential as a neuroprotective agent for cerebrovascular disease. Further studies are needed to clarify its mechanisms and optimal dosing for clinical use.



Effect of agmatine on outcomes associated with bilateral carotid thrombosis (BCT) in mice. **A)** Survival curves following single or repeated agmatine administration, analyzed using the Kaplan–Meier method and log-rank test. **B)** Neurological dysfunction assessed by the NDSS scale. Data are presented as mean ± SEM; *p < .05 (Kruskal–Wallis followed by Dunn's test). **C)** Burrowing behavior recorded over 4 days during the first 2 h of the active phase and again 24 h later. Values are expressed as mean of averages ± SEM; *p < .05. **D)** Coronal brain sections (1 mm) showing mitochondrial activity staining. *(1)* Control (saline); *(2)* BCT (saline); white/pink areas indicate infarcted tissue. *(3)* Quantification of infarct size is presented as mean ± SEM; **p < .05, ***p < .01. **E)** Relative mRNA expression of TNF-α *(1)* and IL-1β *(2)* normalized to reference gene levels. Data are shown as fold change (mean ± SEM); Kruskal–Wallis test with Dunn's post hoc analysis.

Disclosures: M. Miranda-Mosqueda: None. **C. Gomez:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.07/J12

Topic: D.02. Ischemia

Support: Research Division, Faculty of Medicine, UNAM

Title: Evaluation of the neuroprotective effect of agmatine in female mice with recurrent ischemic stroke

Authors: *S. Y. RUIZ[1], M. L. MIRANDA MOSQUEDA[3], C. GOMEZ[2];
[1]Pharmacol., Univ. Nacional Autónoma de México, Mexico City, Mexico; [2]Pharmacol., Univ. Nacional Autónoma de México, Mexico, Mexico; [3]Pharmacol., Univ. Nacional Autónoma De México, México, Mexico

Abstract: Cerebral ischemia represents a major global health concern, accounting for approximately 85% of all cerebrovascular disease cases, which collectively constitute the second leading cause of death worldwide. Despite their prevalence and impact, the development of effective neuroprotective strategies remains an unfulfilled clinical need particularly in females. In this population different factors frequently contribute to delayed medical intervention, resulting in disproportionately higher rates of mortality, disability, depression, and dementia. Our research group proposes agmatine, a biogenic amine, as a potential neuroprotective agent with modulatory activity across multiple components of the ischemic cascade. Notably, it has been shown to attenuate inflammatory responses that exacerbate neuronal injury. Subjects Female CD1 mice (16 weeks of age) Ovariectomy Bilateral removal of the ovaries to induce estrogen deficiency Bilateral Carotid Thrombosis (BCT) Induced via topical application of $FeCl_3$ to one common carotid artery, followed by contralateral application 32 days later to model recurrent ischemia Burrowing Test Employed to quantify spontaneous burrowing behavior, a sensitive measure of hippocampal function and recovery following injury Neurological Deficit Severity Score (NDSS) Utilized to assess the severity of neurobehavioral impairments following ischemic insult Treatment Animals received intraperitoneal agmatine (100 mg/kg) or vehicle 15 minutes after the second thrombotic event. Results: Agmatine treatment led to an overall reduction in neurobehavioral deficits and enhanced burrowing performance. These findings suggest that agmatine confers neuroprotective effects in the context of repeated cerebral ischemic events, and that such effects are modulated by systemic physiological demands. Collectively, our data provide novel insights into sex-specific mechanisms of ischemic injury and recovery, supporting the development of personalized therapeutic strategies that address the distinct clinical needs of women.

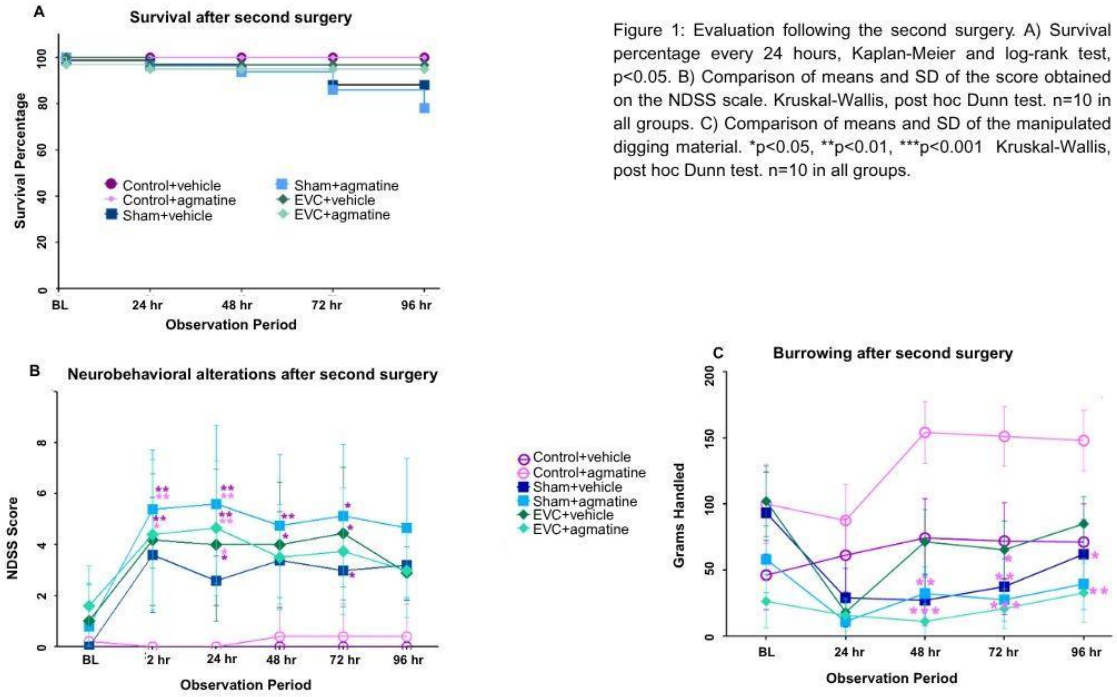


Figure 1: Evaluation following the second surgery. A) Survival percentage every 24 hours, Kaplan-Meier and log-rank test, $p<0.05$. B) Comparison of means and SD of the score obtained on the NDSS scale. Kruskal-Wallis, post hoc Dunn test. n=10 in all groups. C) Comparison of means and SD of the manipulated digging material. *p<0.05, **p<0.01, ***p<0.001 Kruskal-Wallis, post hoc Dunn test. n=10 in all groups.

Disclosures: S.Y. Ruiz: None. **M.L. Miranda Mosqueda:** None. **C. Gomez:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.08/J13

Topic: D.02. Ischemia

Support: R01 NS119395
1T32MH132518
P51 OD010425

Title: Acute accumulation of phosphorylated tau and oxidative stress following ischemic stroke in a non-human primate model

Authors: *N. STANIS[1], A. NOLAN[2], H. JAHANIAN[3], A. YAZDAN-SHAHMORAD[4]; [1]Univ. of Washington, seattle, WA; [3]Radiology, [4]Bioengineering and Electrical Engin., [2]Univ. of Washington, Seattle, WA

Abstract: The connection between vascular disease and Alzheimer's disease remains poorly understood, despite growing evidence that cerebrovascular injury increases the risk of developing dementia. In particular, ischemic stroke is a major vascular event that often precedes or accelerates cognitive decline, yet the molecular pathways linking acute vascular damage to Alzheimer's pathology are unclear. To investigate these mechanisms, we use a non-human primate model of ischemic stroke induced via photothrombotic lesioning, focusing on early biomarker changes during the acute phase (4 hours to 7 days post-stroke). We assessed the accumulation of phosphorylated tau markers (pTau-S422 and AT8), of early conformational changes leading to neurofibrillary tangles in Alzheimer's disease, using immunohistochemistry. We detected phosphorylated tau in the peri-infarct region as early as 4 hours post-stroke, with accumulation persisting through day 7. To explore a potential mechanism for this tau pathology, we examined oxidative stress using 8OHDG, a marker of mitochondrial damage commonly found near amyloid plaques in Alzheimer's disease. We observed increased oxidative stress in the peri-infarct tissue but not in the contralesional hemisphere. These findings suggest that vascular injury may initiate Alzheimer's-like pathology through oxidative stress-mediated tau phosphorylation. This non-human primate model offers a valuable platform for studying the vascular contributions to dementia and for testing potential therapeutic interventions targeting early tau pathology.

Disclosures: N. Stanis: None. **A. Nolan:** None. **H. Jahanian:** None. **A. Yazdan-Shahmorad:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.09/J14

Topic: D.02. Ischemia

Support: Penn Institute for RNA Innovation #4820

Title: Harnessing lipid nanoparticles for post-stroke recovery: a novel therapeutic paradigm

Authors: *I. GOLYNKER[1], S. PIETRZAK[1], H.-T. HUANG[1], S. REYES-ESTEVES[2], K. MORRIS-BLANCO[1];
[1]Cell and Developmental Biol., [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: This study seeks to investigate the clinical potential of lipid nanoparticles (LNPs) for targeted delivery in the rodent brain after stroke. Stroke is a leading cause of death and disability worldwide and is a growing health and economic burden with limited therapeutic options. A major challenge in understanding the clinical potential of therapeutic agents in stroke is the absence of studies utilizing efficient post-stroke delivery to the brain in a translationally relevant model. LNPs encapsulate therapeutic cargo, including mRNA, have recently risen to prominence with the success of COVID-19 vaccines, and have demonstrated effectiveness and safety. In this study, we utilized LNP delivery of Cre-recombinase (Cre) mRNA (mRNA-LNP) in adult male and female Ai6 mice to characterize the efficacy and distribution of LNP cargo in a mouse model of ischemic stroke. Ai6 mice express the green florescent protein ZsGreen1 upon introduction of Cre, making them useful reporter mice to study successful delivery of Cre mRNA cargo within LNPs. As a first step, we characterized changes to cerebral blood flow (CBF) in Ai6 mice subjected to 1h of transient Middle Cerebral Artery Occlusion (MCAo) and subsequently treated with an intracerebroventricular (ICV) injection of mRNA-LNP. We found that both male and female Ai6 mice treated with mRNA-LNP exhibited comparable reduction and subsequent elevation in CBF to wild-type (WT) mice during and 24h after MCAo, respectively. Furthermore, the brains of both male and female Ai6 mice showed similar brain lesion size compared to their WT counterparts 24h after MCAo. Next, to test LNP cargo systemic distribution in mRNA-LNP-treated mice, male and female Ai6 mice were injected various amounts of mRNA-LNP ICV (0, 0.05, 0.2, 0.8, and 1.75ug) as well as intravenously (IV) (0.8ug), and ZsGreen1 fluorescence was quantified using whole-body IVIS imaging 24h after injection. Increased ZsGreen1 signal compared to both vehicle and 0ug ICV was detected across many organs, including the brain, in mice treated with both 0.8 and 1.75ug mRNA-LNP injected ICV, as well as in mice treated with 0.8g IV, indicating successful systemic mRNA delivery using LNPs. Fluorescence imaging confirmed ZsGreen1 expression specifically in the cortex of IV- and ICV-treated mice. Immunostaining for neuronal and glial markers (NeuN, GFAP, and CD11b) within the cortex confirmed the expression of ZsGreen1 in neurons, astrocytes, as well as macrophages. Taken together, these results suggest LNP-mediated delivery of Cre-expressing mRNA is a viable mode of therapeutic cargo delivery in an experimental model of stroke.

Disclosures: I. Golynker: None. **S. Pietrzak:** None. **H. Huang:** None. **S. Reyes-Esteves:** None. **K. Morris-Blanco:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.10/J15

Topic: D.02. Ischemia

Title: S0859 Attenuates Neuroinflammation and Protects Blood-Brain Barrier Integrity in MCAO-Induced Stroke Mice

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Abstract: Cerebral ischemia/reperfusion (I/R) injury during ischemic stroke can lead to devastating outcomes, particularly blood-brain barrier (BBB) disruption, which further exacerbates cerebral edema and hemorrhagic transformation. Our previous study demonstrated that S0859, a Na^+/HCO_3^- cotransporter inhibitor, protects against I/R-induced neuronal death in the CA1 region, reduces astrocyte accumulation, and mitigates spatial memory impairment. However, its effects on BBB integrity have yet to be determined. Therefore, in this study, we employed a transient middle cerebral artery occlusion (MCAO) mouse model to investigate S0859's role in preserving BBB function. We found that intraperitoneal administration of S0859 (30 mg/kg) immediately after reperfusion significantly reduced infarct volume and improved motor function. Notably, S0859 attenuated I/R-induced BBB disruption, suppressed neuroinflammation, and rescued neurons from loss and apoptosis following ischemic stroke. In vitro, S0859 alleviated lipopolysaccharide (LPS)-induced endothelial leakage in bEnd.3 cells by modulating claudin-5 expression. Furthermore, S0859 inhibited the release of inflammatory cytokines, consistent with our prior findings. Together, our results demonstrate that S0859 provides neurovascular protection in cerebral I/R injury by preserving BBB integrity via claudin-5 regulation, attenuating neuroinflammation, and reducing neuronal apoptosis. These findings highlight S0859 as a promising multi-target therapeutic candidate for ischemic stroke.

Disclosures: L. Du: None. **X. Guo:** None. **J. Wu:** None.

Poster

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Title: Electronic cigarette exposure worsens stroke induced inflammation in female rats

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Abstract: The rise in popularity of nicotine-containing electronic cigarettes (ECs) globally necessitates a deeper understanding of their effects on stroke outcomes. This study investigates the influence of EC exposure on post-ischemic inflammation. Adult Sprague-Dawley rats of both sexes were randomly assigned to either air or EC vapor exposure (5% nicotine Juul pods) for 16 nights, followed by transient middle cerebral artery occlusion (tMCAO; 90 minutes) or sham surgery. Post-tMCAO animals were divided into three cohorts. In the first cohort, cortical brain tissue was collected 24 hours after tMCAO or sham surgery for Western blot analysis of inflammasome proteins. The second cohort was sacrificed 21 days post-tMCAO for immunohistochemical analysis of microglial marker ionized calcium-binding adapter molecule-1 (Iba-1). Microglial morphology was assessed via Sholl analysis with three cortical images analyzed per slide and three slides per subject. In the third cohort, ipsilateral cortical tissue was collected 16 days post-tMCAO for RNA sequencing. Quantification of Iba-1 indicated an increase in de-ramified microglia in the cortex of EC-exposed female rats as compared to air-exposed after tMCAO, potentially exacerbating post-stroke infarction. Microglial morphology analysis showed increased cell soma size and decreased branch length in EC-exposed female rats. Sholl analysis demonstrated reduced microglial complexity in EC-exposed group as compared to air-exposed after tMCAO, with a smaller area under the curve and fewer peak intersections in the cortex. RNA sequencing analysis revealed that EC exposure induced 443 upregulated and 453 downregulated genes in male rats, and 537 upregulated and 578 downregulated genes in females ($p<0.05$). In males, differentially expressed genes were enriched in pathways involved in membrane transport and signaling processes following EC exposure alone and immune modulation following ischemic injury in EC-exposed males. The female group showed EC-associated changes in synaptic structure and function, learning and memory, and cellular proliferation and genomic maintenance in the context of stroke recovery. EC exposure exacerbates stroke-induced inflammation and cognitive deficits in female rats. Future research should explore whether EC withdrawal mitigates ischemic severity and determine the necessary duration of withdrawal for potential recovery.

Disclosures: A.P. Raval: None. **I. Cabeda Diaz:** None. **S. Sinder:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

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Program #/Poster #: PSTR443.12/K1

Topic: D.02. Ischemia

Support: AHA Grant 24CDA1269588

Title: Transcranial near-infrared photobiomodulation promotes hippocampal remyelination and rescues working memory after chronic cerebral hypoperfusion in rats

Authors: *J. ZHANG[1], F. KONG[3,2], Z. HUANG[4], P. ZOU[5], Y. ZHANG[6], Q.-G. ZHANG[7], X. ZONG[8];
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Abstract: Objective and rationale Chronic cerebral hypoperfusion (CCH) impairs myelin integrity and memory. We asked whether transcranial photobiomodulation (PBM) at 810 nm or 1064 nm reverses CCH-induced damage in the bilateral common-carotid-artery-occlusion (BCCAO) rat model.Methods Adult male Sprague-Dawley rats (12 wk, 280 ± 20 g) were randomly assigned to sham (S, n = 10), BCCAO (M, n = 10), BCCAO + 810 nm PBM (L, n = 10) or BCCAO + 1064 nm PBM (H, n = 10). PBM was delivered daily (0.05 W cm^{-2}, 12.7 J cm^{-2}, 22 sessions). On day 29-30 working memory was assessed with the Y-maze and novel object recognition (NOR). Hippocampal tissue and blood were collected on day 30 for Western blot, immunohistochemistry and serum biochemistry. All behavioral scoring and band densitometry were performed blinded; β-actin served as loading control. Power analysis ($\alpha = 0.05$, $1-\beta = 0.8$) indicated a minimum of eight animals per group; we analysed ten. All findings were replicated in an independent cohort (not shown).Results BCCAO reduced spontaneous alternation (52 ± 4 %) versus sham (68 ± 3 %, $p < 0.01$, one-way ANOVA + Tukey) and NOR discrimination (0.18 ± 0.05 vs 0.42 ± 0.04, $p < 0.01$). PBM restored performance (810 nm = 64 ± 3 %; 1064 nm = 62 ± 4 %; both $p < 0.01$ vs BCCAO). Hippocampal myelin basic protein (MBP) dropped to 61 ± 7 % of sham after BCCAO but rose to 108 ± 8 % (810 nm) and 96 ± 6 % (1064 nm). Iba-1-positive microglia density and serum TNF-α/IL-6 fell by ~40 % in both PBM groups, while anti-inflammatory IL-10 increased 35 ± 6 %. Serum ALT, AST, BUN and creatinine remained within normal range in all groups.Conclusions Daily transcranial PBM at either 810 nm or 1064 nm reverses CCH-induced cognitive and myelin deficits, coincident with reduced neuro-inflammation, and does so without detectable systemic toxicity. These data support PBM as a non-invasive therapeutic candidate for vascular cognitive impairment and highlight wavelength-specific modulation of remyelination pathways.

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Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.13/K2

Topic: D.02. Ischemia

Support: NIH/NINDS NS124846

Title: Disrupting FOXO4 in non-neuronal cells protects neurons from ischemia/reperfusion caused neuronal injury

Authors: R. BERAGAMA ARACHCHI[1], *F. GORJIPOUR[1], Y. ASADI[2], H. WANG[1];
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Abstract: Abstract Transcriptional regulation is a key process that shapes how cells function and ultimately determines their fate. During ischemia-reperfusion (I/R) events, FOXO transcription factors play a particularly important role, both in vivo and in vitro settings. Previous studies have shown that under I/R conditions in mice, as well as during oxygen-glucose deprivation (OGD), FOXO4 acts to increase inflammation and oxidative stress in both animal and primary neuron mixed culture models. These findings recommend that reducing FOXO4 activity could help protect against I/R-related injury. **Method:** Mixed primary neuronal cultures containing all types of neural cells were established from FOXO4 global knock-out (KO), neuron-specific conditional KO, and wild-type mouse pups. All animals were sacrificed following approved institutional protocols for cell culture preparation. Neurons from each genotype were subjected to a 3-hour oxygen-glucose deprivation (OGD) to model ischemic conditions, followed by a 24-hour incubation period in normal culture conditions before assessing cell viability. Alternatively, to evaluate the responses of neuronal culture to oxidative stress, Menadione was added to the cultures for 24 hours. After treatment, cell viability was measured using a standard ATP assay or MTT assay kit. **Result:** Our study demonstrated that neuronal cultures derived from the global KO mouse pups exhibited improved cell viability compared to those derived from wild-type pups, as measured by both ATP and MTT assays. However, when assessing cell viability in the neuronal cultures derived from the neuron-specific KO pups, we did not observe any significant differences between the conditional KO and the control group. **Conclusion:** Our findings suggest that disrupting FOXO4 activity in non-neuronal cells is neuroprotective against oxidative stress and ischemia/reperfusion-caused cytotoxicity in vitro. Supported by NIH/NINDS NS124846.

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Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.14/Web Only

Topic: D.02. Ischemia

Support: Programa de Becas Posdoctorales UNAM

Title: Mexican Marigold neuroprotection in cerebral ischemia/reperfusion rat model

Authors: *K. L. MARTINEZ-GONZALEZ;
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Abstract: Stroke is the second leading cause of death all over the world, killing nearly 6.7 million individuals every year. Among of these stroke individuals, more than 80% patients account for cerebral ischemia, which are mainly contributed to the occlusion of a cerebral artery, this is one of the most common causes of disability and death in adults and represents a major burden in both western and developing countries worldwide. Multiple pathological processes are involved in I/R injuries, such as cell damage (apoptosis, necrosis, and ferroptosis), oxidative stress, inflammatory response, blood-brain barrier (BBB) breakdown, extracellular matrix (ECM) remodeling, angiogenesis, cardiomyocyte hypertrophy, and fibrosis. The increasing interest in studying the biological properties of Mexican marigold petals (*Tagetes erecta*) is primarily due to their high polyphenol content, which has been described in multiple species of edible flowers, the phytochemical composition of extracts from different parts of *Tagetes* species exhibits antioxidant, anti-inflammatory and enzyme-inhibiting properties; they are characterized by the presence of various compounds (phenylpropanoids, carotenoids, flavonoids, thiophenes and others). *Tagetes erecta* extract strongly inhibited GSK-3β kinase activity in vitro, increasing GSK-3β phosphorylation at SER9, which is indicative of its inactivation, and promoted β-catenin nuclear translocation. During cerebral I/R injury, the inhibition of Wnt/β-catenin signaling leads to mitochondrial damage, including excessive mitochondrial fission, cyt c release, caspase 9 activation, and subsequent caspase three activation, ultimately resulting in cell apoptosis. Based on the background of the antioxidant and anti-inflammatory activity of *T. erecta* reported in vivo and in vitro models in different diseases, we decided to probe neuroprotection of oral administration of the *Tagetes erecta* extract in a rat model of ischemia reperfusion by occlusion of the common carotid arteries (left and right), we observed reduction in levels of oxidative stress (nitric oxide, lipid peroxidation, and protein carbonylation), and increase in total antioxidant capacity and decrease in markers of neuroinflammation (activation of microglia and astrocytes) characteristic of the etiology of CVD in animals supplemented with Tagetes erecta extract. Our results demonstrate that *Tagetes erecta* exerts a neuroprotective effect in this ischemia/reperfusion rat model.

Disclosures: K.L. Martinez-Gonzalez: None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.15/K3

Topic: D.02. Ischemia

Title: Early exercise intervention alleviates neuronal myelin injury in cerebral ischemia rats by inhibiting endoplasmic reticulum stress-induced apoptosis.

Authors: *Q. WANG[1], J. ZHENG[2], X. QI[3], J. WANG[4];
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Exptl. Neurosci., Omaha, NE; [3]Ctr. for Translational Neurodegeneration and Regenerative Therapy, Shanghai, China; [4]Med. Sch. of Tianjin Univ., Tianjin, China

Abstract: Authors *Qiuheng Wang, Junyi Wang, Xinrui Qi , Jialin C. Zheng **Disclosures Qiuheng Wang**:None. **Junyi Wang**:None.**Abstract:**Ischemic strokes are triggered by a disruption in the blood supply to specific areas of the brain and are characterized by loss of myelin and death of oligodendrocytes (OLs). Endoplasmic reticulum stress (ERS) plays a crucial role in the pathophysiology of cerebral ischemia. Excessive or prolonged ERS leads to activation of apoptotic pathways. Studies have confirmed that therapeutic interventions that inhibit ERS-induced cell death provide neuroprotection and are promising in the treatment of ischemic stroke. In this study, we investigated the effects of exercise intervention on ERS and myelin repair after cerebral ischemia, to investigate the effect and potential mechanism of early exercise intervention on myelin. The rats were randomly divided into SHAM group, middle cerebral artery occlusion resting group (MCAO-SED) and middle cerebral artery occlusion exercise group (MCAO-EX). The exercise intervention lasted for 28 days. Before and after intervention, the changes of nerve function, cerebral infarction size, myelin structure and function, and ERS level were observed by means of nerve function score (mNSS), MRI scanning (T2), immunofluorescence, transmission electron microscopy, and expression of endoplasmic reticulum stress-related proteins, respectively. The ultrastructure of myelin sheaths was observed using transmission electron microscope (TEM), and the results showed that the myelin sheaths in the demyelinated areas of the outer capsule of the MCAO-SED group were thinner, with the damaged myelin layer splitting and expanding, and the myelin sheaths around the axons were discontinuously fractured with axons being loosely wrapped by abnormal myelin sheaths. The results in the MCAO-EX group showed increased integrity of myelin in the demyelinated area and denser myelin wrapping the axon. Immunofluorescence results showed that after 28 days of intervention, MBP expression in the striatum of the ischemic semi-dark band was significantly lower in the MCAO-SED group than in the SHAM group, and was significantly increased in the MCAO-EX group compared with the MCAO-SED group after exercise intervention. After 28 days of intervention, compared with the MCAO-SED group, the nerve function of the MCAO-EX group recovered well, infarct volume decreased, myelin integrity increased, MBP fluorescence intensity expression increased, and MBP expression level increased. The expression levels of ATF6, p-IRE1, p-PERK, cleaved caspase 3 were significantly decreased.

Disclosures: Q. Wang: None. **J. Zheng:** None. **X. Qi:** None. **J. Wang:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

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Program #/Poster #: PSTR443.16/K4

Topic: D.02. Ischemia

Support: NINDS Grant R01NS131484
CCDS Malcolm Feist Predoctoral Fellowship

Title: Role of TRAF3 and TRAF6 following ischemic stroke

Authors: *B. AKHTER, K. BROWN, N. AICH, M. BRADFORD, R. MARQUEZ-ORTIZ, E. WILLIAMS, K. RODGERS;
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Abstract: Background: Stroke is a devastating neurological disorder and a leading cause of disability around the world. Although both adults and children can experience neurological impairments after a stroke, the developing brain is known to have a greater capacity for repair and plasticity, allowing for greater functional recovery in pediatric stroke patients. We have observed significant neuronal regeneration and improved motor function 30 days after ischemic injury, using a juvenile mouse model of middle cerebral artery occlusion (MCAO), which is not found in adults. Our preliminary results suggest that juvenile repair and recovery is supported by beneficial immune responses following stroke, while immune responses are detrimental in stroke-injured adults. Stroke activates resident/adaptive immune cells, many of which express toll-like receptors (TLRs). These receptors engage TNF receptor-associated factor (TRAF) adaptor proteins, initiating complex inflammatory signaling pathways that can lead to both protective and damaging effects in the brain.
Methods: To investigate age-related immune signaling in juvenile and adult mice after stroke, we performed immunohistochemistry, gene expression profiling, western blots, neurobehavioral testing, and *in vivo* electrophysiology following immune inhibition.
Results: We found that MCAO-injured juveniles had increased gene expression in TLRs 7-9, stimulating TRAF3 pathway signaling and anti-inflammatory cytokine release (IL-10). In contrast, we found TRAF6 pathway activation and proinflammatory cytokine release in MCAO-injured adults. Surprisingly, adults also signaled through TRAF3 in a non-canonical loop back to the TRAF6 pathway, resulting in proinflammatory signaling via both pathways. Lastly, we found that immune suppression in juveniles resulted in loss of brain regeneration and electrophysiological recovery at 30d, and remarkably, rescued brain repair and plasticity in MCAO-injured adults.
Conclusions: These findings identify an important role for TLR-TRAF signaling in post-ischemic neuronal restoration and functional recovery in juveniles, providing new insights into brain injury in the young and novel targets for stroke treatment in adult/aging populations.

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Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.17/K5

Topic: D.02. Ischemia

Title: Piwil2 modulation mitigates neuroinflammation and stabilizes genomic integrity thus reducing brain ischemic damage

Authors: *R. PATIL[1,2], G. LAUDATI[1], N. DI MURAGLIA[1], S. ANZILOTTI[3], E. ESPOSITO[2], G. PIGNATARO[1];
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Abstract: *Background* - PIWIL proteins are a family of RNA-binding proteins involved in piRNA-mediated gene silencing. PIWIL proteins participate in germline preservation and transposon suppression, as well as germline stem cell differentiation and growth. The PIWIL protein family is related to PIWI-interacting RNAs (piRNAs), which are small RNAs 24-32 nucleotides long. These non-coding RNAs, along with their regulatory PIWIL proteins, play a specific role by potentially affecting proteins involved in the neurogenetic process. PIWIL proteins and piRNAs are significantly expressed in brain cells, particularly in hippocampal regions. Nevertheless, the role of PIWILs in stroke pathophysiology is not clear. *Aim* - This study aims to investigate the role of PIWIL proteins and piRNAs in stroke, their modulation in the brain and peripheral organs, and their impact on inflammation. *Method* - Male C57BL/6J mice were subjected to transient focal ischemia for 1 hr followed by 6 and 24 hours of reperfusion. The blood, cerebral cortex, heart, kidney, liver, and striatum were collected. A proinflammatory panel was utilized to assess cytokine and chemokine levels in plasma samples. RNA sequencing was performed using the Illumina platform, along with small non-coding RNA (sncRNA) sequencing to analyse expression patterns comprehensively. *Result* - In the affected region of the cortex and striatum, all PIWILs were downregulated after 6 hours of ischemia; however, they were upregulated after 24 hours. In addition, PIWIL2 expression increased in the blood, muscle, heart and kidney during both stroke time intervals, whereas the other PIWILs showed a different modulation. Notably, PIWIL1,2, and 4 were shown to express significant colocalization with the endothelial marker CD31 and with the neuronal marker NEUN in the immunofluorescence experiments conducted on brain slices from the cortical and striatal regions 24 hours after ischemia. Silencing PIWIL2 exacerbated proinflammatory responses, further elevating CCL5 and CXCL13 while restoring CCL11, CCL22, and CXCL9 levels compared to 24hrs hours ischemia in plasma. *Conclusions* - Acute inflammation in the brain caused by a stroke within 6 hours result in significant pathophysiological changes, such as downregulation of PIWIL proteins and mRNAs along with chemokine activities. Whereas severe ischemic injury after 24 hours causes extensive damage to neurogenic niches, potentially diminishing neuronal viability, PIWIL proteins and piRNAs play a role in reducing neuroinflammation and in stabilizing genomic integrity post-stroke, thus representing potential druggable target in stroke.

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Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR443.18/K6

Topic: D.02. Ischemia

Title: Neuroprotective effects of orally-administered curcumin and apoaequorin in a brain slice model of ischemic stroke

Authors: *D. SAFARINI[1], B. NATWORA[1], J. R. MOYER, JR.[2];
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Abstract: Stroke, a leading cause of death worldwide, is characterized by interrupted blood flow to the affected area, depriving it of key nutrients, including oxygen and glucose, which results in neuronal injury, followed by neuronal death. In ischemic stroke, apoptosis is one of the main causes of neuronal death. Morphological studies in rats have elucidated the increased vulnerability of CA1 pyramidal neurons to stroke, in comparison to parvalbumin positive interneurons in the hippocampus. Previously published data from our lab indicates that hippocampal infusions of the calcium-binding protein apoaequorin (AQ), isolated from the jellyfish *Aequorea victoria*, is neuroprotective when administered prior to oxygen-glucose deprivation, a commonly used *in vitro* model of ischemic stroke. Curcumin, a turmeric constituent, and one of the most widely studied natural medicines, has various biological functions including anti-inflammatory properties, antioxidant, and anti-apoptotic effects. The present study sought to evaluate whether oral administration of both curcumin and apoaequorin would be more impactful in protecting neurons from an ischemic stroke than either alone. Rats were initially acclimated by introducing 0.33 g of peanut butter (Skippy, natural calcium-free) each day for 3 days after which curcumin (10 mg/kg body weight) and/or apoaequorin (48 mg/kg body weight) were added daily to the peanut butter (for 3 consecutive days). Twenty-four hours after the 3rd dose, acute coronal brain slices containing the dorsal hippocampus were obtained from adult male and female Fisher 344 rats and placed in oxygenated artificial cerebrospinal fluid (aCSF). To model a transient ischemic attack (TIA), half of the slices from each animal were subjected to 5-min of oxygen-glucose deprivation (OGD), while the remaining slices remained in oxygenated-aCSF as controls. All slices were transferred to oxygenated-aCSF with 0.2% Trypan blue for 30-min, after which slices were fixed, subsectioned, and the number of trypan labeled neurons counted. Preliminary data demonstrate that relative to PB-fed rats, the addition of either curcumin or apoaequorin resulted in fewer Trypan labeled neurons in the control as well as the OGD-treated slices. In addition, administration of both curcumin and apoaequorin appeared to provide even more neuroprotection than either alone as measured by a further reduction in trypan-labeled neurons in OGD-treated slices. These data suggest a potential role for curcumin and apoaequorin in protecting hippocampal neurons from ischemic stroke and should inspire additional research aimed at understanding how this neuroprotection is achieved.

Disclosures: **D. Safarini:** 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.; CalciGenix, LLC. **B. Natwora:** 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.; CalciGenix, LLC.
J.R. Moyer, Jr.: 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.; CalciGenix, LLC.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

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Program #/Poster #: PSTR443.19/K7

Topic: D.02. Ischemia

Support: CalciGenix, LLC

Title: Impact of oxygen-glucose deprivation on the function and recovery of hippocampal ca1 neurons

Authors: *B. NATWORA[1], I. MORLEY[1], J. R. MOYER, JR.[1,2];
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Abstract: An ischemic stroke, the most prevalent stroke subtype, is a cardiovascular disease characterized by the loss of oxygen and nutrient-rich blood to the brain due to an occluded vessel. Under these pathological conditions, neurons within local networks exhibit homeostatic failure, which can influence changes in function and potentially lead to delayed death. Consequently, neuronal communication is compromised, triggering life-altering cognitive impairments in survivors. Although it is understood that an ischemic stroke irreversibly destroys parenchymal tissue, some findings suggest that neuronal function can be restored following such a traumatic event, opening questions for further research on prevention and recovery. Given that the hippocampus is a primary candidate for exploring post-stroke dementia, the present study investigated the impact of oxygen-glucose deprivation (OGD) on neuronal function and recovery of CA1 pyramidal neurons in male F344 rats. To evaluate the impact of OGD on neurophysiological properties, biocytin-filled patch electrodes were used to obtain whole-cell recordings from visually identified CA1 pyramidal neurons *before*, *during*, and *after* an ischemic insult. For each experiment, brain slices were transferred to a submerged recording chamber that was continuously perfused with oxygenated-aCSF at 32°C. Once a whole-cell recording was established, intrinsic properties and neuronal excitability were measured under current-clamp conditions. This allowed for an assessment of stability and the collection of baseline neurophysiological data. OGD was then introduced by switching to a perfusion line containing a solution of fructose-aCSF bubbled with 95% N_2/5% CO_2 for 5-minutes. During this ischemic phase, we observed a substantial change in basic membrane function as measured by a significant reduction in neuronal input resistance. This was observed immediately following the 5-min OGD and was also accompanied by a significant decrease in the amplitude of the

depolarizing sag that normally accompanies hyperpolarizing current injections. Remarkably, the input resistance and sag amplitude recovered to values comparable to baseline within around 20 minutes after switching back to oxygenated-aCSF. These observed changes imply a modulation of homeostatic function within hippocampal CA1 pyramidal neurons during a brief ischemic insult. Altogether, these data provide insights into unique mechanisms that may impact not only the functional integrity but also the survival and recovery of hippocampal CA1 neurons during an ischemic stroke, potentially offering avenues to restore both neuronal and cognitive functioning.

Disclosures: B. Natwora: None. **I. Morley:** None. **J.R. Moyer, Jr.:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.20/K8

Topic: D.02. Ischemia

Support: Sino-Danish Center for Education and Research
The Novo Nordisk Foundation (NNF 15OC0016674)

Title: Remote ischemic conditioning miRNAs affects brain endothelial cells during ischemia-reperfusion

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Abstract: Acute ischemic stroke (AIS) is one of the leading causes of death and disabilities, resulting in immediate cell death until treated. However, current recanalization treatments must be initiated within 4.5-6 hours of symptoms onset. Thus, novel treatments are in great demand. Remote ischemic conditioning (RIC) is a promising non-invasive treatment that is thought to activate the body's own protective mechanisms against damaging ischemia. We have found several circulating microRNAs (miRNAs) that change after RIC and have investigated their effect in an *in vitro* stroke model of human brain microvascular endothelial cells (HBMECs) subjected to oxygen and glucose deprivation (OGD) - mimicking the initial stages of AIS. Following transfection of HBMECs with four selected RIC-upregulated miRNAs (RIC-miRNAs); miR-16-5p, miR-144-3p, miR-182-5p, and miR-451a and OGD, RNA was extracted for RNA sequencing. Transcriptional changes were evident with 149 downregulated and 212

upregulated differentially expressed genes, which were specific to both RIC-miRNA transfection and OGD treatment. Pathway analysis of these genes showed them to be involved in cell cycle regulation, DNA replication, and various pathways of energy metabolism. Viability assays on immortalized HBMECs revealed that RIC-miRNAs constitute a cytoprotective effect against the damaging ischemia of the OGD treatment. The cytoprotective effect substantiates the involvement of molecular pathways linked to cell cycle activation which was evident from the transcriptional changes. In conclusion, the selected RIC-miRNAs activate pathways that help HBMECs return to normal physiological conditions after exposure to damaging ischemia. Thus, RIC may be used as an additional treatment to recanalization treatments, which will tweak HBMECs in a cytoprotective direction.

Disclosures: K. Stenz: None. **J. Just:** None. **T.R. Lassen:** None. **K. Vissing:** None. **X. Wang:** None. **K.R. Drasbek:** None.

Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

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Program #/Poster #: PSTR443.21/K9

Topic: D.02. Ischemia

Support: NIH (1R01NS117606)
NSF (1916894)
NIA (1R01AG073659)
UTHealth New Faculty Start-up

Title: Endothelial-targeted miR-34a knockout attenuates ischemic stroke pathology and improves sex-specific behavioral outcomes in mice

Authors: *S. TABASSUM, H. HU, L. DENG, J. DAVIS, A. GUSDON, H. CHOI, X. S. REN; The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Ischemic stroke is a leading cause of mortality and long-term disability, with limited therapeutic options targeting neurovascular protection. Endothelial cells (ECs) are essential for maintaining blood-brain barrier (BBB) integrity; however, ischemic injury impairs EC function, increases vascular permeability, and exacerbates stroke pathology. MicroRNA-34a (miR-34a) disrupts EC mitochondrial function and tight junction stability, contributing to BBB breakdown. While our previous study demonstrated the protective effects of global miR-34a depletion in stroke models, its endothelial-specific role remained unknown. To address this, we generated a novel EC-specific miR-34a knockout mouse model (miR-34a$^{fl/fl}$ Cre^{+}) using Cre-lox technology and subjected the mice to transient middle cerebral artery occlusion (tMCAO). At 24 hours post-stroke, miR-34a$^{-/-}$ mice exhibited significantly reduced BBB permeability, smaller infarct volumes, and improved neurological scores compared to wild-type controls, in both sexes. Behavioral testing at three weeks post-stroke revealed sex-dependent improvements: both sexes

showed increased latency to fall on the rotarod, indicating enhanced motor coordination. Spatial working memory was significantly improved in males, with a similar trend observed in females. Notably, improvements in both recognition memory and spatial learning were exclusive to female miR-34a$^{-/-}$ mice, as demonstrated by enhanced novel object recognition and reduced escape latency, respectively. Immunostaining revealed increased expression of LETMD1, a mitochondrial inner membrane protein involved in calcium homeostasis and mitochondrial function, in CD31^{+} ECs within the infarcted regions of female miR-34a$^{-/-}$ mice, with a similar trend in males. The upregulation of LETMD1 suggests enhanced mitochondrial activity and integrity in ECs, which may underlie the observed improvements in BBB repair and functional recovery. These findings identify a critical, sex-specific role for endothelial miR-34a in stroke pathophysiology and highlight its potential as a therapeutic target for improving post-stroke outcomes.

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Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.22/K10

Topic: D.02. Ischemia

Title: A Translational Multi Model Platform for Preclinical Evaluation of Thrombolytics in Acute Ischemic Stroke

Authors: *A. LETOURNEUR[1], F. LEBRUN[1], H. LEBAS[1], M. BAGUENEAU[1], N. FISCHER[1], E. CLERGUE[1], N. VIOLLE[2], D. VIVIEN[3];
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Abstract: OBJECTIVE We established a translational preclinical platform using complementary rodent models of ischemic stroke to assess new thrombolytic candidates, with rt-PA or tenecteplase (TNK) as clinical benchmarks. We then applied this workflow to evaluate Microlyse, a novel thrombolytic agent.
BACKGROUND Despite decades of research, drug development for ischemic stroke has been hindered by translational issues, leading to clinical failures. We report a series of studies aiming to create a robust and versatile workflow of innovative rodent models enabling precise investigation of drug efficacy, mechanism of action, interactions with gold-standard fibrinolytics, and risks of hemorrhagic transformation (HT) and cerebral bleeding.
METHODS We developed a multi-model translational platform including:
• Two innovative and complementary mouse models of MCA occlusion inducing fibrin- or platelet-rich clots with differential responses to thrombolytics
• Inclusion of clinically relevant comorbidities (diabetes, hypertension)

• Translational and advanced imaging (laser speckle, MRI) to assess recanalization, reperfusion, infarct volume, HT, BBB disruption, and endothelial activation
• A novel neuroscore to monitor functional recovery over 5 weeks in rats
• A refined collagenase-induced ICH model to assess bleeding risks
• rt-PA or TNK used as reference comparators
RESULTS Alteplase improved recanalization and reduced infarct size in fibrin-rich clots within a narrow time window. Like Alteplase, Microlyse reduced lesion volume and improved reperfusion. Platelet-rich clots showed resistance to rt-PA, mimicking poor responders. In this model, Microlyse—unlike Alteplase—reduced lesion volume, showing superior efficacy. In rats, both rt-PA and Microlyse improved neuroscore, correlating with lesion volume at 5 weeks. In mice, comorbidities increased lesion size, HT, and neuroinflammation, while impairing fibrinolysis and enhancing rt-PA-related HT. In diabetic mice, Alteplase showed no benefit on lesion volume, while Microlyse remained effective, indicating broader applicability. In the collagenase model, TNK and some anticoagulants significantly increased bleeding.
CONCLUSIONS This multi-model platform offers a robust, translationally relevant tool for evaluating novel stroke therapies, enabling:
• Efficacy comparison with rt-PA or TNK
• Simulation of high-risk or non-responder subpopulations
• Early detection of safety or interaction risks
Integrated into a comprehensive workflow, these models have already supported development of several agents, including Microlyse, now advancing to clinical evaluation.

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Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.23/Web Only

Topic: D.02. Ischemia

Title: Evaluation of the Neurological Pupillary Index as a predictor of early craniotomy in patients with ischemic cerebrovascular disease a pilot study

Authors: D. ORTEGA DOMINGUEZ[1,2], J. ZEPEDA PÉREZ[2], J. CRUZ[2], G. CARDENAS[2], ***J. MARTINEZ-LAZCANO**[3];
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Abstract: Background: Ischemic cerebrovascular disease (CVD) has increased in frequency in recent years and is the leading cause of disability in adults and the second leading cause of dementia. In some cases, it is imperative to perform rapid and effective decompression in the

early stages of a CVD. Deciding who is a candidate for surgical decompression early on can remain a challenge. The objective of this work was to evaluate the neuropupillary index (NPI) to determine the need for decompressive craniotomy in patients with CVD. Methods: his case-control study was conducted, including patients aged ≥ 18 admitted to the intensive care unit of the INNN MVS during August to December 2024, pupillometry measurements were performed on 59 patients: the control group (patients without a diagnosis of stroke; n = 29) and the case group (patients diagnosed with DCV; n = 30). A data capture form was designed to collect the clinical and sociodemographic characteristics of patients, as well as tomographic findings to assess the EDEMA score and pupillometry data. Results: The groups presented statistically significant age differences (t (57) = 6.6, p < 0.0001), with 65 ± 17 years in the case group vs. 37 ± 15 years in the control group. Regarding the NPI, the mean in patients with right-sided ischemic stroke was 4.41 ± 0.30, on the left side 4.39 ± 0.35 vs 3.1 ± 1.8 on the right and 2.7 ± 2.00 on the left in controls. In cases of ischemic stroke, we found an ASPECT with a mean of 6.7 ± 3.09, in addition, the NIHSS showed that the highest percentage of presentations on the severity scale were moderate stroke (n = 22), followed by moderate/severe (n = 4) and severe presentation (n = 4). Conclusions: The neurological pupil index in ischemic stroke was not presented as a predictive option for early craniectomy because the NIP indices are greater than three.

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Poster

PSTR443: Ischemia: Therapeutic, Interventional, and Translational Studies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

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Topic: D.02. Ischemia

Support: United States (U.S.) Department of Veterans Affairs Biomedical Laboratory R&D (BLR&D) Service Merit Review Award 1I01BX006223-01A1
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Title: Therapeutic interventions for post-stroke rehabilitation

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Abstract: Rehabilitative therapy is critical for reducing stroke-related functional deficits; however, comorbidities may limit patient participation. Low-frequency whole body vibration

(LFV; 40 Hz) offers an exercise-like alternative. Our studies show that one month of post-stroke LFV reduces ischemic damage and improves motor and cognitive function in middle-aged rats. Notably, LFV significantly increased circulating irisin, a muscle-derived hormone. We hypothesize that post-stroke LFV modifies the cerebral transcriptome and that exogenous irisin treatment improves stroke outcome in middle-aged female rats. Middle-aged Sprague-Dawley rats were randomized to sham or transient middle cerebral artery occlusion (tMCAO; 90 min) surgery and divided into two cohorts. Cohort one received either no-LFV (steady platform) or LFV (40 Hz vibrating platform) for 15 minutes twice daily for a week. Cortical tissue was collected for RNA sequencing (RNAseq) and gene enrichment analysis. Cohort two received either saline or irisin (0.2 μg/g BW, PeproTech) at 4.5 hours post-tMCAO and then weekly for a month. Sensorimotor and cognitive function were tested using the cylinder test and Morris water maze (MWM) on Days 7 and 21, respectively. At 1-month post-tMCAO, brains were collected for histological analysis. RNAseq revealed significant ($p<0.05$) differential expression of 581 genes in the cortex due to LFV. Specifically, there was downregulation (log2(fold change) = -2.9; p= 0.03943) of Calcium Voltage-Gated Channel Auxiliary Subunit Gamma 7 (Cacng7) and calcium-release channel activity (GO:0015278), which are both implicated in excitotoxicity following stroke. The expression of Vacuolar Protein Sorting-Associated Protein 37C (Vps37c), a component of an endosomal sorting complex that mediates apoptosis, was also downregulated (log2(fold change) = -7.1; p= 0.01888). In our second cohort, rats treated with irisin for 1-month post-tMCAO, as compared to saline, demonstrated improved contralateral limb use by Day 7 and enhanced spatial learning in the MWM, reducing latency to find the hidden platform on the 4th day of testing (16.5 sec vs. saline; $p<0.05$) and increasing time spent in the target quadrant during the probe trial (9.3 sec vs. saline; $p<0.05$). Additionally, irisin treatment reduced infarct volume by approximately 30%, with mean infarct volumes of 167.68 ± 55.73 mm³ in the saline group and 117.71 ± 42.32 mm³ in the irisin group. Post-stroke LFV alters gene expression consistent with improved stroke outcome, and irisin treatment improves cognitive outcomes in middle-aged rats. Future studies will explore underlying mechanisms of irisin-conferred protection.

Disclosures: S.H. Patel: None. **H.M. Bramlett:** None. **A.P. Raval:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.01/K12

Topic: D.04. Brain Injury and Trauma

Support: NIH 5R01NS122724-04

Title: Evidence of a prolonged therapeutic window for senolytic drug therapy in mice after traumatic brain injury

Authors: *H. D. SINGH, J. WANG, Y. LU, C. CARR, K. M. DHANDAPANI, D. W. BRANN; Dept. of Neurosurg., Augusta Univ., Augusta, GA

Abstract: Traumatic brain injury (TBI) can lead to disability and death. Our previous study revealed that male mice receiving senolytic drug therapy, dasatinib and quercetin (D+Q), for 13 weeks starting at 1-month after TBI rescued cognitive decline and depressive-like behavior through ablation of senescent cells and decreased neurodegeneration. The goal of the current study was to examine whether a prolonged therapeutic window exists for functional benefit of D+Q after TBI. For our current study, adult male mice were subjected to controlled cortical impact (CCI) to induce moderate TBI. Sham mice that had no cortical impact were used as controls. Twelve to fourteen months after TBI, vehicle or intermittent weekly D+Q treatment was administered for 13 weeks by oral gavage. The novel object recognition test was used to evaluate hippocampal-dependent recognition memory, while the forced swim test was used to evaluate depressive-like behavior. Expression of the senescent markers, $p19^{INK4D}$ and $p21^{Waf1/Cip1}$ was also evaluated in the perilesional cortical tissue using Western blot analysis. The results of the novel object recognition test revealed that intermittent weekly D+Q treatment initiated 12 to 14 months after TBI for 13 weeks was able to rescue defects in hippocampal-dependent recognition memory in TBI mice. Similarly, the forced swim test revealed that D+Q treatment significantly rescued depressive-like behavior in TBI mice. Finally, D+Q treatment significantly reduced the expression of $p19^{INK4D}$ and $p21^{Waf1/Cip1}$ in the perilesional cortex of TBI mice. To our knowledge, this is the first long-term study to demonstrate therapeutic potential of D+Q initiated 12 to 14 months after TBI. Our overall results suggest that a prolonged therapeutic window exists for therapeutic benefit of the senolytic compounds, D+Q after TBI.

Disclosures: H.D. Singh: None. **J. Wang:** None. **Y. Lu:** None. **C. Carr:** None. **K.M. Dhandapani:** None. **D.W. Brann:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.02/K13

Topic: D.04. Brain Injury and Trauma

Support: SECIHTI Grant 839363
SECIHTI-PRONACE Grant 322515

Title: Subchronic intranasal administration of NeuroEPO reduces long term consequences of severe traumatic brain injury in male rats

Authors: *F. LÓPEZ PREZA[1], M. NUÑEZ LUMBRERAS[1], L. CONCHA[2], A. FERNÁNDEZ-GUASTI[1], L. L. ROCHA[1];
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Abstract: Traumatic brain injury (TBI) causes persistent deficits and remains a major health issue. Current therapies fail to prevent long-term effects like neurodegeneration. NeuroEPO, a low-sialic erythropoietin, has shown neuroprotective effects in studies. We evaluated the effects of intranasally administered NeuroEPO (0.136 mg/kg), delivered 3 hours post-injury and every 8 hours for 4 consecutive days in male Wistar rats subjected to severe TBI using the lateral fluid percussion injury model. Behavioral, biochemical and magnetic resonance imaging (MRI) assessments were conducted throughout a 31-day period. Compared to sham animals, vehicle-treated TBI rats exhibited sustained sensorimotor impairments (Neuroscore, -28.8%, $p<0.0009$; beam walking test, -42.6%, $p<0.0001$,) depressive-like behavior (12.3 ± 1.9 counts of immobility, $p=0.0009$ vs baseline), elevated levels of malondialdehyde (MDA) (cortex ipsi-, 230.7%, $p<0.0001$ and contra-, 182.7%, $p<0.0001$; hippocampus ipsi-, 462.3%, $p<0.0001$ and contra-, 203.5%, $p<0.0001$; amygdala ipsi-, 194.2%, $p<0.0001$ and contra-, 119.3%, $p=0.005$; thalamus: 193.1%, $p<0.0001$ and hypothalamus: 332.0%, $p=0.0001$), increased catalase activity (cortex ipsi-, 720.3%, $p=0.001$ and contra-, 459.3%, $p=0.007$; hippocampus ipsi-, -241.1%, $p=0.017$ and contra-, 228.0%, $p=0.083$; amygdala ipsi-, 204.6%, $p=0.0003$ and contra-, 121.6%, $p=0.040$; thalamus: 612.1%, $p<0.0001$ and hypothalamus: 699.6%, $p<0.0001$) and brain atrophy evident on MRI (cortex ipsi-, and contra-, $p=0.001$; hippocampus, $p=0.0009$; amygdala ipsi-, $p=0.041$ and contra-, $p=0.023$; thalamus: $p=0.044$; and hypothalamus $p=0.007$). NeuroEPO-treated TBI rats showed a better motor performance (Neuroscore, $p=0.020$ and beam walking test, $p=0.001$, compared to vehicle-treated TBI rats). In comparison to sham animals, NeuroEPO-treated TBI rats showed similar depressive like behavior ($p=0.998$), biochemical profiles (MDA: cortex: ipsi-, $p=0.912$; contra-, $p=0.997$; hippocampus: ipsi-, $p<0.999$; contra-, $p=0.997$; thalamus: $p=0.630$ and hypothalamus: $p=0.491$; catalase activity: cortex: ipsi-, $p>0.999$; contra-, $p=0.991$; hippocampus: ipsi- and contra-, $p>0.999$; amygdala: ipsi-, $p=0.231$; contra-, $p=0.136$; thalamus: $p=0.998$ and hypothalamus: $p=0.751$) and MRI-based structural measures (cortex: ipsi-, $p=0.989$; contra-, $p=0.245$; hippocampus: ipsi-, $p=0.446$; contra-, $p=0.290$; amygdala: ipsi-, $p=0.997$; contra-, $p=0.882$; thalamus: $p=0.224$; hypothalamus: $p=0.966$). These findings support NeuroEPO as a promising therapeutic intervention to reduce secondary damage and improve functional outcomes following severe TBI.

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Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.03/K14

Topic: D.04. Brain Injury and Trauma

Support: DoD RCZB124
USAMRICD Congressionally Appropriated Title 10 funds

Title: Il-6 signaling in traumatic brain injury and post-traumatic epilepsy: biological insights and therapeutic potential

Authors: *A. H. LUBARSKY;
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Abstract: Traumatic Brain Injury (TBI) is a leading cause of death and disability. Neuroinflammation drives secondary injury, worsening recovery and increasing risk of complications like post-traumatic epilepsy (PTE). Interleukin-6 (IL-6), a key inflammatory mediator post-TBI, is linked to poor outcomes and may be modifiable with existing drugs. Dysregulation of its signalling pathways may worsen inflammation, yet its temporal dynamics and cellular mechanisms remain unclear. ELISA was used to quantify plasma IL-6, soluble IL-6 receptor (sIL-6R), and soluble glycoprotein 130 (sgp130) levels in two observational studies, CENTER-TBI and ICON-TBI. ICON-TBI focused on temporal mediator profiles and estimated trans-signaling rates. CENTER-TBI compared IL-6 levels in PTE and non-PTE patients at admission and two weeks post-injury to evaluate IL-6 as a biomarker or therapeutic target. In ICON-TBI (199 samples, n=48; days 2, 3, 5, 7, 42, and 365 post-TBI), temporal dynamics of IL-6, sIL-6R, and sgp130 were profiled. IL-6 peaked within 3 days and gradually declined but remained elevated versus controls. sIL-6R and sgp130 followed similar trajectories to each other, possibly a compensatory response to IL-6. Preliminary estimates of trans-signalling using published equations were inconclusive, suggesting a need for improved quantification. In CENTER-TBI, IL-6 levels were consistently higher in PTE than non-PTE patients at both time points (Acute timepoint: median = 106 [CI 126.7-226.8] vs 37.65 [CI 58.1-148.1] pg/ml, $p < 0.0001$). Combining IL-6 levels at admission or week 2 alone or with clinical variables yielded a robust 6-month PTE prediction tool. Our data establishes the temporal profiles of IL6, sIL-6R, and sgp130, providing insight into IL-6-associated signalling and inflammation. We highlight IL6 as a predictive biomarker of PTE, alone and with clinical variables, suggesting its role in PTE pathogenesis. Ongoing work explores the findings' mechanistic basis via flow cytometry to investigate dysregulation in cellular IL-6R and gp130 expression and employ single-cell RNA sequencing to map their expression across cell types and examine downstream pathways, including the IL-6 amplifier mechanism. We will also investigate tocilizumab in a murine TBI model to explore PTE biology and prevent epileptogenesis.

Disclosures: A.H. Lubarsky: None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR444.04/K15

Topic: D.04. Brain Injury and Trauma

Support: NIH grant R01NS132772-01A1 (YX, LZ)

Title: Therapeutic effects of N-acetyl-seryl-aspartyl-lysyl-proline on improving functional recovery in male and female rats after traumatic brain injury: a dose-response study

Authors: *X. WANG[1], H. PANG[2], M. CHOPP[3,5], Y. ZHANG[6], L. CHEN[7], A. MAHMOOD[8], L. ZHANG[4], Y. XIONG[6], Z. ZHANG[9];
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Abstract: Background: Our previous study has demonstrated that a single dose of *N*-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) improves functional recovery in male rats after traumatic brain injury (TBI). This study was to determine the dose-response effects of AcSDKP on functional recovery in female and male TBI rats. **Methods:** Young Wistar rats were randomly divided into the following groups (n=8/group/sex): 1) Sham); 2) TBI+Vehicle (0.01N acetic acid); 3) TBI+0.4mg AcSDKP; 4) TBI+0.8mg AcSDKP and 5) TBI+1.6mg AcSDKP. Sham animals underwent craniotomies only. TBI was induced by controlled cortical impact. Vehicle or AcSDKP (0.4, 0.8, 1.6 mg/kg/day) was administered subcutaneously via osmotic pumps for 3 days initiated 1 hour after injury. The functional tests including foot-fault, adhesive removal, modified neurological severity score (mNSS) were performed at 1 day post-injury (dpi) and then once weekly. Morris water maze tests (MWM) were performed at 31 to 35 dpi. At 35 dpi, brains were collected for histological analyses. **Results:** In female TBI rats, AcSDKP (0.4-1.6 mg) significantly reduced adhesive removal time at 7 to 35 dpi ($p<0.05$, vs Vehicle). AcSDKP significantly reduced the mNSS at 7 dpi at the 0.8 mg dose and at 35 dpi at all the doses ($p<0.05$). AcSDKP (0.4 and 0.8 mg) significantly reduced the frequency of forelimb footfault at 35 dpi. AcSDKP (0.8 mg) significantly reduced the time (latency) to reach the hidden platform in the MWM at 34 dpi. AcSDKP (0.4 and 0.8 mg) significantly increased % time spent in the target quadrant at 34 and 35 dpi. In male TBI rats, AcSDKP (0.4-1.6 mg) significantly reduced the number of forelimb and hindlimb footfault at 7 to 21 dpi while AcSDKP (0.8 mg) exhibited significant effects at 28 to 35 dpi ($p<0.05$, vs Vehicle). AcSDKP (0.8 mg) significantly reduced the adhesive removal time at 7 to 35 dpi. AcSDKP (0.4-1.6 mg) significantly lowered mNSS scores at 14-35 dpi ($p<0.05$, vs Vehicle). AcSDKP (0.8 and 1.6 mg) significantly reduced the latency at 33 to 35 dpi ($p<0.05$, vs Vehicle). Only AcSDKP (0.8 mg) significantly increased % time at 33 to 35 dpi. Overall, among the 3 doses, AcSDKP (0.8 mg) exhibited significantly better effects than the other 2 doses in both sexes. Histological analyses are underway to further elucidate the underlying mechanisms of these effects. **Conclusions**: AcSDKP exhibits dose-dependent therapeutic effects on functional recovery after TBI in both male and female rats. Among the tested doses, 0.8 mg consistently produced the most significant improvements, identifying it as the optimal dose for promoting recovery and supporting the continued preclinical and clinical development of AcSDKP as a potential treatment for TBI.

Disclosures: X. Wang: None. **H. Pang:** None. **M. Chopp:** None. **Y. Zhang:** None. **L. Chen:** None. **A. Mahmood:** None. **L. Zhang:** None. **Y. Xiong:** None. **Z. Zhang:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.05/K16

Topic: D.04. Brain Injury and Trauma

Support: SPiRE Award # K9J8XA7VF6T7

Title: Therapeutic Modulation of Neuroinflammation, Anxiety, and Cognitive Deficits Following Mild Traumatic Brain Injury: A Multimodal Approach

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Abstract: Traumatic brain injury (TBI) represents a complex and significant global health challenge, with profound impacts on health, mortality, and socioeconomic conditions. TBI occurs due to mechanical forces exerted on the cranium and often results in impairments across cognitive, motor, and affective domains. Chronic neuroinflammation, often marked by persistent microglial activation and the release of inflammatory mediators, plays a critical role in driving synaptic dysfunction and neuronal loss, contributing to the lasting consequences of TBI. Mild TBI (mTBI) can lead to chronic cognitive and other behavioral deficits, largely driven by secondary neuroinflammation, disruption of neuronal metabolism, and dysregulation of the noradrenergic system—a key regulator of arousal, attention, and stress responses. This study investigated the therapeutic potential of methylphenidate (MP) in mitigating mTBI-induced cognitive and anxiety disorders, with a focus on the utility of longitudinal, non-invasive imaging techniques such as positron emission tomography (PET).Twenty-two female adult Sprague-Dawley rats (Charles River Laboratory) had baseline [^{18}F]-FDG PET/MRI, diffusion tensor imaging (DTI), and resting-state functional MRI (rsfMRI) prior to undergoing mTBI. Twenty rats underwent mTBI using a modified Marmarou weight drop model with a 450g weight at 1.25m height. At one-month post-injury, [^{18}F]-FDG PET/MRI imaging was performed to evaluate metabolic activity and inflammatory burden. At two months post-injury, ten rats were treated with 2.5 mg/kg MP daily for three weeks, while the remaining ten rats received saline. Behavioral assays, including the elevated plus maze, passive avoidance test, startle reflex, and Morris Water Maze, evaluated anxiety-like and cognitive performance after TBI and TBI/treatment. At three months post-injury, follow-up imaging using [^{18}F]-FDG PET/MRI, DTI, and rsfMRI assessed metabolic, structural, and functional connectivity changes in the function-specific brain regions. Preliminary results reveal distinct differences in FDG uptake dynamics between the MP-treated and saline-control groups across brain regions critical for cognition and anxiety regulation. In the MP group, stable FDG uptake was observed, indicating that MP may stabilize metabolic activity through its effects on dopaminergic and noradrenergic systems. In addition to behavioral and imaging studies, cellular and molecular analyses of tissue samples are underway to evaluate markers of neuroinflammation and mitochondrial function, offering insights into the mechanisms underlying TBI pathology and MP's therapeutic effects.

Disclosures: K.S. Klippel: None. **D. Plant:** None. **R. Carrascosa:** None. **S. Leon:** None. **G. Hwang:** None. **C. Downie:** None. **G. Cheng:** None. **J. Hou:** None. **F.J. Thompson:** None. **P.K. Bose:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.06/L1

Topic: D.04. Brain Injury and Trauma

Title: The Effects of Mitigating Oxidative Stress on Neuronal Network Hyperexcitability and Astrocyte Reactivity Post-Traumatic Brain Injury

Authors: *S. J. MUFTI[1,2], J. MARTINEZ[1,2], E. ADOLAY[1,2], C. ADAM[1], N. KRISHNAN[2], A. VAN HASELEN[1], J. MILES[1], M. CHEN[1], R. SHI[3,2,1];
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Abstract: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. While primary injury is inflicted by an irreversible mechanical force on the brain, secondary injury, which arises from subsequent biochemical cascades, may be mitigated with proper therapeutic intervention. Among the most critical secondary injuries that can worsen TBI progression is oxidative stress, which originates from the increased generation of reactive oxygen species. Acrolein, a highly reactive aldehyde, is an established biomarker of oxidative stress. Due to the significant role of acrolein in the progression of secondary injury pathology, it is considered an attractive target for pharmacological intervention. Therefore, we wanted to investigate the effect of scavenging acrolein on the functional and structural changes in neuronal networks after TBI. We utilized our unique TBI-on-a-chip model to investigate neuronal activity changes and astrocyte reactivity post-TBI. This *in vitro* system simulates concussive TBI by exposing murine cortical networks on microelectrode arrays to clinically relevant, rapid acceleration injuries, enabling real-time, cell-scale monitoring of electrophysiological and morphological changes following impact injury. Through extracellular recordings of spike activity, we show that networks exposed to 10 rapidly administered 30 g (10 x 30 g) impacts displayed hyperexcitability and sometimes even heightened network synchronization, a hallmark of seizure-like activity. We also show, through immunocytochemical studies, that networks exposed to 10 x 30 g impacts exhibited high fluorescence intensities of acrolein and the astrocyte reactivity marker GFAP, which increased with larger g forces (10 x 200 g). Astrocytes play a key role in maintaining ion and neurotransmitter balance in the extracellular space, and their dysfunction due to increased reactivity can contribute to neuronal hyperexcitability and a higher risk of seizures. Furthermore, we demonstrate that acrolein by itself can elevate GFAP levels even in the absence of impact injury, highlighting its direct contribution to astrocyte reactivity and its potential as a therapeutic target. Treating networks with 50 µM of hydralazine (HZ), an FDA-approved antihypertensive drug with acrolein-scavenging properties, mitigated the

increases in GFAP intensity and neuronal hyperexcitability after impact injury. In summary, our results show that suppressing oxidative stress through acrolein scavenging by HZ reduced astrocyte reactivity and promoted functional recovery in neuronal networks after injury, thereby highlighting the therapeutic potential of HZ post-TBI.

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Poster

PSTR444: Brain Injury: Therapeutic Strategies

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Program #/Poster #: PSTR444.07/L2

Topic: D.04. Brain Injury and Trauma

Support: NJCBIR CBIR20PIL004
NJCBIR CBIR17PIL007
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DOD W81XWH-22–1–0616
DOD W81XWH-22–1–0618

Title: Effects of repetitive mild traumatic brain injury and methylphenidate treatment on cognitive flexibility in rodents

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Abstract: Traumatic brain injury (TBI) disrupts prefrontal cortex (PFC)-mediated executive functions, such as cognitive flexibility, or the ability to shift behavioral strategies according to changing environmental demands. While most symptoms of mild TBI (mTBI) are transient, repetitive (rmTBI) can result in more severe impairments. Executive dysfunction and rmTBI are both associated with PFC catecholamine dysregulation. Methylphenidate (MPH) is a psychostimulant drug that elevates catecholamine levels and is often used off-label to improve executive dysfunction following TBI. However, the ability of MPH to alleviate rmTBI-induced deficits in cognitive flexibility is unknown. In the present experiments, rats received a series of 3 closed-head control cortical impact injuries within one week, followed by daily administration of MPH (0 or 2 mg/kg, i.p.) and weekly evaluation of their cognitive flexibility performance using a strategy shifting task for 4 weeks post-surgery. Rats initially acquired a visual cue strategy. Twenty-four hours after initial acquisition, rats were assessed for retrieval of the visual cue strategy followed by a series of strategy shifting and reversal learning challenges. RmTBI increased response times within the strategy shifting test, indicating slower processing speed. Injured animals also demonstrated reduced throughput scores, a performance index that blends accuracy and response speed. MPH did not improve the performance of injured animals, suggesting the rmTBI-induced impairments observed are greater than what can be remedied by

the dose evaluated. As such, this model presents a useful approach for characterizing rmTBI-induced cognitive inflexibility and evaluating potential treatment strategies for ameliorating these deficits.

Disclosures: C. Knapp: None. **B.D. Waterhouse:** None. **R.L. Navarra:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.08/L3

Topic: D.04. Brain Injury and Trauma

Title: Psilocybin recovers behavioral deficits and promotes neurogenesis after repeated mild traumatic brain injury in male rats

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Abstract: Introduction: Repeated mild traumatic brain injury (RmTBI), commonly referred to as concussion, is associated with persistent cognitive, affective, and neurophysiological impairments. Despite its high prevalence, effective treatments for RmTBI remain limited. Psilocybin, a serotonergic psychedelic compound, has shown promise in preclinical and clinical studies due to its capacity to enhance neuroplasticity, reduce neuroinflammation, and restore functional brain connectivity. In this study, we investigated whether psilocybin could ameliorate behavioural deficits and promote neurogenesis in a rodent model of RmTBI. **Methods:** Male rats received five lateral impact injuries (11 m/s) across five consecutive days or underwent sham procedures. After a brief period of acute behavioural testing, animals were allowed an 8-week recovery period to allow chronic deficits to emerge. Rats were then administered a single intraperitoneal dose of psilocybin (1 mg/kg) or saline, followed by behavioural testing 24 hours later to assess rapid-acting effects on affective, cognitive, sensory, and social function. **Results:** RmTBI produced robust behavioural impairments, including increased immobility in the forced swim test, reduced sucrose preference, diminished social interaction in the novel rat task, and spatial learning and memory deficits in the Morris water maze. RmTBI also resulted in significant reductions in hippocampal neurogenesis, as indicated by decreased numbers of doublecortin-positive immature neurons and reduced dendritic complexity of these cells within the dentate gyrus. Psilocybin treatment reversed multiple RmTBI-induced behavioural deficits, producing antidepressant-like and pro-social effects, restoring performance in the forced swim, sucrose preference, and social interaction tasks. Psilocybin also increased latency in the hot plate test, suggesting reduced nociception. Importantly, psilocybin significantly increased the number of doublecortin-positive neurons in the dentate gyrus and enhanced their dendritic arborization, indicating a restoration of neurogenic capacity and improved neuronal maturation. **Conclusion:**

Together, these findings demonstrate that psilocybin exerts rapid therapeutic effects on mood, sociability, and cognition following RmTBI, possibly by enhancing hippocampal neurogenesis. Psilocybin may represent a novel pharmacological strategy to treat persistent neurological and affective deficits associated with repeated concussions.

Disclosures: J.T. Allen: None. **B.R. Christie:** None. **S.R. Shultz:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

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Program #/Poster #: PSTR444.09/L4

Topic: D.04. Brain Injury and Trauma

Support: National Research Foundation of Korea(NRF) funded by the Ministry of Education (RS-2020-NR049585)
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Title: Sustained BDNF delivery mitigates secondary injury and enhances recovery in a rodent model of traumatic brain injury

Authors: *N. HONG, J. PARK, J.-C. AHN;
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Abstract: Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide, yet no effective pharmacological treatment is currently available. Brain-derived neurotrophic factor (BDNF) plays a crucial role in neural repair and regeneration and has emerged as a key therapeutic candidate in TBI research. Secondary injury processes, including neuroinflammation, are major contributors to long-term neurological deficits after TBI. However, the effects of sustained BDNF delivery during the transition from primary to secondary injury remain poorly understood. To address this, we developed a controlled cortical impact (CCI) model in 12-week-old adult female rats, resulting in significant impairments in both cognitive and motor functions. Sustained delivery of BDNF mitigated these deficits and attenuated secondary injury markers, including astrogliosis (GFAP activation) and microgliosis (Iba1 activation), in injured brain tissue. In parallel, we established an in vitro TBI model by culturing primary rat hippocampal neurons and inducing oxidative stress using hydrogen peroxide (H_2O_2). Treatment with a sustained-release BDNF formulation significantly increased neuronal survival, as evidenced by enhanced NeuN-positive cell counts. Additionally, microelectrode array (MEA) analysis revealed a marked increase in spike rates and network burst activity, indicating functional recovery at the network level. These findings demonstrate that sustained BDNF delivery alleviates both structural and functional damage associated with

TBI. Our results support the development of a robust in vitro-in vivo platform for evaluating BDNF-based neuroregenerative therapies.

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Poster

PSTR444: Brain Injury: Therapeutic Strategies

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.10/L5

Topic: D.04. Brain Injury and Trauma

Support: DoD TP230226

Title: Development of ultra-selective DYRK1A inhibitors as a novel therapeutic modality for traumatic brain injury

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Abstract: Background:
Traumatic Brain Injury (TBI) is a major health concern affecting over 65 million individuals globally each year. Repetitive mild TBI (r-mTBI) leads to chronic neuroinflammation, Tau hyperphosphorylation (pTau), and neurobehavioral deficits. Dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) modulates pTau and immune response mediators, making it a promising therapeutic target. This study evaluates the therapeutic potential of SM15685, a second-generation, ultra-selective DYRK1A inhibitor, in ameliorating TBI-induced neuropathology and functional impairments.
Methods:
Human Tau (hTau) transgenic mice were subjected to five consecutive mild TBIs at 48-hour intervals. Treatment with the DYRK1A inhibitor began an hour after the last injury, continuing for 21 days. Sixty male hTau mice (10 weeks old) were divided into five groups (n=12 per group): r-sham/vehicle, r-sham/Tx (20 mg/kg), r-mTBI/vehicle, r-mTBI/Tx (10 mg/kg), and r-mTBI/Tx (20 mg/kg). Assessments included Rotarod, EPM, optomotor response, and neuropathological evaluations of pTau (specific sites), GFAP, Iba1, CD45/CD68, and Olig2-positive cells co-expressing pTau. Plasma biomarkers (GFAP, NFL-L, total tau) were quantified 21 days post-TBI.
Results:
Daily treatment with the DYRK1A inhibitor SM15685 (20 mg/kg) resulted in a significant reduction in cortical GFAP and CD45/Iba1 expression compared to vehicle-treated animals, indicating attenuated astrocytosis and microglial activation in the superficial layers of the cortex. SM15685 also significantly decreased the number of PHF1-positive oligodendrocytes in the

corpus callosum and lowered plasma levels of GFAP and NFL-L, reflecting reduced neuroinflammation and axonal injury relative to vehicle controls. Functionally, SM15685 significantly improved motor coordination and visual tracking (Rotarod, optomotor response), and reduced anxiety-like behavior and disinhibition (Elevated Plus Maze) compared to vehicle. Although total tau levels in plasma remained elevated, they were unaffected by SM15685 treatment. Conclusion:
SM15685, a highly selective DYRK1A inhibitor, effectively mitigated TBI-induced neuropathology by reducing glial activation, axonal damage, and tau-related abnormalities. These pathological improvements translated into enhanced motor, visual, and behavioral outcomes. These findings support DYRK1A inhibition as a promising therapeutic strategy for addressing both molecular and functional consequences of repetitive mild TBI.

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Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.11/L6

Topic: D.04. Brain Injury and Trauma

Support: Osteopathic Heritage Foundation
NJ Commission Brain Injury Research

Title: Rescuing Cognitive Function After Repeated Mild Traumatic Brain Injury: The Role of Hepatocyte Growth Factor/cMet Signaling

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Abstract: Mild traumatic brain injury (mTBI; or concussion) affects an estimated 3 million Americans each year, representing a significant health concern. Mild TBI can lead to behavioral and cognitive deficits, including impaired working memory, decision-making, and other executive functions. Repeat mTBI is associated with more severe, long-lasting cognitive impairment and brain damage that mimics severe TBI. Dysfunctional working memory is a core

component of diminished quality of life and difficulty returning to work and school. Currently, there are no FDA-approved treatment options to improve cognitive deficits following TBI.The brain hepatocyte growth factor (HGF) and its tyrosine kinase receptor (cMet) system are key mediators of procognitive actions, axonal repair, and other anti-inflammatory and neuronal survival processes. The PLC/PKC pathway has been implicated in improving learning and memory function by potentiating NMDA currents. However, the PI3K/AKT/mTOR, Ras/ERK/MAPK, and STAT3 are additional cMet signaling pathways likely involved in the actions of HGF. Nonetheless, the effects of activating the HGF/cMet receptor signaling in the context of neurological diseases remain unclear.Dihexa, a brain-penetrant small molecule, is a positive modulator of the HGF/cMet receptor system. Prior research has indicated that dihexa can enhance cognitive function, stimulate neurogenesis, and provide neuroprotection in rodent models. We hypothesize that cMet signaling can improve cognitive impairment and act as a neuroprotectant following repeated mTBI. Additionally, we posit that preferential activation of the PLC/PKC/NMDA and PI3K/AKT/mTOR or Ras/ERK/MAPK after dihexa treatment in mTBI underlies its procognitive and neuroprotective actions. Behavioral pharmacology and neuroanatomical approaches were used to assess performance on the T-Maze test of working memory, markers of axonal integrity, and specific signaling cascades following repetitive mTBI and dihexa treatment in rodents. These findings offer crucial insights into a novel therapeutic strategy for repeated mTBI and support the potential role of dihexa in alleviating cognitive deficits resulting from repeated injuries.

Disclosures: K. Martino: None. **D.M. Devilbiss:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR444.12/L7

Topic: D.04. Brain Injury and Trauma

Support: R01NS104117
R01NS109221

Title: Elovanoids are neuroprotective after traumatic brain injury by improving synaptic mitochondrial function and reducing lipid peroxidation

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Abstract: Traumatic brain injury is a major health concern resulting in more than 200,000 TBI-related hospitalizations per year. Currently, there are no effective treatments. Administration of a bioactive lipid derived from very long-chain polyunsaturated fatty acids, termed elovanoids (ELV), protect against oxidative stress, ischemia, and pro-inflammatory signaling. In this study,

we found that intranasal delivery of ELV reduced neurological deficits, protected against oxidative stress, and rescued synaptic mitochondrial function after TBI. The controlled cortical impact (CCI) model was used to induce a cortical injury on the right hemisphere in adult Sprague Dawley rats. ELV (20 ug/dose) or vehicle was delivered intranasally at 1h and 22h after injury, and brains were harvested at 24h or 72h after CCI. Neurological scoring composed of postural reflex and forelimb placement tests were taken daily for 3 days after CCI. 10X Single Cell Multiome (ATAC + GEX) was used to evaluate transcriptomic and epigenetic signatures at the single-cell level. Seahorse XF analyzer was used for measurement of mitochondrial function. Immunohistochemistry was used for protein visualization. ELV reduced neurological deficits on days 2 and 3 after CCI. Immunostaining revealed reduced loss of NeuN+ neurons at the lesion site, reduced CD68+ phagocytic immune cell infiltration, and reduced lipid peroxidation product 4-HNE after ELV treatment. Single-cell gene expression analysis revealed the upregulation of GO pathways, including regulation of synaptic organization in glutamatergic neurons, astrocytes, and other cell types, as well as genes related to antioxidant defense and mitochondrial function by ELV. Measures of isolated synaptosome mitochondrial respiration reveal improved basal and maximal respiration after ELV treatment. Lastly, transcription factor footprinting suggests that ELV upregulated the antioxidant defense gene NRF2 in neurons after TBI. Taken together, our data indicate that ELV reduce lipid peroxidation and synaptic dysfunction by counteracting oxidative stress and inflammation, resulting in improved mitochondrial function and neurological recovery after TBI.

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Poster

PSTR444: Brain Injury: Therapeutic Strategies

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Program #/Poster #: PSTR444.13/L8

Topic: D.04. Brain Injury and Trauma

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Marga und Walter Boll-Stiftung (#210-10-15)
Gerok-Program (Faculty of Medicine, University of Cologne)

Title: Functional and Therapeutic Relevance of Blood-Brain-Barrier Disruption Following Mild Traumatic Brain Injury

Authors: *S. DEMIR[1], S. BLASCHKE[1], N. RAUTENBERG[1], R. MERKEL[2], M. A. RUEGER[1,2];
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Abstract: ***Background*****:** Mild traumatic brain injury (mTBI) is a frequent but underestimated condition that - in some cases - even causes long-term neurological impairment. Especially repetitive mTBI (rmTBI) has been associated with cognitive deficits and the development of chronic traumatic encephalopathy. However, the underlying pathophysiological mechanisms remain poorly understood. To elucidate this gap, we previously reported a novel mouse model of rmTBI with a behavioral phenotype correlating to a mild but widespread blood-brain barrier (BBB) disruption.***Objective*****:** To further target the BBB disruption - as a potential driver of secondary disease progression - we further investigated its microvascular underpinnings as well as connection to neuroinflammatory traits and neural stem cell (NSC) recruitment. Furthermore, we hypothesize that pharmacological preservation or restoration of BBB integrity might ameliorate deficits.***Methods*****:** Male C56Bl/6j mice (n=64) received rmTBI based on five closed-skull impacts over a 10-day period. Functional outcome was assessed via Open Field, Y-Maze, Simi Motion, Moseq-Bucket. Experimental groups included pharmacological BBB stabilization using dexamethasone applied subcutaneously at different time points, as well as non-trauma controls. Ex vivo immunohistochemistry focused on markers of the microvascular unit, neuroinflammation, and NSC recruitment. ***Results*****:** rmTBI induced a distinct neuropsychiatric phenotype with impairment in spatial memory and cognition. Functional deficits correlated with BBB disruption, evidenced by widespread IgG extravasation, especially in hippocampus, cortex, and thalamus. Notably, microvascular dysfunction was markedly decreased by systemic application of dexamethasone in all affected regions. Moreover, perivascular immunoreactivity for Aquaporin-4 and Glial Fibrillary Acidic Protein increased, indicating partial astrocytic reorganization alongside improved BBB integrity. ***Conclusion*****:** Our preliminary data support a causal role for BBB dysfunction in neurological impairment following rmTBI. Based on these findings, we suggest that the BBB may function as both a biomarker of CBI severity, and as potential treatment target to pharmacologically improve recovery from rmTBI.

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Poster

PSTR444: Brain Injury: Therapeutic Strategies

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Program #/Poster #: PSTR444.14/L9

Topic: D.04. Brain Injury and Trauma

Support: FightMND

Title: Investigating the role of IRF7 in chronic neuroinflammation and neural health after traumatic brain injury

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Abstract: Traumatic brain injury (TBI) is a major cause of death and permanent disability worldwide. Prolonged inflammation from TBI can lead to chronic cognitive defects and contribute to onset of neurodegeneration, though the exact mechanisms throughout the brain remain poorly understood. Previous studies show that targeting type-I interferon signalling confers a protective effect after TBI in the short term. Therefore, we investigated the influence of Interferon Regulatory Factor 7 (IRF7), a key mediator of type-I interferon signalling, on microglial activation and neuronal health across longer timepoints following TBI. We performed a moderate controlled cortical impact on wildtype or IRF7 -/- mice over the right cortex (-1.5 mm posterior, +2.5 mm lateral from bregma, 1.5 mm deep, 5 m/s, 100 ms dwell time) and collected brains after either 24 hours, 7 days, 2 weeks, 6 months or 9 months. Earlier studies demonstrate recovered microglial morphology after TBI 6 months post-TBI, along with decreased inflammatory cytokines at 7 days post-TBI. At 6 months post TBI, IRF7 -/- mice displayed less anxiety-like behaviour and enhanced recognition memory abilities. Additional work building on this has also investigated the disruption of parvalbumin (PV) expression and signalling post-TBI. We observe that following a moderate TBI, PV from damaged cells is released into the cytoplasm and localises towards nearby white matter tracts. Interestingly, the number of cells expressing PV significantly increases in the perilesional area, albeit expression is limited almost exclusively to the cytoplasm -- in contrast to homeostatic PV neurons which include nuclear expression. These aberrant PV-expressing neurons are primarily GABAergic as confirmed by immunostaining, and thus we hypothesise that typically non-PV expressing GABAergic cells can upregulate PV expression following extreme oxidative stress in TBI. Preliminary data suggests this effect is lessened in IRF7 -/- mice. Together, these data highlight the intriguing role of IRF7 in TBI and open a potential avenue for more effective treatments for neuroinflammation.

Disclosures: J.L. Hall: None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.15/L10

Topic: D.04. Brain Injury and Trauma

Support: RS-2025-00520396

Title: The Therapeutic Potential of Hexokinase 2 Inhibition in Regulating Microglial Activation and Mitochondrial Dysfunction Following Traumatic Brain Injury.

Authors: *H. JUNG[1], M. PARK[2], S. WOO[4], H. YANG[5], D.-S. SON[3], H. CHOI[6], S. SUH[7]; [1]Dept. of Physiology, Col. of Medicine, Hallym university, Korea, Chunchoen, Korea, Republic of; [2]Dept. of Physiol., Hallym Univ., chuncheon, Korea, Republic of; [3]Data Sci., Hallym Univ., Chuncheon, Korea, Republic of; [4]Physiol. of Med. science, [5]Physiol. of Med. sciences, Dept. of Physiology, Hallym University, Col. of Med., Chuncheon, Korea, Republic of; [6]Neurol., Hallym

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Abstract: Traumatic brain injury (TBI), a condition triggered by external mechanical forces, can result in significant brain damage and functional impairments. A hallmark of TBI pathology is the excessive activation of microglia, accompanied by the upregulation of Hexokinase 2, a key enzyme in glycolysis, to meet increased energy demands. This hyperactivation intensifies inflammatory responses and induces mitochondrial dysfunction. Additionally, heightened mitochondrial metabolic activity in hyperactive microglia generates excessive reactive oxygen species (ROS), further exacerbating oxidative stress and leading to neuronal apoptosis. This study explored the therapeutic efficacy of 3-Bromopyruvic acid (3-BP), a selective Hexokinase 2 inhibitor, administered immediately post-TBI using a stereotaxic approach. 3-BP treatment effectively regulated energy metabolism, attenuated microglial hyperactivation, and restored mitochondrial function. Neuronal survival was assessed via Fluoro-Jade B (FJB) staining, revealing a significant reduction in neuronal apoptosis in the hippocampal CA1 region in the 3-BP-treated group compared to controls. Microglial activity was analyzed using Iba-1 and CD68 staining, focusing on the pro-inflammatory M1 phenotype. Quantitative analyses demonstrated a marked decrease in M1 microglia-associated parameters, including score, intensity, and area percentage, in the 3-BP group. Furthermore, 3-BP administration significantly reduced inflammatory cytokine levels, ROS production, and neuronal cell death under TBI conditions. Behavioral assessments indicated that cognitive deficits were notably alleviated in 3-BP-treated subjects. These findings underscore the potential of Hexokinase 2 inhibition as a therapeutic strategy for mitigating TBI-induced neuronal damage. By targeting excessive metabolic activity and its downstream pathological effects, 3-BP offers a promising approach to preserving neuronal integrity and cognitive function in TBI patients. This study highlights a novel avenue for therapeutic intervention, providing a foundational framework for future translational research.

Disclosures: H. Jung: None. **M. Park:** None. **S. Woo:** None. **H. Yang:** None. **D. Son:** None. **H. Choi:** None. **S. Suh:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.16/L11

Topic: D.04. Brain Injury and Trauma

Support: RS-2025-00520396

Title: Protective effects of phosphodiesterase 5 inhibitor, mirodenafil, on traumatic brain injury-induced neuron death

Authors: *M. PARK[1], H. YANG[3], H. JUNG[4], D.-S. SON[2], H. CHOI[5], S. SUH[6];
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Abstract: Traumatic brain injury (TBI) is a serious neurological condition caused by external physical forces that lead to extensive brain damage. The underlying pathological processes involve complex interactions, including neuronal death driven by cerebrovascular dysfunction, inflammation, and oxidative stress. A key contributor to these processes is the enzyme phosphodiesterase 5 (PDE5), which reduces cyclic guanosine monophosphate (cGMP) levels, leading to impaired vasodilation, reduced cerebral blood flow, and disruption of protective cellular pathways. Nitric oxide (NO) and zinc play significant roles in the progression of TBI-related damage. NO is a signaling molecule that supports cerebral blood flow and redox balance by boosting antioxidant defenses such as glutathione (GSH) levels. Zinc, an essential element for neural function, can become toxic in excess, contributing to oxidative stress and neuronal damage. During TBI, reduced NO availability and disrupted zinc homeostasis exacerbate these harmful effects, with increased PDE5 activity further depleting cGMP and limiting the activation of protective factors like Nrf2 and HO-1. This study explores the therapeutic potential of mirodenafil, a PDE5 inhibitor, in mitigating TBI-induced damage. Administered subcutaneously at 2 mg/kg, mirodenafil was evaluated through histological and biochemical techniques, including markers for neuronal degeneration, zinc accumulation, and NO synthesis. Results showed that mirodenafil reduced neuronal loss, regulated zinc levels, and restored NO signaling. These findings suggest that mirodenafil supports neuronal survival by preserving cGMP levels, enhancing NO function, and mitigating oxidative stress related to zinc dysregulation. This study highlights mirodenafil as a potential therapeutic option for limiting TBI-induced neuronal injury and preserving brain function.

Disclosures: M. Park: None. **H. Yang:** None. **H. Jung:** None. **D. Son:** None. **H. Choi:** None. **S. Suh:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.17/L12

Topic: D.04. Brain Injury and Trauma

Support: SUNY Downstate Health Sciences University Seed Grant
Fellowship in Developmental Neuroscience and Developmental Disabilities

Title: Effect of brivaracetam on changes in synaptic transmission after severe TBI

Authors: *A. MEJIA-BAUTISTA[1,2], H. B. MICHELSON[1], J. H. GOODMAN[2], D. S. LING[1]; [1]SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [2]NYS Inst. for Basic Res., Staten Island, NY

Abstract: Posttraumatic epilepsy (PTE) can occur in up to 40% of patients who sustain a severe traumatic brain injury (TBI). Despite decades of research, there are no therapeutic interventions to prevent PTE. Moreover, in many cases of PTE, seizures cannot be controlled adequately with standard antiseizure medications (ASMs). Antiepileptogenic therapies remain frustratingly elusive, in large part because the epileptogenic mechanisms and chronic changes in cortical synaptic function triggered by TBI are not fully elucidated. Results from our prior studies suggest that early, post-injury administration of brivaracetam (BRV), an FDA-approved SV2A-ligand ASM, may mitigate the development of PTE. The aims of this study are to investigate the changes in cortical synaptic transmission that may give rise to PTE and test the hypothesis that BRV exerts its protective, antiepileptogenic effects by limiting these changes. Specifically, we are investigating the mechanisms by which TBI alters the balance of cortical excitation and inhibition, and how BRV may prevent this pathogenic process. Experiments use the controlled cortical impact (CCI) model of severe TBI in rats and employ whole-cell electrophysiological recordings from layer V pyramidal cells in *ex vivo* slices of neocortex to assess injury-induced changes in excitatory and inhibitory postsynaptic currents (EPSCs and IPSCs). Drug-treated rats are given a single dose of BRV (21mg/kg, IP) immediately after CCI, and electrophysiological assessments are made 4 - 10 weeks after TBI to determine the chronic changes in cortical circuit physiology and the preventative effects of early BRV treatment. Results in CCI-injured animals revealed a 47% increase in the excitatory/inhibitory (E/I) synaptic ratio relative to uninjured controls, indicating a shift toward hyperexcitability. Notably, BRV treatment administered immediately post-CCI injury attenuates this increase, restoring the E/I ratio to levels comparable to those observed in uninjured animals. These findings support the hypothesis that BRV mitigates posttraumatic circuit dysfunction by preserving synaptic balance and may thus serve as a viable strategy for antiepileptogenic intervention following severe TBI.

Disclosures: A. Mejia-Bautista: None. **H.B. Michelson:** None. **J.H. Goodman:** None. **D.S. Ling:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.18/L13

Topic: D.04. Brain Injury and Trauma

Support: This research was supported by the Defense Advanced Research Projects Agency (DARPA) under the Cooperative Agreement HR00112420337

Title: Antiseizure drugs for neuroprotective prophylaxis against traumatic brain injury

Authors: *T. M. RODRIGUEZ[1], A. SANJANA[2], K. BAYONA[3], P. DAVE[3], G. PAVIA[4], L. KOT[3], E. OZGA STASIEWICZ[3], M. SOBOLEWSKA[4], E. VAKNINE[3], M. MORRIS[4], D. S. LING[2], P. A. SERRANO[3];
[1]Biochem., The Grad. Ctr. CUNY, New York, NY; [2]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [3]Psychology, Hunter College, CUNY, New York, NY; [4]Cognitive Neurosci., CUNY Grad. Ctr., New York, NY

Abstract: Traumatic brain injury (TBI) promotes the excessive release of glutamate, leading to the overactivation of glutamatergic receptors and disruption of intracellular calcium (Ca^{2+}) homeostasis. Dysregulation of intracellular Ca^{2+} is a key mediator of neuronal dysfunction and death in the hippocampus and prefrontal cortex, contributing to the development of post-traumatic epilepsy (PTE)—a mechanism associated with exacerbated short-term working memory deficits and anxiety-like behaviors. To date, no effective therapy has been established to prevent PTE, which is often irreversible and resistant to current anti-seizure medications (ASMs), potentially due to missed critical therapeutic windows. Early post-TBI administration of synaptic vesicle 2A (SV2A) ligand-ASMs, levetiracetam (LEV) and brivaracetam (BRV), has been shown to reduce epileptiform activity 30-60 min post-TBI via glutamate inhibition. Our goal is to investigate whether prophylactic administration of LEV (150 mg/kg) or BRV (2.1 mg/kg) 15 minutes prior to TBI prevents PTE onset and improves spatial working memory and anxiety-like responses one-month post-injury using a controlled cortical impact (CCI) model in male Sprague Dawley (SD) rats. We hypothesize that prophylactic LEV or BRV will elicit neuroprotective effects, preventing PTE development and reducing spatial working memory deficits and anxiety-like behavior one-month post-TBI. Male SD rats received a CCI injury (6.0 mm diameter; 2.0 mm depth) at postnatal day 39-65. Animals were randomly assigned to TBI + LEV, TBI + BRV, TBI + Vehicle (0.9% saline), or No TBI + Vehicle groups. The radial 8-arm maze (RAM) assessed spatial working memory errors, and the elevated plus maze (EPM) evaluated anxiety-like behavior one-month post-TBI. LEV pretreatment significantly decreased working memory errors compared to TBI + Vehicle, suggesting a protective effect. In the EPM, TBI + Vehicle animals spent significantly more time in closed arms compared to No TBI controls, indicating heightened anxiety. In contrast, TBI + LEV and TBI + BRV rats spent more time in open arms and less in closed arms than TBI + Vehicle animals, suggesting reduced anxiety-like behavior and increased exploratory activity. Notably, BRV produced a stronger effect, likely due to its ~20-fold higher binding affinity for SV2A compared to LEV. Ongoing studies will assess the dose-response relationship of BRV to determine the optimal neuroprotective dose and evaluate efficacy at one-week post-injury.

Disclosures: T.M. Rodriguez: None. **A. Sanjana:** None. **K. Bayona:** None. **P. Dave:** None. **G. Pavia:** None. **L. kot:** None. **E. Ozga Stasiewicz:** None. **M. Sobolewska:** None. **E. Vaknine:** None. **M. Morris:** None. **D.S. Ling:** None. **P.A. Serrano:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.19/L14

Topic: D.04. Brain Injury and Trauma

Support: Defense Advanced Research Projects Agency (DARPA) under Cooperative Agreement HR00112420337

Title: Prophylactic administration of brivaracetam prevents injury-induced deficits in spatial memory after severe traumatic brain injury in rats

Authors: *A. SANJANA[1], C. HSIEH[1], T. M. RODRIGUEZ[2], P. A. SERRANO[2], D. S. LING[1]; [1]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [2]Dept of Psychology, Hunter College, CUNY, New York, NY

Abstract: Traumatic brain injury (TBI) is a leading cause of disability worldwide, with an estimated global incidence of 27-69 million cases annually. Two major pathological sequelae of TBI are cognitive dysfunction and posttraumatic epilepsy (PTE). Our past electrophysiological, behavioral, and biochemical studies suggested that timely, post-injury administration of the SV2A ligand antiseizure drugs (ASDs), levetiracetam (LEV) or brivaracetam (BRV), prevents the development of PTE in rats following severe controlled cortical impact (CCI) neurotrauma. In this study, we examined the neuroprotective efficacy of prophylactic administration of BRV (0.21 - 21.0 mg/kg) to prevent TBI-induced deficits in cognitive function. Rats (aged P25-36) were randomly assigned to receive a single IP dose of BRV at 15-20 min prior to severe CCI injury. Drug control animals received only the saline vehicle. Sham-injury controls were not subjected to CCI injury. At 5 - 8 weeks post-injury, rats were assessed for spatial memory function using a 4-day active place avoidance (APA) test protocol, consisting of one priming day, two training days, and retention test on the last day. Cognitive performance was assessed using four metrics: (1) time to first shock-zone entry, (2) number of shock-zone entries, (3) percentage of time spent in the shock zone, and (4) maximum shock-zone avoidance time. CCI-injured rats that received only the saline vehicle (CCI saline) exhibited significant deficits in working memory across all four APA metrics relative to sham-injured rats. However, BRV-treated CCI-injured rats (CCI-BRV) demonstrated significantly better memory performance than CCI saline rats, with levels equivalent to sham-injury controls. These findings suggest that prophylactic administration of BRV administration may provide neuroprotection against cognitive deficits caused by TBI. Taken together with our previous investigations, this study suggests that the SV2A ligand ASDs may have broad neuroprotective effects against severe cortical neurotrauma.

Disclosures: A. Sanjana: None. **C. Hsieh:** None. **T.M. Rodriguez:** None. **P.A. Serrano:** None. **D.S. Ling:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

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Program #/Poster #: PSTR444.20/L15

Topic: D.04. Brain Injury and Trauma

Support: Nudo (PI) 07/01/2019 – 06/30/2020 Midwest Stem Cell Therapy Center Pilot Program
NIH Grant 1R01NS123051

Title: Intraparenchymal stem cell delivery enhances motor recovery after traumatic brain injury

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Abstract: Motivation: Nearly 5.5 million people experience a traumatic brain injury (TBI) each year, often resulting in chronic sensory, motor, and cognitive disabilities. Current treatments aim to manage the symptoms of brain injury, but often yield limited functional recovery. Novel therapies are needed to target the underlying damage and promote restoration of function. Stem cell-based therapies have shown promising anatomical and functional outcomes in preclinical models of brain injury. However, efficacy can be hindered by the difficulty of crossing the blood brain barrier. In severe TBI, decompressive craniectomy (DC), the removal of the skull over the injury site to relieve intracranial pressure, is a standard clinical intervention. The DC procedure provides a unique opportunity to bypass the blood brain barrier. Our research focuses on intraparenchymal (IPa) injections of human Wharton's jelly mesenchymal stem cells (hWJMSC) into the viable tissue surrounding the injury to promote recovery. This study explores the effects of IPa injections of hWJMSC at two post-injury time points on motor recovery in a preclinical rat model of TBI. **Methods:** Male Long-Evans rats (10-12 weeks old) were trained on a skilled reach task using their preferred forelimb. After establishing pre-injury baseline behavioral performance, rats were randomly assigned to three groups. All rats received a controlled cortical impact to the forelimb area of primary motor cortex contralateral to the trained forelimb. Rats received 4µl of hWJMSC (50k/µl) IPa injections around the injury site at either 1-day or 1-week post-TBI. Control rats received injections of the vehicle medium 1-day post-TBI. Reach performance was assessed weekly for 8 weeks post-TBI. **Results:** Treatment with hWJMSC attenuated injury severity within the first week in rats that received treatment one day post-injury. By Week 3, both treatment groups recovered to 80% of their baseline reaching success, while untreated controls recovered to about 50% by Week 3 and remained there through Week 8. **Conclusion:** These results suggest that injecting hWJMSC directly into tissue surrounding a cortical injury can substantially mitigate motor impairments after TBI. Additionally, the timing of stem cell intervention appears to align with current clinical interventions windows. **Future Directions**: While this study supports a promising new therapy for TBI, IPa injections are an invasive procedure that may introduce further tissue injury or other complications. To develop a less invasive delivery method, we are currently engineering a hydrogel matrix optimized for stem cell support and sustained release at the injury site.

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Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR444.21/Web Only

Topic: D.04. Brain Injury and Trauma

Support: Department of Defense (GRANT13705040)
National Institutes of Health (R56 NS129438)
National Institutes of Health (1R56NS131465-01)
Falk Medical Research Trust

Title: Chemogenetic manipulation of BLA-vCA1-LHA neural circuit reverses risk-taking behavior following traumatic brain injury in mice

Authors: *A. E. GOWAN[1,2], L. K. PRADHAN[1,2], F. YUAN[1,2], X. GAO[1,2];
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Abstract: Risk-taking behavior is a prevalent psychiatric disorder observed in traumatic brain injury (TBI) patients. The resulting deficits impact both personal and professional quality of life significantly, yet there is currently no effective intervention to treat this symptom. Herein, we utilized the controlled cortical impact (CCI) mouse model to represent TBI to investigate potential therapeutic options for this behavior. The elevated plus maze (EPM) test, which assesses anxiety versus risk-taking/impulsive decision-making in rodents, was used for behavioral testing. Following TBI, mice showed increased risk-taking behavior, characterized by significantly increased open arm time and distance in the EPM test, for up to 12 weeks post-injury. In order to develop a treatment for this behavior, we investigated the neural circuitry mechanisms involved.
Prior studies have implicated the basolateral amygdala (BLA)-ventral hippocampal CA1 (vCA1)-lateral hypothalamic area (LHA) circuit in the regulation of anxiety-related behaviors. Our immunohistochemical analysis using c-fos, a marker for neuronal activity, of the BLA, vCA1, and LHA following TBI showed significant decrease in neuronal activation in vCA1 and LHA, but not BLA, indicating a disruption in the BLA-vCA1-LHA circuit.
Thus, it was determined that re-activation of this circuit could potentially modulate symptoms and this was tested using chemogenetic activation via Designer Receptors Exclusively Activated by Designer Drugs (DREADD). AA8 (pAAV-hSyn-hM3D(Gq)-mCherry) was injected into the vCA1 region 7 days prior to TBI and infected mice were then treated with clozapine-N-oxide (CNO, 5mg/kg, n=5) or saline (n=5) 4 weeks after injury. CNO-treated mice showed significant increase in c-fos stained neuronal activity in both vCA1 and downstream in the LHA, indicating that the vCA1-LHA circuit was re-activated. Behaviorally, CNO-treated mice (n=5) showed a significant decrease in open arm time and distance in the EPM, indicating a reversal of the risk-taking phenotype. Researchers who participated in immunohistochemistry and behavior testing were blind to injury and treatment assignments.

These findings support the idea that TBI-induced damage of the BLA-vCA1-LHA circuit contributes to maladaptive risk-taking behavior and chemogenetic re-activation of this pathway can restore behavioral control. This study defines modulating this neural circuit as a potential therapeutic target for behavioral dysfunction following TBI with a need for further research into non-invasive neuromodulation methods for clinical application.

Disclosures: A.E. Gowan: None. **L.K. Pradhan:** None. **F. Yuan:** None. **X. gao:** None.

Poster

PSTR444: Brain Injury: Therapeutic Strategies

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.22/M1

Topic: D.04. Brain Injury and Trauma

Title: Revealing effects of responsive neurostimulation and epilepsy-foci resection in the human brain using functional ultrasound imaging of interictal activity

Authors: *K. A. AGYEMAN[1,2], D. J. LEE[3], K. WU[3], W. CHOI[3], J. RUSSIN[3], C. LIU[3], V. N. CHRISTOPOULOS[4];
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Abstract: Over 30% of epilepsy patients are refractory to drug treatment and require surgery or (and) neurostimulation. Currently, identifying the precise source of epilepsy and predicting the effectiveness of removing the foci, paramount to surgical intervention is fraught with challenges. Similarly, outcomes of neuromodulation strategies for treating epilepsy are suboptimal, partly due to ineffective functional monitoring needed to elucidate neurostimulation mechanisms and evoked effects.
Herein, we leverage functional ultrasound imaging (fUSI) to characterize changes evoked by focal epilepsy and effects of foci resection - under interictal non-seizure conditions. Additionally, we examine 3 stimulation paradigms of responsive neurostimulation (RNS). To this end, we developed six interictal activity measures from fUSI signal acquired intraoperatively through a cranial window from epileptic foci and normal brain regions pre- and post-resection, and with RNS (Fig.1A-C). Nine patients undergoing epilepsy surgery and RNS device implantation were imaged.
The analysis revealed lower levels of local connectivity (LC) and impulse response of the autocorrelation function (ACF-IR) in signals acquired from normal, compared to epilepsy foci regions, pre-resection. In assessing effects of resection, we found strong increases to the impulse response function settling rate (IRF-SR) but decreases in the LC activity measures of signal acquired from the same normal regions, after resection (Fig.1D). We subsequently determined that RNS evokes distinct spatiotemporal changes to brain hemodynamics - notably, robust reductions to Res-IR, but increases to IRF-SR and ACF-IR (Fig.1E), in a manner akin to the changes evoked by foci resection.
This novel study is significant as it provides analytical capabilities to assess interictal functional

and network activity changes associated with localization and treatment strategies of epilepsy with a new level of precision in vivo - establishing fUSI as a vital investigative tool for monitoring and rehabilitating disorders of the human brain.

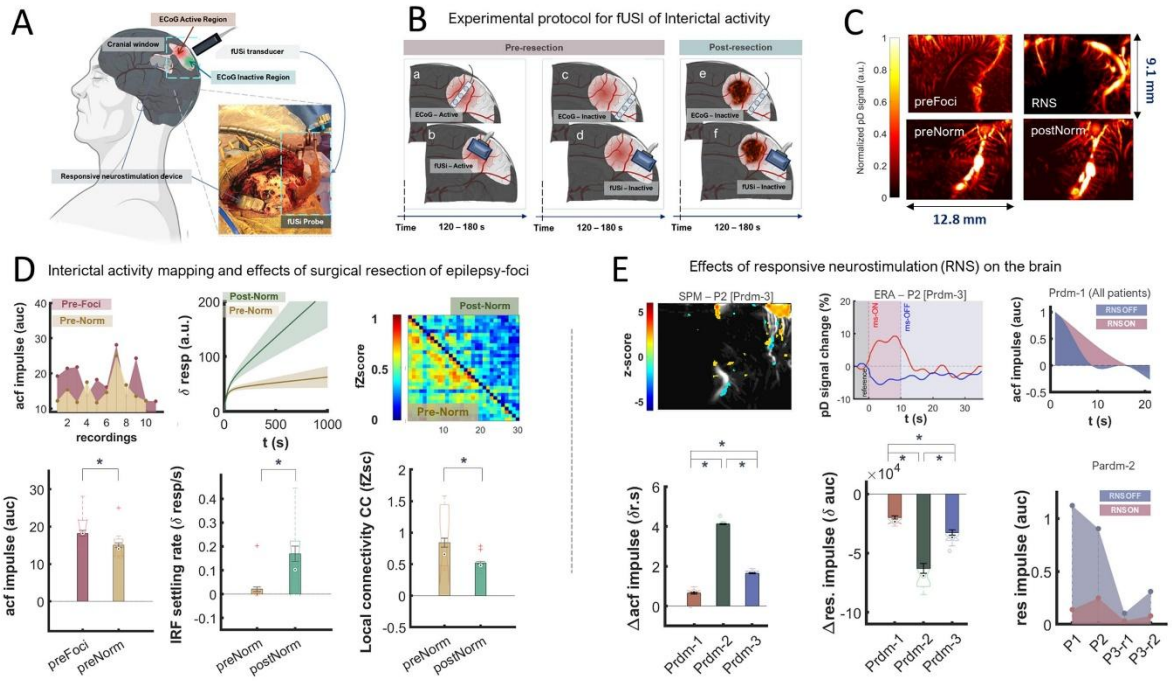


Figure 1: A) Model for studying epilepsy and RNS evoked effects in the human brain. **B)** Experimental protocol for fUSI of epileptic foci/lesional and normal brain regions, pre- and post-resection of foci. **C)** fUSI power Doppler brain vascular map images. **D)** Interictal activity measures pre-resection and post-resection within normal (pre-Norm and post-Norm) and epileptic foci (pre-Foci) regions across patients. **E)** Effects of the RNS stimulation paradigms (prdms) on brain's functional activity and neural network connectivity.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.01/M2

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Non-invasive brain-controlled spinal stimulation restores locomotor function and corticospinal plasticity after incomplete spinal cord injury

Authors: *R. FADLI[1], A. SASAKI[2], Z. BOOGAART[1], A. YUASA[4], H. SAITO[5], N. MUSIKIC[1], J. D. GUEST[3], M. MILOSEVIC[6];
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Abstract: Transcutaneous spinal cord stimulation (TSCS) has emerged as a promising neuromodulation approach for facilitating locomotor function by activating dorsal root afferents and amplifying residual descending input. Integrating TSCS with brain-computer interfaces (BCI) could further enhance neuromodulation through precise synchronization of cortical commands and spinal activation to promote Hebbian plasticity. In this pilot clinical multiple-case study, we evaluated the efficacy and underlying mechanisms of a BCI-TSCS intervention for improving walking ability in individuals with chronic incomplete spinal cord injury (SCI). Two participants, one (P1) with a T10-level injury (AIS D) and another (P2) with a C4-level injury (AIS D), completed one month of conventional walking therapy followed by three months of BCI-TSCS therapy, totaling 12 sessions per month (30-60 min per session). During the BCI-TSCS intervention, the BCI system was used to detect stepping motor imagery in real-time from a single scalp surface electrode. If the BCI system detected the motor imagery within 15 s, TSCS was triggered for 5 s, while participants simultaneously executed a step. Otherwise, TSCS was not triggered, and the subsequent trial was initiated. The system achieved an overall detection success rate of approximately 83%. TSCS was applied using a cathode placed over the T11-T12, T12-L1, or L1-L2 vertebrae level and an anode placed over the umbilicus at the intensity of 70-90% of the motor threshold (range: 25-70 mA). Functional outcomes assessed by the 10-meter walk test (10MWT) and 6-minute walk test (6MWT) showed clinically meaningful improvements. Walking speed increased by 0.18 m/s in P1 and 0.09 m/s in P2. Kinematic and muscle synergy changes during 10MWT were also observed post-therapy. Notably, P2 reduced required minimum body weight support from 50% at baseline to 25% post-therapy. Walking endurance improved by 41.5 m in P1, whereas P2 endurance improved by 28.8 m. These functional improvements were associated with increased corticospinal excitability, indicated by reduction of resting motor threshold to elicit motor-evoked potentials through transcranial magnetic stimulation. Our findings highlight the potential of BCI-TSCS therapy in effectively enhancing motor function and corticospinal connectivity in chronic incomplete SCI, supporting the utility of incorporating cortical descending drive for improved neuromotor rehabilitation.

Disclosures: R. Fadli: None. **A. Sasaki:** None. **Z. Boogaart:** None. **A. Yuasa:** None. **H. Saito:** None. **N. Musikic:** None. **J.D. Guest:** None. **M. Milosevic:** None.

Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.02/M3

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Laterality-targeted and timing-dependent corticospinal plasticity after spinal cord injury

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Abstract: Transcutaneous spinal cord stimulation (TSCS) is an emerging neuromodulatory technique for restoring neuromotor function after spinal cord injury (SCI). TSCS activates large-diameter dorsal root afferents, amplifying residual descending input and increasing spinal excitability. When paired with brain-computer interface (BCI) systems that detect cortical motor intent, TSCS offers a means of precisely timing stimulation to reinforce Hebbian plasticity. However, optimal electrode placement and timing strategies remain underexplored. This study evaluates how targeted TSCS strategies modulate lower-limb motor output and improve gait in individuals with chronic, incomplete SCI. Participants engage in walking and sitting tasks while receiving TSCS with electrode placements designed to stimulate midline or lateral spinal regions. By adjusting cathode and anode positions, stimulation is tailored to recruit ipsilateral motor pools. Step length asymmetry, posterior root-muscle (PRM) reflexes, and gait metrics are analyzed to assess how spatial targeting influences motor coordination. Additionally, temporal synchronization is explored to optimize corticospinal connectivity across the level of injury. This investigation into the alignment of spinal stimulation with cortical motor intent can enhance neuromodulatory effects, further personalizing BCI-TSCS pairing. Current findings suggest that laterality-targeted TSCS preferentially activates ipsilateral motor pools, reflected by significant laterality indices in PRM reflex amplitude. Cortically synchronized TSCS further enhances muscle recruitment compared to asynchronous delivery, consistent with timing-dependent plasticity, although optimal timing may vary with injury level. These findings support the use of targeted and time-locked TSCS as a personalized strategy to improve locomotor control after SCI. Integrating paired activation may enable scalable, non-invasive interventions that leverage residual neural pathways for functional restoration.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

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Program #/Poster #: PSTR445.03/M4

Topic: D.05. Spinal Cord Injury and Plasticity

Support: The Miami Project to Cure Paralysis and The Buoniconti Fund
JSPS KAKENHI Grant number JP24KJ2126

Title: Brain-controlled transcutaneous spinal cord stimulation for restoring lower limb function after incomplete spinal cord injury

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Abstract: Transcutaneous spinal cord stimulation (TSCS) has been supported by growing evidence as a promising intervention for motor function recovery in individuals with spinal cord injury (SCI). The combination of TSCS and brain-computer interface (BCI) technology (BCI-TSCS) has the potential to enhance neuromodulatory effects by integrating spinal activation with voluntary motor intention. This study aimed to investigate the effects of the BCI-TSCS intervention on the lower-limb motor function and neural activity in individuals with chronic incomplete SCI. Participants underwent two different interventions on separate days: (1) BCI-TSCS: TSCS was delivered for 5 sec to the thoracolumbar spinal cord region when the brain activity was detected during motor imagery of ankle dorsiflexion; and (2) Random TSCS: TSCS was delivered in 5-second bursts at random intervals while the participants remained at rest without imagining any movement. Both interventions lasted 30 minutes, and TSCS was delivered at a frequency of 30 Hz with an intensity corresponding to the motor threshold, defined as the lowest intensity required to elicit visible spinal reflexes. The stimulation site was between the T12 and L3 vertebrae regions, where the strongest spinal reflex responses were elicited in the tibialis anterior (TA) muscle, targeting dorsal root sensory fibers. In the BCI-TSCS condition, TSCS was triggered in real-time by the detection of event-related desynchronization of cortical oscillatory activity via electroencephalography during motor imagery of ankle dorsiflexion. Motor performance was evaluated using two tests: the foot tapping test and the lower-extremity motor coordination test. Corticospinal and spinal excitability were assessed by eliciting motor evoked potentials (MEP) and posterior root-muscle reflexes in the TA muscle. All the assessments were conducted before and after each intervention. As a result, motor performance significantly improved after the BCI-TSCS ($p<0.05$). Furthermore, the BCI-TSCS condition showed a significant increase in MEP amplitudes in the TA muscle immediately after the intervention ($p<0.05$), indicating enhanced corticospinal excitability. By contrast, no changes in motor performance or corticospinal excitability were observed after the Random TSCS. Our results suggest that synchronization between the TSCS and cortical activity during motor intent may facilitate connections between neural pathways in the brain and spinal cord. This novel intervention demonstrates the importance of the intent-triggered neuromodulatory approaches for optimizing therapeutic benefits in individuals with incomplete SCI.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.04/M5

Topic: D.05. Spinal Cord Injury and Plasticity

Support: a Grants-in-Aid for Scientific Research (KAKENHI) from the Japan Society for the Promotion of Science (JSPS)(24KK0182)
The Miami Project to Cure Paralysis and The Buoniconti Fund

Title: Altered Muscle Coordination Patterns Underlying Gait Asymmetry After Incomplete Spinal Cord Injury

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Abstract: Restoring effective gait function after spinal cord injury (SCI) is a critical rehabilitation objective, significantly influencing patients' quality of life and social participation. Step length asymmetry (SLA) following SCI is often associated with impaired walking speed, and likely a consequence of lateralized corticospinal damage and maladaptive spinal circuit reorganization which results in asymmetric muscle activations. Therefore, specific neuromuscular deficits and motor patterns underpinning gait asymmetry require further clarification. Neuromuscular coordination during overground walking relies heavily on muscle synergies—functional groups of muscles co-activated to address specific biomechanical demands. This study aimed to identify the neuromuscular coordination deficits associated with SLA by analyzing muscle synergy patterns during overground walking in chronic incomplete SCI subjects (AIS C/D) and able-bodied (AB) controls. Gait analysis was performed using a three-dimensional motion analysis and wireless EMG, which recorded muscle activation patterns from 32 muscles bilaterally across the upper limbs, lower limbs, and trunk groups. Muscle synergies were extracted using non-negative matrix factorization (NNMF). Results showed significantly lower walking speeds in SCI subjects compared to AB controls, and significantly greater SLA in SCI subjects compared to AB subjects. SCI participants who consistently took a shorter step with their less-affected leg were particularly affected. Muscle synergy analysis identified distinct synergies in AB controls and showed less robust muscle synergies in individuals after SCI. Specifically, AB controls exhibited independent synergies related to initial contact preparation, weight acceptance, and push-off, whereas individuals with SCI demonstrated a merging of these synergies on the affected leg. This merging indicates reduced neuromuscular complexity and increased muscle co-contraction on the affected leg, potentially leading to inadequate stance phase function. Consequently, this results in a smaller step length on the less-affected leg, causing increasing SLA. Rehabilitation approaches targeting the normalization and restoration of these merged muscle synergy patterns could potentially improve gait quality by reducing SLA to enhance walking speed.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.05/M6

Topic: D.05. Spinal Cord Injury and Plasticity

Support: State of Florida Grant

Title: Assessing Corticospinal Excitability During Brain-Computer Interface Use in Individuals with Incomplete Spinal Cord Injury

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Abstract: Brain-computer interface (BCI)-mediated stimulation enables real-time detection of motor intention, providing a tool to examine volitional modulation of descending motor pathways. While task-dependent engagement of corticospinal circuits has been demonstrated in individuals without central nervous system injury, its investigation in motor-incomplete spinal cord injury (SCI) remains limited. Here, we used a BCI-triggered transcranial magnetic stimulation (TMS) paradigm to examine whether a switch control-based BCI detection during motor imagery modulates corticospinal excitability in individuals with SCI, and to what extent this modulation reflects cue selectivity. Participants with chronic, motor-incomplete cervical SCI (AIS C/D, T10 and above) completed a single-session BCI-TMS protocol in which motor-evoked potentials (MEPs) were recorded from the stronger tibialis anterior (TA) muscle. Sessions began with a calibration phase of randomized left and right ankle dorsiflexion imagery trials while EEG was recorded. Event-related spectral perturbation (ERSP) maps identified individualized sensorimotor features—specifically, the optimal electrode and frequency band showing maximal event-related desynchronization (ERD) —for configuring the BCI. In the stimulation phase, participants viewed randomized cues. The BCI system monitored real-time ERD at subject-specific electrodes and triggered a single pulse TMS over the leg motor cortex at 120% of resting motor threshold when ERD exceeded a subject-specific threshold. Trials were labeled as congruent when the visual cue matched the hemisphere stimulated (e.g., right leg imagery with left motor cortex stimulation), and incongruent when the cue corresponded to the opposite limb. MEPs from TA showed robust facilitation in congruent trials and moderate facilitation in incongruent trials, indicating task-dependent modulation with limited selectivity. These findings demonstrate that BCI-triggered TMS can investigate task-dependent modulation of corticospinal excitability during volitional motor imagery in motor-incomplete SCI. Observed MEP facilitation suggests preserved descending motor engagement in response to intention-driven cortical activity. However, modest cue selectivity highlights the limitations of non-

lateralized detection and motivates the development of targeted BCIs to detect limb-specific motor intent. Such systems may support more targeted strategies to enhance limb-specific engagement.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

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Program #/Poster #: PSTR445.06/M7

Topic: D.05. Spinal Cord Injury and Plasticity

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International Foundation for Research in Paraplegia
Translational Medical Research Award 2021
Think2Move SNF-32003BE-205563, ANR-21-CE19-0038
European Commission (EIC 2021-Transition Challenges-01-01 ReverseParalysis 101057450, Horizon-EIC-2021-Pathfinder Challenges-01-02 NEMO-BMI 101070891)

Title: A digital bridge between the brain and spinal cord that restores lower limb movements after complete spinal cord injury

Authors: *V. SPAGNOLO[1], L. COQUOZ[1], G. CARPARELLI[1], N. INTERING[1], C. DESCHENAUX[1], S. HERNANDEZ CHARPAK[1], N. HANKOV[1], T. COLLIN[1], I. SAKR[1], S. CRUZ[1], A. GALVEZ[1], F. MARTEL[2], P. CARVALHO[1], M. D'ERCOLE[3], L. BOLE-FEYSOT[1], A. WATRIN[3], S. KARAKAS[2], M. BOSQUET[2], T. AKSENOVA[2], C. HAXAIRE[1], F. BECCE[4], V. AURELI[1], R. DEMESMAEKER[1], J. SQUAIR[1], L. ASBOTH[1], G. CHARVET[2], J. BLOCH[1], G. COURTINE[1], H. LORACH[1];
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Abstract: We previously designed a wireless digital bridge between the brain and spinal cord that restored walking in an individual with incomplete spinal cord injury (SCI). This digital bridge links the decoding of motor intentions recorded at the level of the motor cortex to modulation of epidural electrical stimulation (EES) applied over the lumbosacral spinal cord. Here, we improved various features of the technologies incorporated in the digital bridge, including the recording system WIMAGINE that measures electrocorticographic activity from the epidural surface of brain, and the neurostimulation platform for precise stimulation of the spinal cord developed by Onward Medical. Two participants with chronic thoracic SCI who presented with complete motor and sensory paralysis were recruited in the study. Pre-operative

planning based on anatomical and functional MRI guided the precise implantation of the recording and stimulating devices in a single surgery. After three days of calibration, both participants regained volitional control over the movement primitives that underlie walking, such as knee extension and hip flexion. Both rapidly transited to brain-controlled stepping movements, although partial assistance of leg movements and bodyweight support were necessary at this stage. Eventually, they could regain proportional control over 6 different lower limb joints movements with high accuracy and regained independent walking without bodyweight support. These results are defining the neurological and technological requirements to restore lower limb motor functions after spinal cord injury.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

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Topic: D.05. Spinal Cord Injury and Plasticity

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International Foundation for Research in Paraplegia
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Think2Move SNF-32003BE-205563, ANR-21-CE19-0038
European Commission (EIC 2021-Transition Challenges-01-01 ReverseParalysis 101057450, Horizon-EIC-2021-Pathfinder Challenges-01-02 NEMO-BMI 101070891)

Title: Long term use of a digital bridge to restore lower limb function

Authors: *L. COQUOZ[1,2,3], V. SPAGNOLO[4,2,3], N. INTERING[4,2,3], C. DESCHENAUX[4,2,3], A. GALVEZ[4,2,3], G. CARPARELLI[4,2,3], S. HERNANDEZ CHARPAK[4,2,3], P. CARVALHO[4,2,3], N. HANKOV[4,2,3], T. COLLIN[4,2,3], I. SAKR[4,2,3], F. MARTEL[5,6], M. SIMONDIN[4,2,3], M. D'ERCOLE[7], A. WATRIN[7], S. KARAKAS[5,6], M. BOSQUET[5,6], L. BOLE-FEYSOT[4,2,3], J.-B. LEDOUX[3], F. BECCE[8], V. AURELI[4,2,3], S. CARDA[3], T. AKSENOVA[5,6], R. DEMESMAEKER[4,2,3], L. ASBOTH[4,2,3], G. CHARVET[5,6], J. BLOCH[4,2,3], G. COURTINE[4,2,3], H. LORACH[4,2,3];
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Abstract: A spinal cord injury (SCI) disrupts communication between the brain and the region of the spinal cord responsible for walking, resulting in paralysis. In this study, we reestablished this communication using a digital bridge between the brain and spinal cord. This bridge is composed of fully implanted recording and stimulation systems that establish a direct link between cortical signal and the analogue modulation of epidural electrical stimulation (EES) targeting the lumbosacral spinal cord. Three participants underwent the implantation of the digital bridge: one individual with incomplete tetraplegia (P1, C5 AIS-D, 38-year-old male, 10 years post-injury) and two individuals with complete paraplegia (P1: T8 AIS-A, 38-year-old female, 6 years post-injury; P2: T8 AIS-A, 37-year-old female, 14 years post-injury). Following 2-week of recovery from surgery, a calibration phase was conducted—lasting 27 days for P1 and 10 days for P2 and P3. Cortical signals stabilized within the first month after implantation and then remained stable over periods of months and years. This long-term stability enabled stable decoding of movement intentions in all three participants who successfully used the system to recover up to 6 different movements of the legs. They then engaged in an intensive neurorehabilitation program lasting 4 to 6 months, including walking, standing, joint-specific movements, strength training, balance exercises, and tone regulation. Throughout this period, participants used various assistive devices and received different levels of assistance. Preliminary results suggest that rehabilitation supported by the digital bridge restored independent walking in all participants, but only participants with incomplete SCI showed neurological recovery that persisted when the bridge was turned off.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

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Program #/Poster #: PSTR445.08/M9

Topic: D.05. Spinal Cord Injury and Plasticity

Support: ReWIRE: Horizon Europe, Marie Skłodowska-Curie Actions (MSCA) Doctoral Network, Grant ID: 101073374

Title: A digital bridge between the brain and spinal cord that restores arm and hand movement after spinal cord injury

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Abstract: Cervical spinal cord injury (SCI) disrupts the communication between the brain and the regions of the spinal cord that produce arm and hand movements, resulting in permanent impairments of upper-limb motor function. Epidural Electrical Stimulation (EES) can improve arm and hand movements in people with SCI and stroke. EES recruits large diameter afferent fibers where they enter the spinal cord, which leads to the activation of motor neurons embedded in the segments innervated by the stimulated roots. Based on this physiological principle, arm and hand movements could theoretically be produced by delivering EES with spatial and temporal sequences that coincide with the desired movements. Here, we hypothesized that decoding of desired movements from brain activity could modulate the location and timing of EES applied to the cervical spinal cord to restore volitional control of impaired arm and hand movements in people with chronic tetraplegia. We enrolled two participants presenting with incomplete C3/C4 SCI that led to near complete paralysis of the arm and hand on one side of the body. Two electrode arrays were implanted in each participant to cover spinal segments spanning C4 to T1. The arrays were each connected to implanted pulse generators endowed with real-time triggering capabilities (ONWARD IPGs). In a second surgery, we implanted a 64-electrode system (WIMAGINE) over the epidural surface of the sensorimotor cortex to record electrocorticographic (ECoG) signals. We optimized electromyographic activity and induced kinematics with various stimulation parameters, building a heuristic myotome with frequential preferences for motor neuron activation. From the ECoG signals, we built algorithms to decode up to 6 isolated movements. We then modulated optimized EES parameters based on this decoding and observed improved performance of arm and hand movements, including during functional tasks. Rehabilitation augmented by this digital bridge led to neurological improvements that persisted even when the bridge was turned off. These preliminary results are compatible with long-term stability and safety profiles of the digital bridge that must now be confirmed in a broader population of patients.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

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Program #/Poster #: PSTR445.09/M10

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Ontario Neuro-trauma Foundation 2016-RHI-PREV-1019
Natural Sciences and Engineering Research Council of Canada DGRGPIN-201706790
Ontario Graduate Scholarship

Title: Improved reactive foot placement after balance training in people with incomplete spinal cord injury

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Abstract: Falls are a leading cause of injury and loss of independence among individuals with incomplete spinal cord injury (iSCI), partly due to impaired reactive stepping. In a previous cross-sectional study, we found that individuals with iSCI exhibit inadequate foot placement during the first reactive step in a lean-and-release (LR) test. Our longitudinal findings also showed that balance training improves reactive stepping performance. However, it remains unclear whether these improvements reflect changes in foot placement strategies. This study aimed to examine 1) how foot placement, quantified using margin of stability (MOS), is affected by balance training, and 2) whether MOS is associated with clinical measures of balance and mobility. Data from 12 individuals with iSCI were analyzed. Participants completed an 8-week conventional or perturbation-based balance training (3x/week), which included stable, unpredictable, and participant selected tasks. Reactive stepping was assessed using the LR test, which simulates a forward fall, before and after balance training, and at a 3-month follow-up. We calculated the average and variability of foot placement measures, including extrapolated center

of mass (XCOM), base of support (BOS), and MOS. Clinical measures of balance and mobility included the Mini-Balance Evaluation System Test (mini-BEST) and Community Balance and Mobility (CB&M) scale. We found a significant increase in average MOS and a reduction of MOS variability after balance training (μ_MOS:p=0.015; variability of MOS: p=0.008). In addition, we found no change in average BOS (p=0.878) from balance training, but a significant reduction in BOS variability from pre- to post-training (p=0.020) and from pre-training to follow-up (p=0.038). In contrast, the average XCOM decreased significantly from pre- to post-training (p=0.003) and from pre-training to follow-up (p=0.033), while XCOM variability did not change from balance training (p=0.298). Across time points, average MOS was significantly correlated with mini-BEST scores (pre: r=0.642, p=0.024; post: r=0.842, p=0.001; follow-up: r=0.547, p=0.066) and CB&M scores (pre: r=0.585, p=0.046; post: r=0.680, p=0.015; follow-up: r=0.636, p=0.030), except for mini-BEST score during follow-up. MOS variability was not significantly correlated with clinical measures, except with mini-BEST score at post-training. In conclusion, individuals with iSCI demonstrated improved reactive foot placement strategies after balance training, characterized by increased and more consistent MOS. These changes were significantly associated with improved clinical measures of balance and mobility.

Disclosures: J.W. Lee: None. **K. Chan:** None. **J. Unger:** None. **M. Heffernan:** None. **K. Musselman:** None. **K. Masani:** None.

Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.10/M11

Topic: D.05. Spinal Cord Injury and Plasticity

Support: CN SCIRTS Pilot Award

Title: Kinematic assessment using a small portable 3D camera for seated balance: Does it measure up to force plate center of pressure in individuals with spinal cord injury

Authors: *M. N. HATCH[1], P. S. PIRBHOY[2];
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Abstract: ***Objectives:*** There exists a major gap in the field regarding measuring and tracking trunk stability in people with spinal cord injury (SCI) despite its impact when performing various activities of daily living and ranked importance by people with SCI. This is partly due to the lack of available quantitative measures that currently exist. Small portable depth camera systems have shown great promise for movement analysis in a variety of clinical populations, and may be suitable for measuring trunk stability in SCI. In this study we: (1) assessed movement reliability using center of pressure (CoP) from force plates across a standardized set of seated trunk tasks, and (2) assessed the feasibility of predicting CoP using a single 3-dimensional camera, in thoracic-lumbar SCI. ***Methods/ approach:*** Seventeen individuals with thoracic-lumbar SCI

passed pre-screened for this study, with 13 subjects enrolled. Subjects had to be at least 12 months post injury, able to sit unsupported for 60 seconds, have a T1-L2 inury, and be free of pressure sores in the feet, thighs or hips. Subjects performed 15 different static and dynamic seated tasks (5 reaching and 8 leaning) while being simultaneously recorded by force plates and a 3D Microsoft Kinect sensor, twice within 2 weeks, and to their fullest extent. 3D data was post-processed in MATLAB using a custom models. Max CoP excursion and mean velocity were computed from both the force platforms and the estimated CoP from the depth camera. Intra-class correlation coefficients were used for movement reliability. Bland-Altman was used to determine reliability between the devices. ***Results:*** All participants completed the seated tasks with no issues. Reaching tasks displayed very high reliability (ICC > 0.90) in CoP end excursion from the force plate. Leaning tasks were mixed, with the back leaning tasks displaying slightly lower reliability (~0.80), and 1 task - leaning straight back - displaying the lowest reliability overall at 0.68. Mean velocities for all leaning and reaching tasks displayed excellent reliability across tasks. Movement reliability was similar for predicted CoP from the depth camera. When comparing reliability between devices, differences arose between tracking from the chest (upper body) versus from the hips. ***Conclusion(s):*** Portable 3D cameras reliably measure trunk stability in people with SCI. However, 3D tracking from the chest versus the hips for endpoint metrics can show different movements and results in some individuals.

Disclosures: M.N. Hatch: None. **P.S. Pirbhoy:** None.

Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.11/M12

Topic: D.05. Spinal Cord Injury and Plasticity

Support: NIH Grant R01 HL150581
NIH Grant R01 HL168294
Kentucky Spinal Cord and Head Injury Research Trust

Title: Characterizing volitional cough techniques to inform respiratory rehabilitation strategies for individuals with spinal cord injury

Authors: *N. S. THARU[1], A. M. WILLHITE[1], I. SHEKHOVTSOV[1], A. BULLOCK[2], T. PITTS[4], A. V. OVECHKIN[3];
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Abstract: Coughing is essential for maintaining airway hygiene and preserving respiratory function. Individuals with high-level spinal cord injury (SCI) frequently experience impaired cough due to paresis of both primary and accessory respiratory muscles. This deficit compromises their ability to clear airway secretions and foreign material, markedly increasing

the risk of pulmonary complications. Despite this clinical challenge, targeted rehabilitation strategies to retrain effective cough in individuals with SCI remain undeveloped.
As part of a broader effort to establish a respiratory rehabilitation framework for chronic SCI, this pilot study aimed to characterize cough impairments and evaluate the efficacy of distinct coached cough techniques. Five individuals with chronic SCI and five healthy controls were assessed using three voluntary cough paradigms: (a) less coached cough, (b) time-coached cough, and (c) super-coached cough with biofeedback. All participants received standardized instructions for each maneuver. To assess respiratory musculature fatiguability, we also evaluated respiratory and cough function following a 3-minute inspiratory-expiratory pressure threshold loading task. Primary outcome measures included spirometry and surface electromyography (sEMG) recorded during cough.
The results showed that individuals with SCI had reduced inspiratory peak flow (IPF) and expiratory peak flow (EPF), along with delayed recruitment of large respiratory motor units. Of the techniques tested, the time-coached cough elicited the highest IPF and EPF values, with shorter rise times and faster IPF-to-EPF transitions. This approach also facilitated broader muscle activation and more rapid recruitment of peak sEMG. Moreover, the inspiratory-expiratory loading task appeared to act as a priming stimulus enhancing neuromuscular readiness and improving peak expiratory flow and other cough-related parameters. These findings support the feasibility of structured, cue-based cough training as a promising strategy to improve airway clearance and mitigate respiratory complications in individuals with SCI. Future work will focus on targeted interventions to enhance recruitment of large motor units for effective cough restoration.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.12/Web Only

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Functional outcome and topographical analysis of cervical epidural stimulation for upper limbs weakness and spinal cord injury: from trial period to permanent implantation

Authors: *S.-T. TSAI[1], H.-L. HUANG[2], Y.-C. CHEN[3];
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Abstract: Background: Dreadful experience of upper-limb motor impairment after cervical spinal cord injury represents a significant burden for patients. The effective treatment for motor deficit during the chronic phase is limited. We tested temporary cervical spinal cord stimulation (SCS) combined with rehabilitation to explore whether it could facilitate motor recovery in

patients with severe arm impairment.Methods: Two participants with cervical spinal cord injury and persistent upper-limb paralysis more than one year were recruited. Two linear SCS electrodes were implanted with specific targeting dorsolateral epidural space to excite the cervical spinal roots and their connected muscular activity. We did neurophysiological mapping intra-operatively and post-operatively with electromyography (EMG) to identify the electrodes with maximal muscular excitation. Clinical evaluation was done with scores for spinal cord injury to examine the effectiveness of motor recovery.Results: After 30 days of combined cervical SCS and rehabilitation, both facilitated motor recovery in the severely impaired upper limb and enabled voluntary movements. The lateral electrodes where close to the existing cervical dorsal roots could reach segmental muscular contraction with less stimulating amplitudes. Enhanced muscle activation patterns were consistently noted in targeted areas. One individual with chronic spinal cord injury and AIS grade A was even able to independently hold the folk during meal using the severely impaired right hand after permanent SCS implantation.Conclusions: Through direct activation of cervical roots, cervical SCS can stimulate impaired circuits to reactivate neural pathways, and enhance neuroplasticity to sustain improvement of functional movement for impaired upper-limb deficit from cervical spinal cord injury. Our results suggest that long-term cervical SCS and design of individualized electrodes might be warranted for addressing various central nervous system injury related upper-limb impairment.

Disclosures: S. Tsai: None. **H. Huang:** None. **Y. Chen:** None.

Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.13/M13

Topic: D.05. Spinal Cord Injury and Plasticity

Support: NIH R01 (ZZK)
Craig H. Neilsen Fellowship (PC)
Lantheous (ZZK)

Title: Task specific rehabilitation therapy improved intraspinal blood flow and functional recovery following cervical unilateral injury in a rodent

Authors: *G. J. HERNANDEZ[1], Z. Z. KHAING[3], P. CHANDRAN[1], A. ODARENKO[1], J. ROBERTS[2], N. LAM[2], P. GARNES[2];
[1]Neurolog. Surgery, [2]Univ. of Washington, Seattle, WA; [3]Univ. of Louisville, Louisville, KY

Abstract: Despite significant research efforts, there are little to no ways of mitigating damage in the cervical spinal cord following traumatic spinal cord injuries (SCI). Cervical spinal cord injuries (cSCI) are especially detrimental, leading to functional deficits in breathing and upper limb function, greatly impacting quality of life. We hypothesized that animals treated with

physical therapy (PT) following a cSCI would have functional improvement and improved blood flow compared to animals without treatment. Here we used a unilateral cSCI model and performed a Task Specific Training - Forelimb Reaching Task (FRT) as a PT treatment (PT = FRT 4x/wk) in adult female Long Evans Rats. Behavioral testing consisted of FRT, and Forelimb Score (FLS). Two cohorts were used; Cohort 1 received training from 2- 14wpi; Cohort 2 received training from 4-10wpi. Behavioral analysis of Cohort 1 showed increased general locomotor functional recovery recorded using FLS in SCI+PT group (n=7) compared to SCI group (n=5) ($p<0.01$). FRT data showed a trend towards slight improved skilled recovery following proposed spontaneous recovery only, although this difference did not reach statistical significance. Hemodynamic measurements were performed using contrast enhanced ultrasound (CEUS) imaging at three time points: prior to injury, immediately following Injury, and the end of experimental period. CEUS imaging showed a trend of increased blood volume at the injury center in the SCI+PT group (n=5) compared to SCI (n=4) groups. Histological studies examining microvessel density showed that SCI+PT group had increased microvessel density 1mm caudal to the injury compared to SCI ($p<0.05$). In summary, our study showed that early physical therapy training can improve intraspinal blood flow, improved microvessel density and improve functional recovery.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.14/M14

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation (PC)
NIH R01 NS121191 (ZZK)
Lantheous (ZZK)

Title: Intermittent hypoxia improves intraspinal blood flow and recovery after SCI

Authors: *P. P C[1,4], A. ODARENKO[2,5], L. N. CATES[3,5], M. BRUCE[2], Z. Z. KHAING[6,5]; [1]Neurolog. Surgery, [3]Dept. of Neurolog. Surgery, [2]Univ. of Washington, Seattle, WA; [4]Anatom. sciences and Neurobio., [5]Anatom. Sci. and Neurobio., [6]Univ. of Louisville, Louisville, KY

Abstract: Spinal cord injury (SCI) is a devastating condition leading to loss of motor and sensory function. While most research has focused on the lesion epicenter, growing evidence suggests that region below injury also undergo significant neuronal and vascular alterations that can affect the recovery of function. The lumbar spinal cord, contains critical locomotor circuits which innervate the hind limbs, making it an important target for interventions aimed at restoring function. Recent analyses from our lab using contrast enhanced ultrasound (CEUS) imaging have

revealed a reduction in blood volume and increased vascular resistance with injury severity in the lumbar region following a thoracic (T8/9) injury in chronic stage in rats. Interestingly, these vascular alterations were accompanied by a reduction in both serotonin innervation and pericyte coverage in the lumbar region. These cellular changes may compromise the regulation of vascular tone contributing to impaired intraspinal blood flow. We hypothesize that vascular and cellular alterations in the caudal region of the spinal cord contribute to the functional deficit after SCI and improving the blood flow through intermittent hypoxia (IH) training can enhance recovery. To investigate this, we utilized a severe contusion injury model (250Kdyne + 2s dwell time) at T8/9 in adult female Long-Evans rats. IH training began at 4-week post injury (wpi) and continued for 5 weeks. Animals were exposed to 5 minutes cycles of alternating hypoxia (10% oxygen) and normoxia (21% oxygen) 10 times daily, for 5 days a week. CEUS imaging was used to assess blood volume and flow velocities within the lumbar spinal cord at acute (before IH training), and chronic (at 11 wpi (after IH training)) timepoints. Results showed that the IH training group exhibited a progressive improvement in the BBB score, with a gradual improvement in locomotor function observed across weekly assessment up to 11 wpi, compared to the SCI group (BBB score at 11wpi for SCI (10.4± 0.60), SCI +IH (12.5 ± 0.5); n=5/group). Additionally, the preliminary results showed that IH training improved the blood volume and vascular resistance in the distal region. Notably, in SCI+IH animals, the vascular response to hypoxia increased markedly from the acute stage (5.3% in GM and 16.88% in WM) to the chronic stage (−100.05% in GM and −72.95% in WM), indicating an improved vascular response in the chronic stage with IH training. Combined, our finding suggests that IH training ameliorates hypoperfusion in regions caudal to the injury, and this may correlate with improved functional recovery.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.15/M15

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Trans-synaptic anterograde tracing of connectivity in complex regenerating circuits

Authors: M. MANSOOR[1], I. LAZAROVITS[2], A. SALCIDO[2], Y. MAGAÑA[4], M. J. CASTLE[3], ***J. KOFFLER**[4];
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Abstract: Cell therapy offers a promising strategy for treating spinal cord injury (SCI). However, stem cell-derived neurons extend axons in a disorganized manner, greatly diminishing the likelihood of establishing appropriate connectivity across the injury site. In addition,

implanted stem cells form a highly complex network of interconnections within the graft, meaning that any signal traveling caudally from the brain must efficiently traverse multiple synapses. But are they on the right path, and do they reach the correct target caudal to the injury?We hypothesize that spatial organization plays a pivotal role in enabling the formation of functional neural circuits that support improved recovery following SCI. We are using 3D-printed scaffolds engineered with linear microchannels designed to align and guide axons within SCI site. HSV tracing provides a uniquely powerful tool to study these neural relays, allowing us to visualize both anatomical and functional connections across the injury site, even within dense neural network. We used a rat T10 complete spinal cord transection model, followed by acute implantation of scaffolds seeded with rat E14 spinal cord stem cells. Eight weeks post-implant, we injected AAV9-Cre into the motor cortex, targeting the corticospinal tract (CST). Four weeks later, we delivered HSV-1 strain H129ΔTK-TT into the CST for trans-synaptic anterograde tracing. We monitored tdTomato expression by HSV at the lumbar spinal cord 2-4 days post-injection and observed that longer incubation times was beneficial. To detect HSV-labeled neurons we developed a new method for RNAscope in situ hybridization that uses a mixture of RNA probes to detect multiple highly expressed HSV immediate early transcripts. Because replicating HSV rapidly kills host cells and tdTomato requires sufficient protein translation to be detectable, we hypothesized that labeling early viral transcripts would broaden the temporal window for detection and increase the number of HSV-labeled neurons. We found HSV labeling in the intact lumbar spinal cord caudal to the injury site. HSV-labeled host neurons expressed NeuN and ChAT. These target neurons were located within the intermediate zone where known CST projections and synaptic connections exist. These data suggest that the organized neural relay formed within the scaffold closely resembles the connectivity of the original CST tract. Together, these findings demonstrate that HSV tracing and sensitive HSV RNA detection are useful tools to study complex neural circuits in the CNS. Our data provide evidence that 3D-printed scaffolds facilitate the formation of appropriate spatial connectivity across SCI site.

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Poster

PSTR445: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.16/M16

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Craig H Neilsen Fundation 1165211
Morton Cure Paralysis Fund
The Nakatomi Foundation

Title: Applications of transcutaneous spinal cord stimulation after acute spinal cord injury: a case series

Authors: *R. NAKAHARA, S. NASSON, E. PUTSCHE-YOUNG, E. CHUNG, L. WINSTON, S. BURNS, D. CRANE, C. T. MORITZ, S. SAMEJIMA;
Univ. of Washington, Seattle, WA

Abstract: Spinal cord injury (SCI) at or above the sixth thoracic spinal segment (T6) impairs cardiovascular control, leading to severe autonomic dysreflexia (AD) and orthostatic hypotension (OH). Transcutaneous spinal cord stimulation (tSCS) has shown improvements in motor, sensory, and autonomic function in individuals with chronic SCI. Preclinical evidence suggests that spinal cord stimulation promotes myelination and functional recovery in the acute and subacute stages of SCI. Little clinical studies have, however, investigated the effect of tSCS on functional recovery shortly after the injury onset. This study aimed to evaluate the feasibility of tSCS in individuals with subacute motor-complete SCI. Three individuals with SCI (P1: 32 years old (y/o), C4 American Spinal Injury Association Impairment Scale (AIS) A; P2: 31 y/o, T4 AIS A; and P3: 21 y/o, T6 AIS A) were included. tSCS was delivered at the T11-T12 and L1-L2 spinous processes using surface electrodes with biphasic pulses (1 ms, 30 Hz, 196.5 ± 7.9 mA [160-200 mA]) for 60-90 minutes. The intervention was conducted in a seated position without any concurrent therapy. P1 received five tSCS sessions, which started 26 days post-injury in the inpatient unit. P2 and P3 started tSCS sessions 81 days and 114 days post-injury, respectively. Both participants completed 18 sessions in the outpatient setting. Neurological function, cardiovascular function and standardized questionnaires for autonomic function were assessed at baseline and post-intervention. All participants completed the assigned tSCS sessions with 100% adherence and no adverse events. No episodes of AD or OH were observed throughout the intervention period. The ISNCSCI exam in the absence of tSCS, conducted 2 days post-intervention in P1 and P2, and 6 days post-intervention in P3, revealed improvements in the neurological level of injury and AIS (P1:C4 AIS A to C5 AIS A; P2: T4 AIS A to T5 AIS B; P3: T6 AIS A to T6 AIS B). All participants presented improved bowel function, as evidenced by the time needed for bowel management and the neurogenic bowel dysfunction score. There was no change in bladder function. These findings present preliminary feasibility data on lumbosacral tSCS in the subacute stage of SCI. Potential contributions from tSCS in addition to spontaneous recovery remain unclear. Further research will assess the safety and efficacy of tSCS in promoting autonomic recovery in a larger sample with appropriate controls.

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Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.01/N1

Topic: E.01. Somatosensation – Pain and Itch

Support: NIA 4R33AG075419

Title: Upregulation of potassium channels through AAVs reduces nociceptor firing as a treatment for chronic pain in an aged population

Authors: *S. E. GEIS, C. A. BANNERMAN, A. H. HELD, R. Y. MEIR, P. SENARATNE, S. ST PIERRE, B. WAINGER;
Neurol., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Chronic pain and high-impact chronic pain affect approximately 36% and 13.5% of people aged above 65 years, respectively. The yearly economic burden of chronic pain and high-impact chronic pain has been shown to exceed over $500 billion. Our group has recently demonstrated efficacy of an intrasciatic nerve injection of adeno-associated viruses (AAV) formulated with either a human synapsin (hSyn) promoter or a short promoter (sProm). The AAVs drive overexpression of potassium channels, thus dampening nociceptor responses in adult mice within inflammatory and neuropathic pain models. However, whether the AAVs still effectively work within an aged animal is unknown. Here, we present evidence that demonstrates a successful transduction of ipsilateral neurons within lumbar dorsal root ganglia (L3-L5) using AAV delivery of eGFP with both the hSyn promoter and the sProm in male and female aged mice (18 months, n=4 per condition). Our exploratory immunohistochemistry analysis reveals no difference in the percentage of transduced neurons between hSyn and sProm. We also evaluated the transduction rates of specific neuronal subpopulations between the two promoters. We assessed the percentage of transduced neurons that express calcitonin-gene-related peptide (CGRP), isolectin B4 (IB4), and neurofilament 200 (NF200). Additionally, we used a high-content calcium imaging assay to detect changes in optical threshold for calcium flux in dissociated sensory neurons from TrpV1::ChR2 mice following intranerve AAV delivery of potassium channels. We found that injection of AAVs using either promoter in the aged mice significantly decreased the percentages of nociceptors activated by increasing trains of optical stimuli. Together, these data provide evidence that AAV delivery of potassium channels shows congruent effects in aged animals to those previously shown in younger animals. This work highlights the potential use of AAV localized injections to treat severe focal chronic pain in the elderly.

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Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.02/N2

Topic: E.01. Somatosensation – Pain and Itch

Title: Innovative Approach for Diabetic Foot Neuralgia with KLS-2031, Novel Triple-genetic AAV, Produced Sustanined Therapy

Authors: Y. CHOI[1], H. JI[1], K.-R. KIM[1], Y. LEE[1], J. LEE[1], H. LEE[2], ***S.-O. HONG**[1], S. KIM[1]; [1]KOLON LIFE SCIENCE, Seoul, Korea, Republic of; [2]Kolon Life Sci., Seoul, Korea, Republic of

Abstract: ***Background and Objectives***
Peripheral neuropathy is the most common type of diabetes-related nerve damages, which often affects patients' feet. Diabetic peripheral neuropathy (PDPN) significantly deteriorates patients' quality of life, imposes a substantial socioeconomic burden and curative treatment is not available. Limited sustainability of current pharmacological treatments with the adverse effects evokes a the need for novel, durable, and well-tolerated therapeutic modalities. This study investigates the analgesic efficacy of KLS-2031, a recombinant adeno-associated virus (AAV) vector expressing glutamate decarboxylase 65 (GAD65), glial cell line-derived neurotrophic factor (GDNF), and interleukin-10 (IL-10), in rodent models of PDPN.
Methods
PDPN was induced in male and female Sprague-Dawley rats *by* streptozotocin (STZ) administration. KLS-2031 was delivered to the dorsal root ganglia (DRGs) through transforaminal epidural injection following the onset of mechanical allodynia. Behavioral assessments were conducted using *von Frey filament* testing on bilateral hind paws. Therapeutic efficacy was compared among pregabalin, duloxetine,and KLS-2031 treatment groups. In addition, the therapeutic effect of KLS-2031 was assessed in STZ-induced diabetic rats treated with subcutaneous insulin implants to simulate patients under glycemic control. Immunohistochemical analyses of lumbar (L4) DRGs and L1 spinal cord segments were performed to elucidate the underlying mechanisms of action.
Results
KLS-2031 treatment resulted in robust and sustained improvement of mechanical allodynia in both sexes, with no significant gender-related differences in analgesic response. A single administration of KLS-2031 produced superior and longer-lasting pain control compared to daily administration of pregabalin or duloxetine. Notably, KLS-2031 maintained efficacy in insulin-treated diabetic rats, indicating its potential utility in clinically relevant scenarios. Histological analyses revealed that KLS-2031 mitigated neuroinflammatory responses in both peripheral and central nervous tissues.
Conclusions
KLS-2031, a triple-genic AAV-based gene therapy, demonstrated potent and durable analgesic effects in preclinical models of PDPN, independent of sex or glycemic control. These findings support the therapeutic potential of KLS-2031 as an attractive intervention for PDPN and further clinical trial is being prepared.

Disclosures: **Y. Choi:** A. Employment/Salary (full or part-time): Employed/Full-time, Kolon Life Science. **H. Ji:** A. Employment/Salary (full or part-time): Employed/Full-time, Kolon Life Science. **K. Kim:** A. Employment/Salary (full or part-time): Employed/Full-time, Kolon Life Science. **Y. Lee:** A. Employment/Salary (full or part-time): Employed/Full-time, Kolon Life Science. **J. Lee:** A. Employment/Salary (full or part-time): Employed/Full-time, Kolon Life Science. **H. Lee:** A. Employment/Salary (full or part-time): Employed/Full-time, Kolon Life Science. **S. Hong:** A. Employment/Salary (full or part-time): Employed/Full-time, Kolon Life

Science. **S. Kim:** A. Employment/Salary (full or part-time): Employed/Full-time, Kolon Life Science.

Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.03/N3

Topic: E.01. Somatosensation – Pain and Itch

Support: FRIA scholarship
FWA scholarship

Title: AAV-mediated overexpression of Prdm12 in sensory neurons reduces pain and neuronal excitability in a mouse model of inflammatory pain

Authors: *M. DANNAWI[1], L. A. PATTISON[1], E. J. BELLEFROID[2], E. S. SMITH[1];
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Abstract: Inflammatory joint pain is characteristic of arthritis and various musculoskeletal disorders that affect millions globally. The *Prdm12* gene encodes a conserved zinc finger transcriptional regulator expressed selectively in the nervous system. In humans, *PRDM12* mutation can cause congenital insensitivity to pain (CIP) or midface toddler excoriation syndrome (MiTES). Prdm12 is prominently expressed in developing somatosensory ganglia, where it plays a crucial role in nociceptor development, its expression being maintained in mature C-LTMRs (C-low threshold mechanoreceptors) and nociceptors. Despite recent advances exploring the role of Prdm12 in neuronal excitability and pain behavior, the impact of Prdm12 overexpression has never been explored.Here we firstly conducted intravenous injection of AAV-PHP.S viral vectors encoding Prdm12-GFP (Prdm12-AAV) or GFP alone (Control-AAV) and observed no overt changes in behaviour. When examining the properties of sensory neurons in vitro, we observed an increase in rheobase alongside decreased neuronal responses to capsaicin and ATP, indicating a downregulation of TRPV1 and P2X ion channels, respectively. We next conducted intraarticular administration of viral constructs in female mice to determine how Prdm12 overexpression in knee-innervating sensory neurons alters their excitability and modulates inflammatory joint pain induced by intraarticular administration of complete Freund's adjuvant (CFA). Prdm12 overexpression in knee-innervating neurons decreased inflammation-induced changes in digging and weight bearing and prevented inflammation-induced neuronal hyperexcitability as well as decreasing macroscopic voltage-gated ion channel conductance. Our findings suggest a significant role of Prdm12 in modulating neuronal excitability in adult animals, highlighting its importance in pain perception and its potential as an analgesic target.

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Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.04/N4

Topic: E.01. Somatosensation – Pain and Itch

Support: NINDS UH3 NS123964 (RCL)
NINDS R21 NS105880 (RCL)
NINDS 3R21NS105880-01S1 (RCL)
DoD W81XWH-19-1-0525 (RCL)
Department of Anesthesiology, Perioperative Medicine, and Pain Management, University of Miami Miller School of Medicine, Miami, Florida

Title: Biosafety and efficacy of rdHSV-CA8* analgesic gene therapy for chronic pain via the intra-articular route in mice

Authors: *G. Z. ZHUANG[1], M. B. KANDEL[2], W. F. GOINS[4], C. D. SARANTOPOULOS[3], J. C. GLORIOSO[5], Y. KANG[2], R. C. LEVITT[2];
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Abstract: Gene therapy represents a promising approach to the global health challenge of chronic pain by offering precise, localized, long-lasting neuromodulation while minimizing systemic exposure and side effects. Preclinical studies of a replication-defective HSV (rdHSV) gene therapy expressing an analgesic carbonic anhydrase-8 peptide variant (vHCA8*) produces profound, long-lasting analgesia and treats chronic arthritis pain. **In this study, we provide the first non-GLP biosafety, efficacy, biodistribution, shedding, and histopathology examination of rdHSV-CA8*** administered in a High-Dose (HD) 1E6 PFU, Mid-Dose (MD) 1E5 PFU or Low-Dose (LD) 1E4 PFU via the intra-articular knee route in naïve BALB/c mice. **Routine clinical safety** assessments are made at Baseline and weekly thereafter for 8 weeks. There were no changes in body weight, body temperature or any abnormal clinical safety observations during daily cage checks for any treatment. **Efficacy** of vHCA8* wild type (WT) was evaluated by mechanical paw withdraw threshold (**PWT**), thermal withdraw latency (**TWL**) and weight-bearing (**WB**). vHCA8*WT increased mechanical **PWT** measured by von Frey filaments in a dose-dependent manner, as compared to the S100P null mutant negative control virus (vHCA8*MT-HD). PWT in the vHCA8*WT-HD group was increased above Baseline

(analgesia) and greater than the vHCA8*MT-HD negative control starting on D7 and persisting through D177. PWT in the vHCA8*WT-MD group was also greater than vHCA8*MT-HD starting on D19 to 26 and 73. PWT in the vHCA8*WT-LD group did not differ from Baseline or vHCA8*MT-HD. **TWL** for mice treated with vHCA8*WT-HD and -MD were higher than Baseline and vHCA8*MT-HD and sustained from D7 through D174 using the Hargreaves's method. Despite persistent increases above Baseline (analgesia) for the PWT and TWL vHCA8*-HD group, PWT and TWL never reached cut-offs indicating mechanical and thermal sensory responses were preserved. **WB** used as a measure of motor function was unchanged through D71 for all treatment groups, demonstrating motor functions were preserved after all vHCA8* treatments. qPCR was used to examine vHCA8* **biodistribution and shedding** across all major tissues. Viral genomes remained where they were injected, and there was no evidence of shedding. H.E. was used to evaluate knee **histopathology**. No persistent inflammation or injury was observed in tissues including cartilage, muscle, subchondral bone and, bone marrow near the injection site. Our data in mice demonstrate vHCA8* gene therapy exhibits a desirable safety profile with high levels of dose-dependent persistent analgesia for up to 6 months.

Disclosures: G.Z. Zhuang: A. Employment/Salary (full or part-time): University of Miami Miller School of Medicine. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Adolore Biotherapeutics, Inc.. F. Consulting Fees (e.g., advisory boards); Adolore Biotherapeutics, Inc.. **M.B. Kandel:** None. **W.F. Goins:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Adolore Biotherapeutics, Inc.. **C.D. Sarantopoulos:** None. **J.C. Glorioso:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Adolore Biotherapeutics, Inc.. **Y. Kang:** None. **R.C. Levitt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Adolore Biotherapeutics, Inc..

Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.05/N5

Topic: E.01. Somatosensation – Pain and Itch

Support: Department of Defense SC210210

Title: Engineered chromaffin cells derived from peripheral blood hiPSCs as a novel cell therapy for chronic SCI pain

Authors: *S. JERGOVA[1], B. RAHIMI[1], J. LEE[2], A. EESWARA[1], H. CUKIER[1], J. SAGEN[1]; [1]Univ. of Miami, Miami, FL; [2]Physiol., Lake Erie Col. of Osteo. Med., Lakewood Ranch, FL

Abstract: Chronic pain following spinal cord injury (SCI) significantly diminishes quality of life and interferes with rehabilitation, highlighting the need for innovative pain management strategies. Chromaffin cells, known for their high secretory capacity and production of analgesic substances, are promising candidates for cell-based therapies. Human induced pluripotent stem cells (hiPSCs) offer a renewable and patient-specific source for deriving chromaffin-like cells, potentially eliminating the need for immunosuppression. Previously, we generated recombinant hiPSC-derived chromaffin cells engineered to release the NMDA receptor antagonist serine-histogranin (SHG), alone or in combination with the opioid peptide endomorphin-1 (EM1), and demonstrated their analgesic efficacy in a rat model of SCI pain. In this study, we further investigated the impact of different gene configurations (1SHG, 6SHG, 1SHG/EM, 6SHG/EM) on peptide expression, aiming to optimize therapeutic output for translational application. To improve graft survival and restrict cell diffusion, we developed a polydimethylsiloxane (PDMS)-based anchoring matrix. The matrix was fabricated by coating a petri dish with a ~50 μm layer of PDMS, into which 20-40 μm^3 microparticles were embedded and subsequently removed, creating microchamber indentations. Chromaffin cells were seeded onto the cured PDMS scaffold, and their viability and catecholamine release were assessed. All recombinant cell lines expressed their respective peptides, as confirmed by FLISA and immunocytochemistry, with SHG levels varying according to gene copy number. Cells cultured on the PDMS matrix exhibited stable survival and catecholamine secretion. In vivo, intrathecal grafts of both recombinant and non-recombinant chromaffin cells led to a progressive reduction in mechanical, thermal, and cold hypersensitivity in the clip compression SCI model. The analgesic effect was partially reversed by administration of specific anti-peptide antibodies, supporting the contribution of released peptides to pain relief. The anchoring matrix with cells was detected in animals several weeks post grafting. These findings highlight the therapeutic potential of peripheral blood-derived hiPSC chromaffin cells for managing chronic SCI pain, with further benefits achievable through gene engineering and silicon polymer-based delivery systems.

Disclosures: S. Jergova: Other; The University of Miami and J.S. and S.J. hold rights to intellectual property used in the study and may financially benefit from the commercialization of the intellectual property. **B. Rahimi:** None. **J. Lee:** None. **A. Eeswara:** None. **H. Cukier:** None. **J. Sagen:** Other; The University of Miami and J.S. and S.J. hold rights to intellectual property used in the study and may financially benefit from the commercialization of the intellectual property.

Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.06/N6

Topic: E.01. Somatosensation – Pain and Itch

Support: Department of Defense CP230155

Title: Attenuation of chronic pain in rat models by hiPSCs-derived chromaffin cell grafts

Authors: *B. RAHIMI, S. JERGOVA, C. MARQUEZ, P. BIRRIEL, A. EESWARA, G. SERVADEI, O. GOOKIN, J. SAGEN;
Univ. of Miami, Miami, FL

Abstract: Chronic pain significantly impairs quality of life, underscoring the need for more effective and lasting treatment strategies. Current therapies for chronic pain are often ineffective and short-lasting. Chromaffin cells, with their strong secretory capacity and ability to produce pain-relieving compounds, show potential for cell-based therapies; when delivered intrathecally, they can continuously release analgesic molecules into the CSF. This study explores a new chronic pain treatment using human skin donor-derived hiPSC-based chromaffin cell (hCC) transplants to provide lasting relief and reduce dependence on multiple medications. Immunosuppression would not be required, as chromaffin cells can be generated from the patient's own cells. In the in vitro phase of our study, chromaffin cells were differentiated from skin-derived hiPSCs, and their identity was confirmed by immunostaining and secretion assays. To improve graft retention and limit cell diffusion, hCCs were embedded in Vitrogel prior to transplantation. In in vivo phase, we evaluated the therapeutic efficacy of hCCs in managing different forms of chronic pain in rat models, (1) low back pain (LBP) was established by puncturing the lumbar intervertebral disc; (2) knee osteoarthritis (OA) pain was induced by injecting monosodium iodoacetate (MIA) into the infrapatellar ligament; and (3), peripheral neuropathic pain was modeled via chronic constriction injury (CCI) of the sciatic nerve. In each, animals were divided into two groups: one received hCCs, while the control group received human fibroblasts. One week after pain induction—once animals demonstrated both allodynia and hyperalgesia—80K cells were transplanted intrathecally. Behavioral assessments include acetone test, Von Frey, weight bearing, knee bend, and plantar heat were conducted weekly for 12 weeks following transplantation. Cell survival was assessed 12 weeks post-transplantation. Rats treated with intrathecal hCCs showed a progressive reduction in pain behaviors across all models. Cell survival was confirmed via immunohistochemistry by tyrosine hydroxylase as a specific chromaffin cell marker and NuMA as human cell marker, and functional activity was validated by detecting catecholamines in the CSF by ELISA , indicating that transplanted cells remained viable and functioned as intended. These findings suggest that skin fibroblast-derived hCCs are a viable and effective therapeutic option for alleviating various types of chronic pain. Their long-term survival and sustained analgesic activity support the potential of this approach for durable pain management.

Disclosures: B. Rahimi: None. **S. Jergova:** Other; The University of Miami and J.S. and S.J. hold rights to intellectual property used in the study and may financially benefit from the commercialization of the intellectual property. **C. Marquez:** None. **P. Birriel:** None. **A. Eeswara:** None. **G. Servadei:** None. **O. Gookin:** None. **J. Sagen:** Other; The University of Miami and J.S. and S.J. hold rights to intellectual property used in the study and may financially benefit from the commercialization of the intellectual property.

Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.07/N7

Topic: E.01. Somatosensation – Pain and Itch

Support: Cancer Prevention & Research Institute of Texas grant RP220626

Title: Converting activated microglia to GABAergic neurons for curing oral cancer pain

Authors: S. LIU, ***F. TAO**;
Texas A&M Univ. Col. of Dent., Dallas, TX

Abstract: Chronic pain is a debilitating symptom of oral squamous cell carcinoma (SCC), which significantly impairs patients' well-being and quality of life. Current treatments for oral cancer pain are limited and often ineffective. Here, we tested a novel cell conversion strategy for treating such pain by converting activated microglia into functional GABAergic neurons in the spinal trigeminal nucleus caudalis (Sp5C), a key brainstem region involved in orofacial pain processing. We prepared an oral cancer pain model by injecting SCC cells into the left side of the tongue, which produced a progressive decrease in head withdrawal thresholds and caused microglial activation in the ipsilateral Sp5C. To reprogram the activated microglia, we injected AAV5-CD68-NeuroD1-2A-Dlx2-2A-eGFP into the Sp5C two weeks after tumor induction. Three weeks after viral infection, we harvested Sp5C tissues and immunostaining showed that GFP-positive cells were no longer co-labeled with the microglial marker Iba1 but were instead co-labeled with GABA, indicating a successful glia-to-neuron conversion. Our pain behavioral testing showed that mice receiving the NeuroD1/Dlx2 AAV exhibited significantly increased head withdrawal thresholds compared to the control group, suggesting that the glia-to-neuron approach can be used to treat oral cancer pain. To assess functional activity of the converted GABAergic neurons, we performed dual-color fiber photometry in the Sp5C and measured pain behaviors simultaneously. We found that chemogenetic activation of the converted GABAergic neurons increased both iGABASnFR-indicated GABA release and jRGECO1a-indicated activity of GABAergic neurons in the Sp5C. More importantly, specific activation of the converted GABAergic neurons significantly attenuated the oral cancer pain. These findings demonstrate that *in vivo* reprogramming of microglia into GABAergic neurons in the Sp5C could be developed into a promising gene therapy for chronic oral cancer pain.

Disclosures: S. Liu: None. **F. Tao:** None.

Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.08/N8

Topic: E.01. Somatosensation – Pain and Itch

Support: NINDS/1UG3NS127258-01A1
NINDS R01 NS052372

NINDS 1 P20 RR15576 01
Lisa Dean Moseley Foundation (1709JC/1812JC/1909JC/JC0920)

Title: Human mesenchymal stem cells mitigated postsurgical neuropathic pain

Authors: J. ZHANG[1], Q. FAN[2], *J. CHENG[3];
[1]Neurosciences, Cleveland Clin. Fndn. Lerner Res. institute, Cleveland, OH; [2]Dept. of Neurosci., [3]Neurosciences and Pain Mgmt., Cleveland Clin., Cleveland, OH

Abstract: Chronic post-surgical pain is a pervasive and debilitating condition with complex underlying mechanisms and limited treatment options. Despite their addictive risks, opioids remain widely prescribed in the perioperative setting for moderate to severe postsurgical pain in the US. Given the significant societal and economic toll of opioid use disorder, developing safer, non-addictive treatment alternatives is urgently needed. Mesenchymal stem cells (MSCs), particularly those derived from human umbilical cord tissue (hUC-MSCs), have emerged as promising candidates for therapeutic intervention due to their immunomodulatory, anti-inflammatory, and regenerative properties. This study evaluates the efficacy and mechanism of hUC-MSCs in attenuating chronic pain in a murine chronic constriction injury (CCI) model, which mimics nerve entrapment and postsurgical neuropathic conditions and is widely used a model of complex regional pain syndrome type II. UC-MSCs were characterized by flow cytometry and confirmed for multipotency through adipogenic and osteogenic differentiation assays. Mice subjected to CCI displayed persistent mechanical allodynia, thermal hyperalgesia, heightened glial activation, and elevated pro-inflammatory cytokines within the spinal cord and the sciatic nerve. Administration of UC-MSCs at the injury site at the time of the CCI surgery significantly alleviated pain behaviors, suppressed the expression of IL-1β and TNF-α, and modulated macrophage polarization by promoting a shift from pro-inflammatory M1 to anti-inflammatory M2 phenotypes. RNA-seq analysis revealed a downregulation of genes associated with inflammation, collagen degradation, and demyelination in hUC-MSC-treated mice. Furthermore, hUC-MSCs inhibited CCR2 expression and reduced monocyte infiltration via interactions with local Schwann cells and macrophages. Peak immune cell infiltration occurred at 14 days post-injury, with a marked decline observed by day 28 in treated animals. Notably, therapeutic outcomes varied depending on the source of hUC-MSCs, and intravenous administration was less effective than localized delivery. These findings highlight the importance of cell origin and administration routes in optimizing treatment efficacy. Collectively, this study supports the potential of hUC-MSCs as a targeted, non-opioid strategy for preventing neuropathic pain and encourages further translational research to refine clinical applications.

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Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.09/N9

Topic: E.01. Somatosensation – Pain and Itch

Support: Department of Florida of Health COPBC - University of Miami

Title: Evaluation of hiPSC-derived GABAergic neural progenitor and chromaffin cell transplants with exercise in reducing chronic pain in a spinal cord injury rat model

Authors: G. SERVADEI, L. TIERNEY, R. M. JOSEPH, A. EESWARA, B. RAHIMI, S. JERGOVA, *J. SAGEN;
Univ. of Miami, Miami, FL

Abstract: Managing chronic pain following a spinal cord injury (SCI) presents challenges with traditional drug treatments, as systemic medications often lead to unintended side effects and carry risks of misuse, particularly with analgesics and opioids. Previous findings in our lab showed promising results using cell therapy to achieve prolonged attenuation of chronic pain. Transplantation of rat GABAergic neural progenitor cells (NPCs) or chromaffin cells selectively targets chronic neuropathic pain in rodent models. The current study aims to improve NPC transplantation strategies by using human induced pluripotent stem cells (hiPSCs) and a relatively non-invasive intrathecal cell administration route. Potential enhancement of NPC survival and analgesic relief using co-transplantation with chromaffin cells or combination with exercise were evaluated. We generated GABAergic NPCs and chromaffin cells using the same hiPSC lines, derived from human skin fibroblasts. Four weeks following clip compression SCI, male and female Sprague Dawley rats received GABAergic hiPSCs (30,000), chromaffin hiPSCs (60,000) or co-grafts of GABAergic and chromaffin hiPSCs (30,000:60,000) in Vitrogel by intrathecal injection into the spinal subarachnoid space. While animals receiving either ILT, chromaffin hiPSC or GABAergic NPC grafts alone or with training exhibited significant reductions in neuropathic pain, animals receiving GABAergic NPC and chromaffin cell co-grafts in conjunction with exercise exhibited the most efficient and stable attenuation of these pain responses. Results were comparable between male and female animals. ELISA analysis indicated significant reduction of elevated SCI-induced pro-inflammatory cytokines IL1β and TNFα in serum of all treatment groups. The reduced CSF norepinephrine in untreated SCI was increased towards baseline intact levels only in animals receiving co-grafts in combination with ILT. Implementation of ILT promoted enhanced co-graft survival in the spinal subarachnoid space and increased levels of endogenous GABA within the spinal dorsal horn. Co-transplantation of GABAergic NPCs and chromaffin cells significantly reduced microglial activation within the spinal cord. These results reinforce the viability of cell transplantation as a clinical approach for managing chronic spinal cord injury (SCI) pain and its potential to address challenges related to human cell sourcing and transplant success.

Disclosures: G. Servadei: None. **L. Tierney:** None. **R.M. Joseph:** None. **A. Eeswara:** None. **B. Rahimi:** None. **S. Jergova:** Other; The University of Miami and J.S. and S.J. hold rights to intellectual property used in the study and may financially benefit from the commercialization of the intellectual property. **J. Sagen:** Other; The University of Miami and J.S. and S.J. hold rights to intellectual property used in the study and may financially benefit from the commercialization of the intellectual property.

Poster

PSTR446: Non-Opioid Biologics for Pain Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.10/N10

Topic: E.01. Somatosensation – Pain and Itch

Support: Nsf82371233

Title: Identification of non-opioid peptides to selectively relieve mechanical pain by activation of TRPV4 channels

Authors: M. TANG[1], Z. ZHANG[2], ***Q. TANG**[3], R. ZHANG[4];
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Abstract: Mechanical hyperalgesia is a primary symptom of clinical pain but there remains a therapeutic challenge for severe mechanical and chronic forms of neuropathic pain. Here we identified several low molecular weight peptides based on the natural toxin GsMTx4, that could alleviate mechanical hyperalgesia in rodent pain models. These peptides, which we call type I (e.g. Pept 01) and type II (e.g. Pept 02, Pept 03, and Pept 04), selectively reduced mechanical pain but failed to impact thermal or cold stimuli. Interestingly, the anti-hyperalgesic effects of these peptides were comparable with morphine, yet, they were resistant to naloxone (an μ-opioid receptor antagonist) and lacked the side effects of morphine-produced, e.g. tolerance and conditioned place preference (CPP). Among them, an 11-residue peptide (referred to as Pept 03), exerted an even more potent anti-hyperalgesic effect compared with morphine in certain conditions when administered intradermally (i.d.) or intraperitoneally (i.p.). Pharmacological inhibition of TRPV4 by short peptides in a heterogeneous expression system, combined with the use of TRPV4-selective inhibitor in mice suggests that TRPV4 channels may act as the potential target for the short peptides in alleviating the form of mechanical pain. This study introduces several natural toxin-based peptides as promising non-opioid analgesics, paving the way for developing selective and potent painkillers in the form of mechanical pain.

Disclosures: M. Tang: None. **Z. Zhang:** None. **Q. Tang:** None. **R. Zhang:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.01/N11

Topic: E.02. Somatosensation – Touch

Support: ERC-2015-CoG-682422
ERC-2023-ADG-101142335
DFG FOR 2143
NIH R01 NS123711
SFB 1315

Title: Thermal encoding by GABAergic inhibitory interneurons in the posterior insular cortex

Authors: *G. GÜNEY[1], M. VESTERGAARD[2], M. CARTA[3], J. F. POULET[1];
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Abstract: The processing of sensory information by the neocortex is at the heart of conscious perception and is known to involve a dynamic interaction between synaptically connected GABAergic inhibitory interneurons and excitatory pyramidal neurons. One hypothesis is that sensory feature encoding in pyramidal neurons is shaped by different interneuron types performing specific functional roles. Here, we address this in the mouse thermal cortex. The thermal system is a fundamental pathway required for accurate object identification, pain perception, and body temperature regulation, and is one that is highly developed in the mouse. Recently, we identified a region of the posterior insular cortex (pIC) that contains somatotopic maps of thermal and tactile information and is required for non-painful thermal perception (Vestergaard et al., 2023; Bokiniec et al., 2023). Two-photon imaging has shown that pIC pyramidal neurons have a fine-scale and dynamic encoding of skin temperature, but, to date, there is no information on the encoding of temperature by cortical interneurons. Here, I present our recent two-photon imaging of interneuron subtypes during thermal stimulation of the forepaw in awake mice. pIC interneurons respond to non-painful cooling and warming with strong and reliable responses. Future work aims to understand the role of interneurons in thermal perception with the use of a two alternative forced choice thermal perception task.

References:

Vestergaard M, Carta M, Güney G, Poulet JFA. The cellular coding of temperature in the mammalian cortex. Nature 614(7949): 715-731 (2023)
Bokiniec P, Whitmire CJ, Leva TM, Poulet JFA. Brain-wide connectivity map of mouse thermosensory cortices. Cereb Cortex 33(8): 4870-4885 (2023)

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Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.02/N12

Topic: E.02. Somatosensation – Touch

Support: JSPS KAKENHI Grant 23KJ2122
JSPS KAKENHI Grant 21H05242
JSPS KAKENHI Grant 24K00513
JSPS KAKENHI Grant 24K21506

Title: The effects of chemogenetic suppression of the projection from the primary somatosensory cortex to the secondary somatosensory cortex on a forelimb sensorimotor learning.

Authors: *Y. YOSHINAGA[1,3], N. SATO[2];
[1]Dept. of Psychological Sci., Kwansei Gakuin Univ., Nishinomiya-shi, Hyogo-ken, Japan; [2]Psychological Sci., Kwansei Gakuin Univ., Nishinomiya, Hyogo, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan

Abstract: Active touch has attracted much attention lately as a sensation that cannot be separated from motor processes. Many studies on active touch in rodents focused on the whisker system. Compared to the well-studied whisker system, active touch with the forepaws remains poorly understood. There are many differences between the whisker system and the forepaw, which are particularly evident during object manipulation. We previously developed a new behavioral task, the Reach-to-Grasp and Tactile Discrimination task (RGTD task) to examine active touch with a forepaw during object manipulation and its changes in the course of sensorimotor learning. In the RGTD task, animals are required to (1) extend their forelimb to an object, (2) grasp the object, and (3) rotate the grasped object with the forelimb. The animals must determine the direction of the rotation based on active touch sensations arising during the period of the grasping. In this study, we first examined the effects of DREADD suppression of the primary somatosensory cortex forelimb area (fS1) on the task performance. The suppression procedure was implemented in two phases: (1) following the completion of the discrimination task (test phase), and (2) during the subsequent learning sessions for new stimulus-response associations. The correct ratio in DCZ administered sessions in the test phase was lower than saline administered sessions only in DREADD positive group. The suppression of the fS1 also impaired the learning of the new texture discrimination. Next, we suppressed the secondary somatosensory cortex-projecting neurons (S2p neuron) in the fS1. The suppression of the S2p neurons did not affect the task performance in the test phase, but it decreased the learning of the new texture discrimination. This difference suggests that the S1-S2 pathway does not play an essential role in executing well-learned sensorimotor behaviors but rather contributes to the acquisition of novel sensorimotor mappings during the learning. The suppression of the entire fS1 affected well-learned movements and learning, suggesting that other S1 pathways play an important role in object manipulation based on active touch. The S1 to S2 circuit might be involved in sensory-motor learning, modifying other circuits such as the S1-motor cortices circuits that would be responsible for executing well-learned movements.

Disclosures: Y. Yoshinaga: None. **N. Sato:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

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Program #/Poster #: PSTR447.03/N13

Topic: E.02. Somatosensation – Touch

Support: NIH R00NS119739
NIH P50NS123103
Georgia Tech/Emory Center for the Engineering of Living Tissues (GTEC)

Title: Progression of abnormal signaling in primary somatosensory cortex of MitoPark mice

Authors: *R. ZHANG[1,2], R. QI[2], A. J. EMANUEL[2,1];
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Abstract: Parkinson's disease (PD) patients suffer from non-motor symptoms including touch hyposensitivity, which likely worsens sensorimotor dysfunction. Yet, how sensory deficits relate to PD pathology is unclear. In a progressive mouse model, MitoPark ($DAT^{Cre};Tfam^{fl/fl}$), PD symptoms arise from mitochondrial dysfunction in dopamine transporter-expressing cells. To assess tactile processing in this model, we performed *in vivo* multielectrode array recordings in forepaw primary somatosensory cortex (S1). We analyzed baseline firing rates and responses to controlled-force paw indentations at four stages: 12 weeks (prior to motor symptoms), 15 weeks (when symptoms first appear), 24 weeks (overt symptoms), and 28 weeks (severe symptoms). Overall, MitoPark S1 was more excitable than littermate control, both at baseline and in response to tactile stimuli, at timepoints after PD symptoms appear. Specifically, at 12 weeks, evoked firing rates (grand mean across all S1 neurons) were lower in MitoPark relative to littermate controls. In contrast, evoked firing rates were higher in 15-, 24-, and 28-week MitoPark mice vs. age-matched controls. Analysis of cell-type specific response showed that layer V regular-spiking (RS) neurons in 12-week MitoPark mice had lower evoked firing rates (30.0 ± 2.2 and 37.8 ± 2.8 Hz for MitoPark and controls, respectively [mean ± SEM]), while that in 15 to 28-week MitoPark mice was increased (differences of 17.0 ± 4.5, 27.0 ± 4.3, and 17.0 ± 4.9 Hz for 15, 24, and 28 weeks, respectively). Baseline firing rates of RS units followed a similar pattern between 15 and 28 weeks (differences of 3.4 ± 1.0, 3.2 ± 0.8, and 3.7 ± 1.0 Hz for 15, 24, and 28 weeks, respectively), with no difference at 12 weeks (rates of 5.6 ± 0.5 and 5.9 ± 0.6 Hz for MitoPark and controls, respectively). The fraction of responsive MitoPark RS and fast-spiking (FS) neurons during stimulus onset or offset was decreased at 12 weeks but increased in RS neurons at 15-28 weeks and FS neurons at 28 weeks. MitoPark RS neurons shifted from hyposensitive at 12 weeks to hypersensitive at 28 weeks, while MitoPark FS neurons were hyposensitive at 12-24 weeks but became hypersensitive at 28 weeks. We examined tyrosine hydroxylase (TH) immunostaining of the midbrain and forebrain to evaluate pathology in the same animals. As expected, TH staining in the midbrain and striatum declined in MitoPark mice with age. Similarly, the total length of TH^+ fibers within forepaw S1 was shorter in 15-, 24-, and 28-week MitoPark relative to age-matched controls. Our results support the idea that dopamine loss in PD contributes to abnormal tactile signaling in S1 that may lead to aberrant tactile perception in PD patients.

Disclosures: R. Zhang: None. **R. Qi:** None. **A.J. Emanuel:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.04/N14

Topic: E.02. Somatosensation – Touch

Support: Travel Grant PR.INT Research School Ruhr-University Bochum
DFG Grant SCHE 1913/7-1

Title: Anxiolytic Effects of Social Touch: Moderating Influences of Trauma and Social Interaction Experiences

Authors: *L. STEVENS[1], J. PACKHEISER[2], N. HAIHAMBO[3], M. LANGE[3], E. BAGRATIONI[3], D. SCHEELE[2];
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Abstract: Objective: Trauma-exposed individuals often display a pattern of touch aversion and avoidance. Surprisingly, however, it is still unclear whether trauma experiences are associated with altered anxiolytic effects of social touch and if these consequences differ depending on previous interaction experiences. Methods: We are in the process of recruiting 200 healthy adults (100 women) with varying levels of trauma experiences assessed with the Childhood Trauma Questionnaire (CTQ) and the Trauma History Questionnaire (THQ). Participants are randomly assigned to a positive interaction paradigm (PIP) and a non-social control task. Subsequently, participants perform a threat of shock task and in half of the trials they receive c-tactile optimal touch on their forearm by the experimenter of PIP or an unfamiliar person.
Results: We will analyze self-rated tension and psychophysiological measures (such as electrodermal activity and heart rate variability) during a countdown before shocks as the primary outcome to evaluate the anxiolytic effect of touch. Furthermore, we will investigate whether the anxiolytic effects differ between contexts (PIP vs. control) and if they are related to trauma experiences (CTQ and THQ scores). As a secondary readout, we will explore emotion regulation processes involved in anxiolytic touch by analyzing Functional Near-Infrared Spectroscopy (fNIRS) neuroimaging data of the prefrontal cortex.
Discussion: With this study, we aim to contribute to a better understanding of the complex social sequelae of trauma experiences, specifically relating to the processing of social touch.

Disclosures: L. Stevens: A. Employment/Salary (full or part-time): Department of Social Neuroscience, Faculty of Medicine, Ruhr University Bochum, Germany, Research Center One Health Ruhr of the University Alliance Ruhr, Ruhr University Bochum, Germany. **J. Packheiser:** A. Employment/Salary (full or part-time): Department of Social Neuroscience, Faculty of Medicine, Ruhr University Bochum, Germany, Research Center One Health Ruhr of

the University Alliance Ruhr, Ruhr University Bochum, Germany. **N. Haihambo:** A. Employment/Salary (full or part-time): Department of Social Neuroscience, Faculty of Medicine, Ruhr University Bochum, Germany, Research Center One Health Ruhr of the University Alliance Ruhr, Ruhr University Bochum, Germany. **M. Lange:** A. Employment/Salary (full or part-time): Department of Social Neuroscience, Ruhr University Bochum,, Research Center One Health Ruhr of the University Alliance Ruhr, Bochum. **E. Bagrationi:** None. **D. Scheele:** A. Employment/Salary (full or part-time): Department of Social Neuroscience, Faculty of Medicine, Ruhr University Bochum, Germany, Research Center One Health Ruhr of the University Alliance Ruhr, Ruhr University Bochum, Germany.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.05/N15

Topic: E.02. Somatosensation – Touch

Support: NIH F31 Grant 1F31NS141317-01
NIH R01 Grant NS127777

Title: Representation of bimanual signals in the human neocortex

Authors: *E. DENGHAUSEN[1], A. MACKLIN[2], L. WANG[1], J. M. YAU[1];
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Electrical and Computer Engin., Rice Univ., Houston, TX

Abstract: We use our two hands together or independently to sense and interact with our environment. Even when the hands are used independently, sensory inputs on one hand influence tactile perception on the other hand. What computations underlie bimanual cue combination and where these are implemented in the brain remain poorly understood. We addressed these knowledge gaps by measuring cortical activity in healthy participants undergoing functional neuroimaging while receiving tactile stimulation to their left hand, right hand, or both hands simultaneously. Cluster analysis on voxel-wise responses revealed a small set of hand-selectivity patterns reflecting differential responsivity across the unimanual and bimanual stimulus conditions. These response "motifs", which all comprised a degree of bimanual responsiveness, were systematically distributed over brain regions in a manner that reflected the somatosensory cortical hierarchy. To better understand the nature of the distributed bimanual responses, we will fit encoding models capturing linear and nonlinear computations involving the left and right hand sensory inputs. We will test the hypothesis that touch-responsive brain regions implement multiple computations to support bimanual processing. Collectively, this work will reveal the distributed nature of bimanual processing and establish the computations underlying bimanual touch.

Disclosures: E. Denghausen: None. **A. Macklin:** None. **L. Wang:** None. **J.M. Yau:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.06/N16

Topic: E.02. Somatosensation – Touch

Support: NINDS U01NS103558

Title: Cortical coordination: cholinergic and noradrenergic dynamics in sensorimotor task learning and execution

Authors: *A. HWANG[1], S. A. HIRES[2];
[1]Neurobio., [2]Biol. Sci., USC, Los Angeles, CA

Abstract: Cholinergic and noradrenergic systems are among the most vulnerable neural circuits affected in age-related neurodegenerative disorders like Alzheimer's Disease (AD) where their dysregulation contributes directly to many symptoms of cognitive decline. The effect of this degeneration on coordinated neuromodulator dynamics and the degree to which the resulting dysregulation impairs cognitive performance remains unresolved. Understanding the systemic role of these widely projecting neuromodulatory circuits in the manifestation of cognitive decline will provide insight towards how disruption of signaling contributes to the development of neuropathological diseases. Given that noradrenergic and cholinergic signaling drives network-wide brain state coordination to promote learning, arousal, and memory, we aim to characterize cholinergic and noradrenergic release dynamics across learning and execution of a sensorimotor task in wildtype and AD models of neurodegeneration. To simultaneously record cholinergic and noradrenergic release activity, we developed a two-photon *in vivo* imaging technique using dual-colored GPCR Activation Based sensors (GRABs) broadly expressed in cortical neurons. Here we demonstrate across learning, consistent codeveloped patterns of neuromodulatory release emerge in cortex of wildtype mice, where distinct periods of synchronization and desynchronization of acetylcholine (ACh) and NE dynamics are observed across behavioral events. These results suggest a level of coordination between task related noradrenergic and cholinergic release. Understanding the role of coordinated neuromodulatory dynamics in this context will provide a foundation for clarifying the impact of cholinergic and noradrenergic dysregulation in the progression of neurodegenerative diseases.

Disclosures: A. Hwang: None. **S.A. Hires:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.07/O1

Topic: E.02. Somatosensation – Touch

Title: Temporal masking of cortical sensory activity in primary somatosensory cortex in infant rats

Authors: *N. SATTLER[1], J. C. DOOLEY[2];
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Abstract: Thalamocortical loops play a crucial role in motor control and sensory processing, providing precisely tuned feedforward inhibition between the thalamus and cortex for a variety of adaptive functions. In the first postnatal week of life—a critical time in development in which spontaneous activity from peripheral sensory structures drives activity in the developing thalamus across sensory modalities—thalamocortical loops have yet to develop the inhibitory components of their circuitry. Instead, they function as an excitatory feedback loop, often producing brief bursts of runaway 8-40 Hz oscillations between the thalamus and cortex known as spindle bursts. In the somatosensory system, these spindle bursts are predominantly evoked by twitches—rapid movements of the skeletal muscles occurring exclusively during REM sleep. Although we know these developmentally transient properties serve to amplify incoming sensory information at these ages, we know very little about how the temporal dynamics of these immature circuits may serve to gate or mask incoming sequential activity from the sensory periphery, and consequently, their potential effects on these early experience-dependent developmental processes. Here, we harness the temporally discrete and bursty nature of twitches to examine the temporal relationship of peripheral activity and cortical activation in the somatosensory system. We performed large-scale extracellular recordings across the forelimb region of primary somatosensory cortex (S1) of postnatal day 5 rat pups, alongside simultaneous high speed video recordings for 3D-kinematic reconstruction of the limbs. Current work is focusing on whether sequential twitches of varying inter-twitch intervals produce amplified or masked cortical responses, particularly as a function of their alignment with ongoing spindle bursts.

Disclosures: N. Sattler: None. **J.C. Dooley:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

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Program #/Poster #: PSTR447.08/Web Only

Topic: E.02. Somatosensation – Touch

Support: NIH grant R01NS129982

Title: Interhemispheric modulation of neuron responses from superficial through deeper layers of area 3b cortex in monkeys

Authors: *J. L. REED[1], H. QI[2], J. H. KAAS[3];
[2]Dept Psychol, [3]Psychology Dept., [1]Vanderbilt Univ., Nashville, TN

Abstract: Previous studies in primary somatosensory cortex area 3b reveal neuron response modulation when a site inside the excitatory receptive field (RF) is stimulated alongside a site outside the RF, including the opposite hand. The hand representation in primates is unique in that there are very few, if any, callosal connections between hemispheres for left and right area 3b. When stimuli are presented to both hands, the term interhemispheric modulation is used because each hemisphere of cortex represents the opposite hand in area 3b. When we refer to neurons that show interhemispheric modulation, we use the term extra-hand RF. Our goal is to determine the sources and properties of the extra-hand RF. Supragranular layer neurons receive primary input from layer 4, as well as longer intrinsic connections likely related to the cortical basis of interhemispheric modulation. The properties of neuron responses designated by layer are expected to relate to the source of the extra-hand RF. We used multichannel arrays to record from area 3b in adult squirrel monkeys (*Saimiri boliviensis*, *S. sciureus*, n = 2, 1 female) and owl monkeys (*Aotus trivirgatus*, *A. azarae*, n = 6, 3 female). The recordings were primarily from layer 3; however, we recorded from superficial through deep layers with multi-contact linear arrays in 2 squirrel monkeys and 1 (female) owl monkey. Spike signals were acquired and timed to computer-controlled indentations to the skin on selected sites. Stimuli were presented to one spot on the hand, or stimuli were paired and presented to matched or unmatched sites on both hands. When sites on both hands were stimulated simultaneously or asynchronously, neurons across nearly 2mm of cortical depth showed response magnitude suppression relative to single-site stimulation (42% of supragranular, 52% of layer 4, 77% of infragranular recordings), or facilitation (4% of supragranular, 17% of layer 4, and 4% of infragranular recordings), or no change in firing (54%, 31%, 19%, respectively). Interhemispheric modulation occurs throughout the cortical column, with minimal differences in latency between neurons recorded from supragranular and granular layers, but additional recordings from granular and infragranular layers are needed. We interpret our results as one piece of evidence that points to subcortical contributions to the extra-hand RF in area 3b.

Disclosures: J.L. Reed: None. **H. Qi:** None. **J.H. Kaas:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.09/O2

Topic: E.02. Somatosensation – Touch

Support: Welcome Trust Discovery Award
Academy of Medical Sciences Professorship

Title: Higher-order thalamic input to layer 1 modulates layer 5 apical dendrites in somatosensory cortex

Authors: *D. JANG[1], R. M. BRUNO[2];
[2]Physiology, Anat. & Genet., [1]Univ. of Oxford, Oxford, United Kingdom

Abstract: Cortical layer 5 (L5) pyramidal neurons have apical tufts in layer 1 (L1) that can produce dendritic plateau potentials. The tuft-wide events can increase the gain of the neuron's response to other synaptic inputs as well as trigger synaptic plasticity. How these events are initiated in vivo remains an open question. High-order thalamus is a potential candidate, given its dense innervation of L1. Furthermore, we have previously shown that high-order thalamus more strongly activates pyramidal neurons, at least in layer 2/3, than corticocortical inputs do. Here, we investigated the potential of high-order somatosensory thalamus (PO) to trigger plateau potentials in apical dendrites of L5 pyramidal neurons in mouse primary somatosensory cortex. We expressed excitatory opsin in PO to enable photoactivation of PO terminals in L1. We simultaneously recorded local field potential (LFP) in L1 to measure the sum depolarization of neurons in superficial cortex and attempt to infer apical tuft activity. At low optogenetic stimulation intensities, we observed small single-peaked LFPs, consistent with post-synaptic depolarization, which were proportional to the stimulation intensity. At higher power, we observed a striking double-peaked LFP response characterized by a prominent initial peak followed about 10 milliseconds later by a second, slightly smaller peak, lasting tens of milliseconds. This long second peak is suggestive of a dendritic plateau potential. While plateau potentials are thought to be associated with robust sensory input in behavior, these double-peak LFP responses, observed in the absence of direct stimulation of the sensory periphery, suggest high-order thalamus alone may be sufficient. The resulting prolonged cortical activity may be a mechanism by which high-order thalamic modulation of L1 dendrites could enhance distributed or weaker input, such as sensory signals arriving via layer 4.

Disclosures: D. Jang: None. **R.M. Bruno:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.10/O3

Topic: E.02. Somatosensation – Touch

Title: Active touch exploration of materials: An fNIRS investigation of Aesthetics

Authors: *T. JACOBSEN, B. E. MARSCHALLEK, A. LÖW;
Exptl. Psychology Unit, Helmut Schmidt Univ. / Univ. of the Federal Armed Forces Hamburg, Hamburg, Germany

Abstract: The sense of touch stands out of all sensory modalities as the only active sense and haptic processing may go in hand with hedonic evaluation ("Does it feel good?"). In a previous fNIRS study, we found a link between subjective pleasure ratings and (left) frontal brain activity when materials (woods, textiles) where actively explored using the right hand. Here, we aim to

extend our findings by using a broader range of materials and collecting ratings about their sensory properties (roughness, bumpiness) in addition to aesthetic judgements. 38 participants actively explored 54 different material samples taken from nine materials (ceramic, glass, leather, metal, paper, plastic, stone, textiles, wood) while brain activity was registered using fNIRS (51-channels).
Linear mixed-modelling of the ratings showed that smoother and more even surfaces were judged as more pleasant and, when controlled for these sensory features, paper and leather were judged as the most pleasant materials, while stone and metal were perceived as least pleasant. Initial analysis of the fNIRS data revealed that contra-lateral sensory-motor activity was evoked by active touch. The individual, trial specific ratings were used as additional regressors (parametric modulators). Sensorimotor activation was modulated by the judged sensory properties, but not by the individual aesthetic ratings. On the other hand, frontal brain activity tended to be related to the perceived hedonic value of the stimuli.

Disclosures: T. Jacobsen: None. **B.E. Marschallek:** None. **A. Löw:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.11/O4

Topic: E.02. Somatosensation – Touch

Support: NIH U19 NS107466

Title: Active Sensing Involves Superior Colliculus-Driven Coordination of Head, Vibrissa, and Eye Movements

Authors: *A. FASSIHI[1], J. DUCKWORTH[2], D. KLEINFELD[2];
[1]Univ. of California San Diego, San Diego, CA; [2]Physics, Univ. of California San Diego, La Jolla, CA

Abstract: Across sensory systems, animals coordinate the movements of multiple effectors to actively explore their environment. In rats, the vibrissae, head, eyes, and snout move in a coordinated manner to gather tactile and visual information. In vision, rapid eye movements are typically followed by head turns toward a visual target. Similarly, in the vibrissa system, rhythmic whisking is coordinated with head and body motion during tactile exploration. While the neural mechanisms underlying eye-head coordination have been extensively studied in both primates and rodents, the circuitry supporting vibrissa-head coordination remains essentially understudied. To investigate how the nervous system organizes orofacial coordination during active sensing, we developed a behavioral task in which rats used coordinated head and vibrissa movements to orient toward and locate reward delivery spouts on either side of the animal's head. As the movement sequence progressed, the tongue was used to contact the spout and obtain a water reward. Rats produced precise and consistent head, eye, and vibrissa movements,

with trajectories and timing tightly coupled to reward location. To examine the underlying neural mechanisms of coordinated orofacial movement, we inactivated the deep layers of the superior colliculus (dSC). Unilateral dSC inactivation distorted head and vibrissa movements, exaggerating ipsilateral turns and reducing contralateral ones, resulting in a consistent steering bias and altered vibrissa tip path. Comparable steering biases were observed in tongue and eye movements. During head turns, the ipsiversive vibrissa consistently led in phase, a turn-dependent offset abolished by dSC inactivation, indicating disrupted temporal coordination. In summary, we developed a novel behavioral paradigm to study orofacial coordination during goal-directed behavior in freely moving rats, and found that the dSC is critical for coordinating orofacial movements at both high and low levels of motor control.

Disclosures: A. Fassihi: None. **J. Duckworth:** None. **D. Kleinfeld:** None.

Poster

PSTR447: Thalamic and Cortical Processing in Somatosensation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.12/O5

Topic: E.02. Somatosensation – Touch

Support: NIH Grant U19 NS107466
NIH Grant U19 NS137920
NIH Grant U24 EB028942

Title: Spatial encoding of distal objects through the confluence of exafferent inputs and reafferent self-motion signals

Authors: *P. YAO[1], R. LIU[2], R. IYER[3], D. GOLOMB[4], D. KLEINFELD[3];
[1]Neurosci. Grad. Program, UCSD, La Jolla, CA; [3]Physics, [2]Univ. of California San Diego, La Jolla, CA; [4]Ben-Gurion Univ. Negev, Beer-Sheva, Israel

Abstract: René Descartes likened a blind traveler's walking stick to a sensory extension of the body, demonstrating that forces transmitted along a probe can evoke haptic perception at a distance. Which neural signals allow the brain to assign egocentric coordinates to such distal contacts? We tackled this question in the rodent vibrissa system, a canonical model of active sensing. Theory identifies three candidate signals that could, in principle, provide the requisite spatial information: bending torque at the follicle during contact, the torque's rate of change, and reafferent signals that report the self-motion of the vibrissa. The confluence of any two of these signals are sufficient to compute the location of contact in terms of position along the plane spanned by whisking. To assess which of those signals were available to the cortex, we employed adaptive-optics two-photon microscopy to monitor synaptic inputs from thalamocortical boutons to the layer IV of barrel cortex while head-fixed mice rhythmically whisked against a pole. Touch-evoked responses in individual boutons followed a Weber-like logarithmic relationship with bending torque, spanning more than two orders of magnitude while

retaining sensitivity to the minute deflections; in contrast, the torque derivatives only weakly encoded. Approximately one-third of boutons were tuned to a specific phase of the whisk cycle, and together their preferred phases spanned the entire 0-2π range, forming orderly maps within each cortical column. Further analysis revealed that the activity of these phase-sensitive boutons reflects an additive, rather than multiplicative, confluence of exafferent bending torque and reafferent phase. These data provide strong evidence that the location of touch is computed from responses that encode solely torque, a holonomic constraint on coordinates, plus responses that encode torque plus self-motion.

Disclosures: P. Yao: None. **R. Liu:** None. **R. Iyer:** None. **D. Golomb:** None. **D. Kleinfeld:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.01/O6

Topic: E.04. Interoception

Support: MRC Grant MR/W002426/1
Wellcome Trust Grant 225856/Z/22/Z
BBSRC Grant BB/R006210/1

Title: Loss of Piezo2 expression in sensory neurons during aging drives loss of colonic control.

Authors: *L. A. PATTISON, E. BRADLEY, V. D. DAHMEN, A. L. HURST, M. DANNAWI, S. J. NICHOLSON, J. R. F. HOCKLEY, E. S. SMITH;
Dept. of Pharmacol., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Conscious control of defecation is an important physiological function, dependent on an ability to sense gut fullness and urgency to defecate. Somatosensory neurons from dorsal root ganglia expressing the mechanically gated ion channel Piezo2 confer mechanosensation to the gastrointestinal tract, loss of which negatively affects colonic motility. Bowel function declines with age; among society the elderly are the most affected by fecal incontinence and functional gastrointestinal disorders, which diminish quality of life. Left unmanaged, the complications arising from fecal incontinence can be fatal. Despite this, the molecular basis of age-associated deterioration of colonic control remains unresolved. We hypothesized that loss of Piezo2 expression by sensory neurons innervating the colon during aging would result in reduced colonic mechanosensitivity and subsequently impair ability to control bowel movements. To address this, we studied transgenic Piezo2-GFP-Cre mice of varying ages (9-111 weeks old). Behavioral studies confirmed impaired colonic motility among older mice, with increased presentation of constipation-like behavior (e.g. lower stool output). The colon of each mouse was then injected with retrograde tracer, permitting post-mortem assessment of Piezo2 expression in colonic sensory neurons. Immunohistochemistry staining revealed an age-dependent decrease in

Piezo2 expression in colon-projecting sensory neurons. Co-staining with markers such as calcitonin gene related peptide (CGRP) to identify peptidergic neurons, allowed further investigation among distinct neuronal populations. Histological staining of colon sections revealed no overt age-related change in colon macrostructure. These findings suggest that a decline in Piezo2-expressing sensory neurons serving the colon during aging negatively affects colonic motility and stool behavior. To validate this, we utilized diptheria toxin encoding adeno-associated viruses (AAVs) to enable Cre-mediated ablation of Piezo2-expressing colonic sensory neurons in young mice. The young mice with compromised colonic sensory innervation presented with similar deficits in colon motility to what was observed in aged mice, no effect being observed in a cohort injected with a mCherry encoding AAV. Taken together these data identify changes in the innervation of the colon that occur through aging that can impact colon function, with loss of Piezo2 specifically implicated.

Disclosures: L.A. Pattison: None. **E. Bradley:** None. **V.D. Dahmen:** None. **A.L. Hurst:** None. **M. Dannawi:** None. **S.J. Nicholson:** None. **J.R.F. Hockley:** None. **E.S. Smith:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.02/O7

Topic: E.04. Interoception

Support: Innovative Science Accelerator Program (ISAC) Award 23AU4374

Title: Transcriptomic analysis of TRPV1+ kidney-innervating spinal and vagal sensory neurons

Authors: *B. DAILEY-KREMPEL[1], L. O'BRIEN[2], M. S. RIEDL[1], Y. ZHANG[3], D. GOHL[2], L. VULCHANOVA[1];
[1]Neurosci., [2]Genomics Ctr., [3]Minnesota Supercomputing Inst., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Recent clinical and preclinical studies have suggested an interoceptive role of afferent renal nerves (ARNs) in homeostatic processes beyond reflexive regulation of fluid and electrolyte balance. Our research has been focused on identifying the integration of ARN inputs within brain interoceptive circuits as well as the subtypes of ARNs. Ablation of TRPV1+ ARNs (~85% of ARNS) with capsaicin has been shown to be effective in lowering blood pressure in several preclinical neurogenic hypertension models, highlighting TRPV1+ ARNs as a subtype of interest. ARNs originate in T6-L2 dorsal root ganglia (DRG) and preferentially innervate the renal pelvis. However, a recent study identified ARNs near glomeruli in the renal cortex, and few studies suggest vagal afferent innervation via the nodose ganglia (NG). Although chemo- and mechanosensitive ARNs have been identified in the renal pelvis, the diversity of ARNs and their functional impact remain poorly understood. To identify subtypes of ARNs, we hypothesized that the expression of axotomy-induced genes, e.g., neuronal injury marker *Atf3*, following a

unilateral nephrectomy will enable the transcriptomic identification of ARNs. We used Parse Biosciences single-cell RNA sequencing to compare the expression of axotomy-induced genes between left and right T6-L2 DRG and NG neurons 24 hours after nephrectomy of the right kidney. Data processing was completed in R using singleCellTK for quality control, SingleR for cell type reference annotation, and Seurat for data visualization and analyses. After quality control steps, we annotated 7,300 cells into known DRG subtypes and *Phox2b*+ nodose neurons. Analyses identified clusters that highly expressed *Atf3* in DRG cell populations: Aδ-low threshold mechanoreceptors (LTMR), C-LTMR/TH, several CGRP+ subtypes, e.g., γ, ε, θ, nonpeptidergic nociceptors, nodose subtypes NG12-18, and an unassigned cluster. These DRG cell types are either thinly myelinated (Aδ) or unmyelinated (C-fibers) which agrees with prior renal afferent tracing and electrophysiology studies. We separated 2,142/7,300 cells that highly expressed *Atf3* (198/2,142 *Trpv1*+), and ran FindMarkers with MAST to identify differentially expressed genes between the nephrectomized and intact ARNs. Defining the transcriptional subtypes of kidney-innervating sensory neurons in DRG and NG will allow us to identify genes that can be used to selectively target renal afferents. This gained ability will provide the opportunity to investigate the physiological roles and anatomy of these neurons as well as transcriptional changes under pathophysiological conditions, adding insight to their interoceptive role.

Disclosures: B. Dailey-Krempel: None. **L. O'Brien:** None. **M.S. Riedl:** None. **Y. Zhang:** None. **D. Gohl:** None. **L. Vulchanova:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

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Program #/Poster #: PSTR448.03/O8

Topic: E.04. Interoception

Support: NIH Grant DK129315

Title: Epithelial cell signaling modulates responses of intrinsic primary afferent neurons of the mouse ileum to mechanical stimulation

Authors: J. KOSAREFF, C. HALL, A. BEYDER, *D. R. LINDEN;
Mayo Clin., Rochester, MN

Abstract: Sensory neurons called intrinsic primary afferent neurons (IPANs) exist within the myenteric and submucosal plexuses to provide the gastrointestinal (GI) tract with intrinsic reflex circuitry. Advillin (Avil) marks IPANs and mechanical stimulation of the mucosa causes increased calcium activity in Avil/GCaMP IPANs. While IPANs may be mechanosensitive their processes do not extend into the epithelium and thus interact with epithelial cells to respond to luminal mechanical and chemical stimuli through enterochromaffin cells, which release serotonin (5-HT) and ATP. IPANs express nAChR and ongoing cholinergic tone from nerve

endings or Tuft cells affect GI function. The aim of this study is to map the mucosal mechanical receptive fields of IPANs and test the contribution of epithelial cells to IPAN mechanical responsiveness. Full-thickness ileum segments from Avil/GCaMP6f mice were pinned flat in Krebs and automated acquisitions were made while deforming the mucosa at 24 points in a 4mm^2 area using closed-loop linear stages. Mean fluorescence intensity of soma was analyzed (custom Python) to categorize response type (quiescent responder, spontaneous, non-responder) and response characteristics including response latency (immediate <0.5s, delayed, post-stim >25s). To test the role of enterochromaffin cells, the same set of experiments were repeated with the addition of ondansetron (1 μM), GR 113808 (30nM), and suramin (500 μM). These blockers decreased spontaneous myenteric neurons and increased non-responders (Basal: Avil 41%/21%/38% N=118, Blockers: 37%/9%/54%, N=101; p=0.05, Chi-square) with no change in submucosal neurons (Basal: Avil 47%/34%/19%). Blockers increased the frequency of immediate responses and decreased the frequency of delayed responses in submucosal neurons (Basal: Avil 19%/64%/17%, Blockers: 36%/38%/26%) (p=0.04, Chi-square) with no change in myenteric neurons (Basal: Avil 20%/50%/30%). To test the role of ongoing cholinergic transmission, the nAChR antagonist hexamethonium (Hex; 300 μM) and the acetylcholinesterase inhibitor neostigmine (Neo; 3 μM) were used. Hex decreased and Neo increased responding myenteric neurons (Basal: Avil 41%/21%/38%, N=118, Hex: 25%/16%/59%, N=94, Neo: 50%/2%/48%, N=71; p=0.007, Chi-square). Hex increased and Neo decreased immediate responses in submucosal neurons (Basal: Avil 19%/64%/17%, Hex: 29%/41%30%, Neo: 0%,25%,75%; p=0.006, Chi-square). Collectively, these results demonstrate mucosal mechanical receptive fields of IPANs that are modulated rather than mediated by neuroepithelial signaling of 5-HT, ATP, and acetylcholine.

Disclosures: J. Kosareff: None. **C. Hall:** None. **A. Beyder:** None. **D.R. Linden:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.04/O9

Topic: E.04. Interoception

Support: HHMI
Damon Runyon Cancer Research Foundation, DRG-2405-20
NIH R01AT012051
NIH R35 NS105067

Title: Mechanotransduction in parturition

Authors: *Y. ZHANG[1], R. SERVIN[3], A. PATAPOUTIAN[4], Y. WANG[2];
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Abstract: Mechanical forces are extensively involved in pregnancy and parturition, but their precise roles and molecular mechanisms remain poorly understood. Here, we identify mechanically activated ion channels PIEZO1 and PIEZO2 as key mechanotransducers required for efficient labor progression. Genetic deletion of *Piezo1* and *Piezo2* in mice resulted in weakened uterine contractions and severe parturition defects. Tissue-specific knockout experiments revealed that while deletion of PIEZO channels in either the uterine tissue or sensory neurons alone resulted in modest defects, their combined loss significantly slowed labor progression, demonstrating an additive effect. Moreover, single-nuclei sequencing indicated that loss of PIEZO function was associated with reduced expression of connexin43 (Gja1) in uterine smooth muscle cells, suggesting a mechanistic link to impaired contraction coordination. These findings highlight the critical role of PIEZO1 and PIEZO2 in sensing mechanical forces during parturition and suggest new avenues for therapeutic intervention in labor dysfunction.

Disclosures: Y. Zhang: A. Employment/Salary (full or part-time): Scripps Research. **R. Servin:** None. **A. Patapoutian:** None. **Y. Wang:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.05/O10

Topic: E.04. Interoception

Support: ANR UNTOUCH
ANR EMOTACT

Title: Feeling though the body: Uncovering the autonomic signatures of affective tactile texture exploration

Authors: M. BUFO[1], M. PETERS[1], R. H. WATKINS[2], J.-M. AIMONETTI[1], *R. ACKERLEY[1];
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Abstract: Tactile perception is shaped not only by direct sensory afferent input, but also by other ongoing central mechanisms, such as emotional and affective processes, which in turn can be influenced by wider factors like personality traits and physiological arousal. While previous studies have established links between touch sensitivity and emotional states, there is growing interest in identifying the links between body physiological state and personality traits with the processing of touch. Presently, we investigated the physiological and perceptual correlates of material exploration by measuring pupil diameter, electrodermal activity (EDA), and heart rate variability (HRV), as well as pleasantness ratings, in response to touching textures with different affective properties, including unpleasant, neutral, and pleasant surfaces. Healthy human volunteers signed informed consent forms and the study was approved by an ethical committee. Participants took part in experiments where they completed tactile detection and discrimination

tasks, rated the pleasantness of various surfaces, and completed standardized personality questionnaires. They readily classified each surface as pleasant, neutral, or unpleasant. During the material exploration phase, physiological responses were recorded in real time. Eye-tracking (PupilLabs eye-tracker in a Vive HTC virtual reality environment) was used to monitor pupil diameter, while EDA and HRV data were collected via skin conductance sensors and ECG, respectively (ADInstruments with LabChart). Analyses revealed a significant main effect of texture type on pupil diameter ($p < 0.001$), with rougher, more unpleasant textures, such as hessian, eliciting greater pupil dilation than smoother, more pleasant materials like leather or velour. This suggests heightened arousal and attentional engagement with more intense tactile stimuli that were classified as negative in terms of affect. We are in the process of analyzing the EDA and HRV, where based on the pupillometry findings, we predict that EDA will also increase for rougher materials, reflecting sympathetic nervous system activation. Similarly, we expect HRV to decrease in these conditions, indicating a shift toward higher physiological arousal. These results support the idea that the autonomic nervous system is sensitive to tactile properties of materials and may serve as a useful index for evaluating individual affective responses to touch. The integration of pupillometry, EDA, and HRV provide a perspective on tactile-emotional interactions, with implications for sensory and affective computing, and personalized haptic interface design.

Disclosures: M. Bufo: None. **M. Peters:** None. **R.H. Watkins:** None. **J. Aimonetti:** None. **R. Ackerley:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.06/O11

Topic: E.04. Interoception

Title: Increased visual dependence in people with Joint Hypermobility: A pilot study

Authors: Y. WANG[1], C. M. ALEXANDER[2], *P. H. STRUTTON[1];
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Abstract: Introduction: People with symptomatic joint hypermobility may rely more on visual input to maintain balance due, in part, to poor proprioception, but evidence is limited. This pilot study used a virtual reality (VR)-based Rod and Disk Test (RDT) to measure visual dependence (VD) in 3 groups, in 3 head positions in the yaw plane, to manipulate proprioceptive input. Methods: With ethical approval and written, informed consent, 21 people with symptomatic hypermobility, 15 people with asymptomatic hypermobility and 21 non-hypermobile healthy controls were recruited and matched for age and sex. Each participant completed a VR-based RDT in neutral head position, 45° left head rotation, and 45° right head rotation. Each condition included 12 trials. VD was calculated from the results of the RDT by subtracting the mean rod

alignment error using a static background from the mean rod alignment error using a dynamic background. Shapiro-Wilk tests explored for data normality. Kruskal-Wallis with Mann-Whitney U post hoc tests, explored for differences between groups in the different head positions. Results: With the head in a neutral position there were no group differences (p=0.33); median [IQR] VD values were 1.22 [1.01 - 1.49] in the asymptomatic group, 0.90 [0.52 - 2.12] in the symptomatic group, and 0.65 [0.23 - 1.67] in the control group. In left head rotation there were group differences (p=0.01); VD was greater in both symptomatic (1.61 [1.11-2.76]; p=0.01) and asymptomatic groups (1.48 [1.01-2.70]; p=0.02) compared to controls (0.88 [0.30-1.52]). In right head rotation there were also group differences (p=0.03); VD in the symptomatic group (1.59 [0.76-2.64]) was greater than the controls (0.58 [0.24-1.11]; p=0.01) but not the asymptomatic group (0.55 [0.25-1.69]). No differences were observed between symptomatic and asymptomatic groups. Conclusion: These preliminary findings suggest that VD is greater during head rotation in individuals who are hypermobile. Data collection continues and it will be interesting to see whether in the powered study, the presence of symptoms (e.g. pain) in people with hypermobility impacts their dependence on vision.

Disclosures: Y. Wang: None. **C.M. Alexander:** None. **P.H. Strutton:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.07/O12

Topic: E.05. Auditory and Vestibular Systems

Title: Validity and reliability of a virtual reality-based Rod and Disk Test to assess visual dependence

Authors: *Y. WANG[1], C. M. ALEXANDER[2], P. H. STRUTTON[1];
[1]Surgery and Cancer, Imperial Col. London, London, United Kingdom; [2]MSk Lab., Imperial Col. Healthcare NHS Trust, London, United Kingdom

Abstract: Introduction: Postural stability is supported by vision and the degree to which an individual depends on vision is called visual dependence. Visual dependence increases with pathologies where balance is compromised, such as in those with vestibular disorders. Visual dependence can be measured using the Rod and Disc Test (RDT), which is traditionally delivered through a PC. This limits the setting and environmental context, we have therefore developed a virtual reality (VR) version. This study aimed to evaluate the validity and reliability of the VR-based RDT. Methods: A cross-sectional and an intra-rater test-retest design were used. With ethical approval and written, informed consent, thirty participants (15 with symptomatic hypermobility and 15 healthy controls) were recruited for the study of validity. The hypermobile group was included to increase the likely range of visual dependence. Fifteen additional healthy participants were recruited to study intra-rater test-retest reliability. Visual dependence was assessed using both VR and PC-based RDT in three head positions in the yaw plane: neutral, 45°

left rotation and 45° right rotation. Spearman's rank correlation tested for construct validity and Intraclass Correlation Coefficients (ICC) evaluated test-retest reliability. Results: Moderate to good correlations between VR and PC delivered tests were found. Spearman's rank correlation coefficients in the 3 head positions were 0.7 (neutral), 0.5 (left rotation) and 0.6 (right rotation); $p < 0.05$ in all cases. The VR-based RDT showed moderate intra-rater test-retest reliability (ICC = 0.59 and 0.65) in neutral and in left head rotation respectively. This was not the case for head right rotation (ICC = 0.01). The PC-based RDT showed poor intra-rater test-retest reliability in left, right and neutral head positions (ICCs = 0.38, 0.41and 0.05 respectively). Conclusions: The VR-based RDT demonstrates acceptable validity, but test-retest reliability was dependent on head position, the reasons for this are unclear. These data partially support the use of VR-based testing of visual dependence in varying contexts and environments.

Disclosures: Y. Wang: None. **C.M. Alexander:** None. **P.H. Strutton:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.08/O13

Topic: E.04. Interoception

Title: Monitoring Sensory Recovery Post-Targeted Muscle Reinnervation via Kinesthetic Illusions

Authors: *Y. ZHANG[1], J. SCHOFIELD[2];
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Abstract: Targeted muscle reinnervation (TMR) is a surgical technique that redirects nerves from an amputated limb to remaining muscles in the residual limb. By connecting nerves from the lost limb to residual musculature, TMR creates new sites for detecting muscle activity. When patients attempt moving their missing hand or limb, specific muscle activation patterns occur in their residual limb which can be measured allowing more intuitive control in prosthetic devices. However, natural sensory feedback remains elusive. Previous work has shown that Kinesthesia, the sense of limb or hand movement, can be created by through strategic vibration introduced to the reinnervated muscles. However, little is known about the time course of this sensory restoration in the initial months of healing, rehabilitation, and nerve regeneration following TMR surgery. Understanding these factors could inform rehabilitation timing, prosthetic prescriptions, and the design of prosthetic interfaces, ultimately improving patient outcomes. In this work, we conducted a case study with an individual who had undergone TMR following trans humeral-level upper-limb amputation. The assessments took place at three timepoints 5, 9, and 12 months after surgery. A handheld massage gun delivered 90 Hz vibrations at a force of 2-5 N for 10 seconds at various points on the reinnervated biceps muscle. The participant replicated the sensed movements using their remaining intact limb and rated how realistic these sensations felt

on a scale from 0 to 5. During testing sessions, clear illusions of elbow flexion and extension were consistently experienced at various regions of the biceps and brachialis areas of the residual which were reinnervated by the median and ulnar nerves. The participant's ratings improved from 2.3 ± 1.1 at 5 months to 4.5 ± 0.7 at 9 months, suggesting enhanced sensory nerve regeneration. This study demonstrates that vibration-induced kinesthetic illusions reliably occur in muscles reconnected via TMR and strengthen over time as nerve regeneration progresses. Mapping these illusions to specific nerve reinnervation areas provides valuable insights into peripheral nerve regeneration and brain adaptation. These insights could guide rehabilitation schedules and improve prosthetic designs by incorporating vibration-based feedback to make artificial limbs feel more natural and responsive.

Disclosures: Y. Zhang: None. **J. Schofield:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.09/O14

Topic: E.04. Interoception

Support: NIH/NICHD R01 HD090642
NIH/NIBIB T32 EB025816

Title: Computing muscle state from proprioceptive signals during in situ work loops

Authors: *J. D. STEPHENS[1], P. NARDELLI[2], L. H. TING[4], T. C. COPE[3];
[1]Coulter Dept. of Biomed. Engin., [3]Applied Physiol. and Engin., [2]Georgia Inst. of Technol., Atlanta, GA; [4]Biomed. Engin., Emory Univ. and Georgia Tech., Atlanta, GA

Abstract: Proprioception is a vital component of motor control in animals, and many motor disorders are associated with the dysregulation of proprioceptive-motor circuits. One key obstacle in the study of proprio-motor dysfunction is the limited ability to record sensory signals during behaviors such as locomotion. While motor signals are readily available experimentally through techniques like electromyography, sensory signals are not, and computational models of sensory feedback are needed to investigate proprio-motor function. In order to develop better models of proprio-motor control, it is critical to understand the mechanical state variables that are signaled by peripheral sensors. Two key proprioceptive sensors are the muscle spindle (MS) and tendon organ (TO). We have recently used novel computational approaches to suggest that central control circuits may combine MS and TO feedback to compute force-related mechanical state variables (Stephens et al, 2025, *to appear*). We hypothesize that MS and TO signals can be combined to dissociate forces generated by the muscle from forces imposed on the muscle. However, these results were based on recordings from stretches applied to passive muscle and a model of eccentric contraction, and the stretch patterns implemented did not suitably represent rhythmic behaviors like locomotion. For this purpose, we collected data from MS and TO

afferents during *in-situ* work loops of the triceps surae of the rat by applying sinusoidal stretches to the muscle-tendon unit while phasically activating the muscle in a locomotor-like paradigm. This resulted in stretches that rapidly alternate between passive stretching and shortening, and eccentric or concentric contraction. Preliminary results from group Ia and Ib afferents show activity from group Ib afferents during eccentric contraction, and from both Ia and Ib afferents simultaneously during passive stretch. Interestingly, the transition from eccentric contraction to passive stretch is accompanied by a rapid increase in firing from the Ia. We predict that additional recordings from group II afferents will allow us to decode active and passive forces, and identify the rapid firing from the Ia as a potential 'transition' signal. Such analysis can offer insight into the control variables of spinal circuits during balance control and locomotion.

Disclosures: J.D. Stephens: None. **P. Nardelli:** None. **L.H. Ting:** None. **T.C. Cope:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.10/O15

Topic: E.04. Interoception

Support: iBehave

Title: Developing new tools to dissect the function of proprioceptor subtypes in rhythmic behaviors

Authors: *Q. SILVERMAN[1], J. EISDORFER[2], V. E. ABRAIRA[2], G. GATTO[3];
[1]Univ. of Cologne, Cologne, Germany; [2]Cell Biol. and Neurosci., Rutgers, The State Univ. of New Jersey, Warren, NJ; [3]Neurol., Univ. Hosp. Cologne, Cologne, Germany

Abstract: From a simple reflex to planned motor sequences, the ability to coordinate muscle contractions to form meaningful behaviors requires continuous and immediate information on the position and movement of body parts. Proprioception, when lost, leaves patients unable to walk, stand, or even perform simple mundane movements. This suggests proprioception plays a pivotal role in reporting and updating spatial body awareness and muscle state. Proprioceptors and the networks processing their information have indeed evolved to not only report stretch and load of individual muscles, but also to represent relative positions and movements of muscles across joints, limbs, and body axes. These finely tuned and integrated circuits provide the feedback needed for motor commands to flexibly balance the demands for precision and speed while also providing the robustness to orchestrate and learn complex behaviors.
Proprioceptors have been historically classified into three main types: the muscle spindle-innervating type Ia and type II afferents sensing the rate of change and the static stretch of the muscle, respectively, and type Ib afferents that innervate the tendons and sense muscle load, or force. Although these distinct proprioceptor types were described more than 100 years ago, there are still no genetic or viral handles to individually map their connectivity and assess their

contribution to motor behaviors and their adaptation. To fill this gap of knowledge, we developed a novel triple intersectional genetic approach that by combining a Dre-dependent *FlpO* mouse line with specific *Dre* and *Cre* alleles allows us to target distinct types of proprioceptors. Our approach also enables the use of existing Flp- and Cre-dependent mouse lines to express chemogenetic or optogenetic effectors.
By crossing our newly generated *Runx3-Dre* mouse line with the *Calb2-Cre* line, we were able to specifically label type Ia proprioceptors and dissect their connectivity to individual muscles, within the spinal circuits, as well as to brainstem nuclei. Leveraging the new genetic handles we generated and the anatomical blueprints we reconstructed, we will now investigate the contribution of Ia proprioceptors to well-characterized rhythmic behaviors such as the scratch reflex or locomotion. Together our data will assess the role individual proprioceptor types take on and how they broadcast crucial information to the distributed sensorimotor circuits across the central nervous system.

Disclosures: Q. Silverman: None. **J. Eisdorfer:** None. **V.E. Abraira:** None. **G. Gatto:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.11/O16

Topic: E.04. Interoception

Support: NSF HDR Grant 2117997
NIH Grant UL1TR002529

Title: A mechanism for encoding of multi-limb proprioception

Authors: *M. H. LIPTON, M. C. DADARLAT;
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Abstract: Proprioception, the sense of the body's position and motion in space, is essential for executing precise and coordinated movements. Bilateral movements further extend proprioceptive demands by requiring integration of multiple proprioceptive signals from the limbs. Theoretical interpretations of sensory integration suggest neural populations encoding unisensory features (e.g. proprioception of a single limb) combine additively to achieve a multisensory representation. Recent studies have revealed sensorimotor cortical populations involved in the encoding of unilateral forelimb proprioceptive movements and propose a movement vector framework to represent the absolute position of the limb. However, no mechanism currently exists to interpret how proprioception from multiple limbs is encoded and integrated in the sensorimotor cortex. Here, we developed a novel behavioral paradigm to investigate neural mechanisms of bilateral forelimb proprioceptive encoding. We trained head-fixed mice (n=3) to grasp a handle with each front paw while each limb was extended to one of three distances in the horizontal plane: 0, 4, or 12 mm. Two limbs with three movement

distances results in 8 movement combinations. We performed two-photon mesoscopic calcium imaging during this passive movement task to capture the activity of approximately 2000 neurons per mouse in cortical layers 2/3 of the right sensorimotor cortex. Approximately 30% of these neurons were significantly modulated by at least one set of limb movement combinations. Interestingly, of these significantly modulated neurons, 25% were responsive to two or more movement combinations, suggesting neurons preferentially respond to a reliable movement pattern. Further, we identified clusters of neurons that exhibit distinct response profiles to limb extension, flexion, and reward delivery during the task. To investigate a potential encoding mechanism for bilateral proprioceptive movements, we first performed principal component analysis to reduce the dimensionality of the large neural dataset. In this latent space, we found that the neural responses to bilateral movements were proportional to the difference between the neural responses of unilateral contralateral and ipsilateral limb movements. This observation of additive integration is consistent with previous findings investigating integrative mechanisms of auditory and visual sensory inputs. Together, these results provide a foundation on which to investigate neural encoding of bilateral proprioception in an active behaving state.

Disclosures: M.H. Lipton: None. **M.C. Dadarlat:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.12/Web Only

Topic: E.04. Interoception

Support: JSPS KAKENHI Grant-in-Aid for Early-Career Scientists (no. 21K17472)

Title: Effects of controlled anterior tibial translation on sensorimotor function and mechanoreceptor morphology after anterior cruciate ligament injury

Authors: *S. MASUDA[1], M. NAGAI-TANIMA[2], K. HAYASHI[2], T. AOYAMA[2];
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Abstract: Anterior cruciate ligament (ACL) injuries impair both mechanical stability and proprioceptive signaling. Although gold-standard reconstruction treatment procedures aim to restore joint stability, they often provide limited support for sensory function. This study investigated whether controlling anterior tibial translation could help preserve sensorimotor function and mechanoreceptor morphology after ACL injury, using the Controlled Anterior Translation of the Tibia (CATT) model. Male Wistar rats (12 weeks old) were randomly assigned to three groups: Sham-operated (Sham), ACL transection (ACLT), and ACLT with CATT intervention (CATT). Each group was further divided into subgroups for evaluation at 1, 2, 4, and 8 weeks postoperatively (n = 6 /time point). In the CATT group, a tibial bone tunnel was created posterior to the femoral condyle, and a double suture was applied to limit anterior

tibial translation. Sensorimotor performance was assessed using the balance beam test. Histological analysis was used to evaluate ligament healing, and immunofluorescent staining targeting neurofilament and S100 protein was used to quantify mechanoreceptors at the ACL attachment sites. Statistical significance was defined as $P < 0.05$, using one-way ANOVA with Tukey-Kramer or Games-Howell post hoc tests for group comparisons and Pearson's correlation coefficients for correlation analyses. At 8 weeks post-surgery, the ACLT group showed significantly impaired balance beam performance and a reduction in morphologically normal mechanoreceptors, along with an increase in atypical mechanoreceptors, compared to the Sham group. In contrast, the CATT group demonstrated significantly better behavioral performance and preservation of typical mechanoreceptors than the ACLT group. Histological analysis revealed partial restoration of ligament continuity in the CATT group, beginning at 2 weeks and observed through 8 weeks. A significant positive correlation was observed between mechanoreceptor count and behavioral performance, suggesting that mechanoreceptor integrity contributes to sensorimotor recovery. These findings indicate that anterior tibial translation control via CATT promotes ligament healing and proprioceptive preservation following ACL injury and supports its potential as a function-focused conservative strategy that extends beyond mechanical stabilization.

Disclosures: S. Masuda: None. **M. Nagai-Tanima:** None. **K. Hayashi:** None. **T. Aoyama:** None.

Poster

PSTR448: Peripheral Mechanisms: Mechanosensation and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.13/P1

Topic: E.04. Interoception

Support: NINDS Grant 1R01NS135005
Sloan Research Fellowship FG-2024-21522

Title: Activity-dependent refinement of intersegmental proprioceptive reflexes in the developing spinal cord requires $Na_V1.6$ and C1qA signaling

Authors: C. NAGARAJA, ***A. R. MURALI**, S. ORTIZ, T. N. GRIFFITH;
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Abstract: Proprioceptors are specialized sensory neurons that detect muscle stretch and body position. A subset of proprioceptors form group Ia afferents that make monosynaptic connections with spinal motor neurons to mediate reflexes, such as the stretch reflex. Proprioceptive Ia afferents target motor neurons of the same spinal segment, yet it remains unclear how this specificity is established during early development. Using *ex vivo* spinal cord electrophysiology preparations from neonatal mice of both sexes, we identified a developmental period during which proprioceptive la afferents evoke both segmental (L5) and intersegmental (L4) responses.

Intersegmental responses (L4/L5) were prominent at postnatal days (P) 4-7 (31.15%, ± 19.87%), declined during P8-10 (11.9%, ± 5.26%), and were absent by P11-13 (3%, ± 6.7%), suggesting a period of activity-dependent synaptic pruning and refinement. During the same time window, we found that microglial numbers increase in motor regions of the spinal cord (P4-7 = 22.57 microglia/imaging area; P11-13 = 34.36 microglia/imaging area, P = 0.02), implicating them in the refinement process. To test the role of neural activity in this process, we analyzed $Na_V1.6$ conditional knockout ($Na_V1.6^{cKO}$) mice, in which proprioceptor activity is impaired in the first two weeks of postnatal development, then subsequently lost by P14. Intersegmental reflex responses persist in $Na_V1.6^{cKO}$ mice up to P11-13 (28.63%, ± 17.19%) compared to floxed controls of the same age (0.31%, ± 0.88%), indicating disrupted synaptic refinement. Interestingly, microglia numbers in the ventral region of the spinal cord were not different between $Na_V1.6^{cKO}$ mice and floxed littermate controls at P9. On the other hand, $Na_V1.6^{cKO}$ mice showed reduced C1qA expression in the ventral spinal cord compared to controls at P9, suggesting impaired activation of complement-mediated pruning pathways. C1qA is a component of the classical complement cascade that initiates synaptic pruning by tagging synapses for microglial elimination. Consistent with this, C1qA knockout mice also retain intersegmental responses at P11-13 (27.1%, ± 11.7%). Collectively, these findings identify an important postnatal window during which segmental specificity of proprioceptive circuits emerges and suggest that proprioceptor activity induces C1qA-mediated elimination of excessive intersegmental synapses.

Disclosures: C. Nagaraja: None. **A.R. Murali:** None. **S. Ortiz:** None. **T.N. Griffith:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.01/P2

Topic: E.05. Auditory and Vestibular Systems

Support: CONACYT grant CF-2019-6390
DGAPA-PAPIIT-UNAM IN208622

Title: Genetic and environmental influence on variation of the auditory cortex and white matter morphology in Mexicans: a twin study

Authors: *G. ROBLES RODRÍGUEZ[1], D. RAMÍREZ GONZÁLEZ[1], I. ESPINOSA MÉNDEZ[1], E. ZALDÍVAR MORALES[2], A. SOLARI[5], T. V. ROMAN-LOPEZ[1], E. PASAYE[1], M. E. RENTERÍA[6], A. MEDINA-RIVERA[3], A. RUIZ-CONTERARAS[4], S. ALCAUTER[1]; [1]Inst. de Neurobiología, UNAM, Querétaro, Mexico; [2]Cognitive Neurosci., Univ. Nacional Autónoma de México, UNAM, Mexico, Mexico; [3]Lab. Internacional de Investigación sobre el Genoma Humano, Univ. Nacional Autónoma de México, UNAM, Querétaro, Mexico; [4]Facultad de Psicología, Univ. Nacional Autónoma de México, UNAM, Mexico, Mexico; [5]Univ. del Valle

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Abstract: The auditory cortex resides in Heschl's gyrus (HG), whose morphology varies between individuals and hemispheres, exhibiting single or duplicated gyri. Duplications are classified as common stem (CSD) or common posterior (CPD) duplications and have been linked to individual differences in music, language, cognition, and psychiatric conditions. However, the genetic contributions to HG morphological variation remain unclear. Twin studies allow estimation of heritability (the proportion of phenotype variance attributable to genetic factors) by comparing monozygotic (Mz; 100% shared DNA) and dizygotic twins (Dz; ~50% shared DNA), particularly relevant in genetically admixed populations such as Mexico's. We analyzed 392 twins (244 Mz, 148 Dz) from the Mexican Twin Registry. MRI data were acquired on a 3T Philips scanner (T1w: 1 mm^3; DWI: 2.3 mm^3, 32/64 directions, b=1000/2000 s/mm^2). Fractional anisotropy (FA) was calculated using MRtrix, and cortical measures from FreeSurfer. HG morphology was classified with TASH and MCAI: 131 participants had right HG duplications and 249 with single HG. For the left hemisphere: 56 with HG duplications and 324 with single HG. FA differences in acoustic radiations were assessed with TBSS. Heritability was estimated using Falconer's formula and ACE models.The ACE model showed heritability of .56 for cortical thickness in left HG, while right HG was mostly shaped by environment (A = .09, C = .29, E = .29). Surface area showed A = .34 and E = .65 in right HG; and C = .19, E = .80 in left HG. Volume estimates were A = .34, E = .65 for right HG, and C = .21, E = .78 for left HG. HG duplication concordance was unexpectedly higher in Dz twins in both hemispheres, reinforcing the environmental contribution. For FA, no group differences survived correction (e.g., right: t = -1.42, p = .16), yet twin correlations revealed strong genetic effects: FA heritability was .76 for right HG and .63 for left HG. These findings highlight the different roles of genetics and the environment in the morphology of the brain's auditory system. While HG anatomical variations are mostly explained by environmental factors, variations in the mean FA of acoustic radiations were mostly explained by genetic factors. This may indicate that, despite the morphology of the auditory cortex, the acoustic radiations seem to be unaffected by these changes in the gray matter. As we observed, in this case, the white matter is not as susceptible to plastic processes, since no differences were observed between duplicates and singles. A possible next step would be to evaluate the tonotopy in the cortex and assess whether it is affected by the morphological changes.

Disclosures: G. Robles Rodríguez: None. **D. Ramírez González:** None. **I. Espinosa Méndez:** None. **E. Zaldívar Morales:** None. **A. Solari:** None. **T.V. Roman-Lopez:** None. **E. Pasaye:** None. **M.E. Rentería:** None. **A. Medina-Rivera:** None. **A. Ruiz-Conteraras:** None. **S. Alcauter:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.02/P3

Topic: E.05. Auditory and Vestibular Systems

Support: PAPIIT-UNAM Grant IA204224

Title: Study of the auditory pathway nuclei in young adults using magnetic resonance imaging and brainstem auditory evoked potentials

Authors: *P. OCAMPO LUNA[1], M. FAIR[1], C. C. CARBAJAL-VALENZUELA[2], M. GARCIA-GOMAR[1], A. ESCALANTE ORNELAS[3], M. HERNÁNDEZ CAMACHO[3]; [1]Escuela Nacional de Estudios Superiores Unidad Juriquilla, Univ. Nacional Autónoma de México, Querétaro, Mexico; [2]Psicología y Educación, Facultad de Psicología y Educación, Univ. Autónoma de Querétaro, Querétaro, Mexico; [3]Neurofisiología Clínica Juriquilla, Querétaro, Mexico

Abstract: *In vivo* studies of the auditory pathway at brainstem level are scarce due to the difficulties posed by its depth and small size for its exploration in magnetic resonance imaging (MRI). *In vivo* studies in humans are being carried out by a few research groups, using high-resolution equipment unavailable in Mexico. In electrophysiology, the standard study for functional exploration of this pathway are the brainstem auditory evoked potentials (BAEP); however, there's an ongoing debate regarding the origin of the neural generators of this recorded synchronous activity. Therefore, the objective of this project was to explore the relationship between BAEP and MRI-derived measures of the auditory brainstem nuclei. Specifically, we aimed to examine correlations between structural features of the superior olivary complex (SOC) and wave III and between the inferior colliculus (IC) and wave V, using conventional 3 Tesla MRI and BAEP recordings in young adults (age range 18-24 years). A total of 31 young adults (15 women,16 men) participated in this study, of which 23 (13 women, 10 men) completed both studies. For the MRI acquisition we used the following parameters: b=1000 s/mm2 with 64 directions, TE/TR=85/15116 ms, voxel size=2x2x2 mm3; b=2000 s/mm2 with 64 directions, TE/TR=85/15116 ms, voxel size=2x2x2 mm3; 4 interleaved volumes with b=0 s/mm2 and a diffusion volume with reverse phase encoding; T1 with TE/TR=3.7/8.1 ms, voxel size=1x1x1 mm3. BAEP were elicited using 100 μs click stimuli at 70 dB nHL and 11.4 Hz, presented in both rarefaction and condensation polarities. White noise at 40 dB nHL was delivered to the contralateral unstimulated ear. Derived diffusion tensor images (DTI) parameters including fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were extracted, alongside latency and amplitude measures of BAEP waves. Three bilateral nuclei were registered from a 7 Tesla atlas in standard space (Illinois Institute of Technology) to the 3 Tesla maps in subject space, including SOC, IC and Medial Geniculate Body. Shapiro-Wilk normality test was used to determine the use of a Pearson correlation as parametric test, or Spearman correlation as non-parametric test. Results indicated significant ($p \leq 0.05$) positive correlations in amplitudes of waves III and V with ADC measurements of SOC and IC nulcei respectively. Although significant correlations were observed, sample size limits the generalizability of the findings, and analysis of the cochlear nucleus remains pending. These results provide a foundation for further investigation of BAEP generators and its relation with structural measures.

Disclosures: P. Ocampo Luna: None. **M. Fair:** None. **C.C. Carbajal-Valenzuela:** None. **M. Garcia-Gomar:** None. **A. Escalante Ornelas:** None. **M. Hernández Camacho:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

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Program #/Poster #: PSTR449.03/P4

Topic: E.05. Auditory and Vestibular Systems

Support: National Research Foundation of Korea(NRF) funded by the Ministry of Education (RS-2020-NR049585)
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Title: Optogenetic Stimulation of Assembloid using LGR5+ Inner Ear Organoids and Spiral Ganglion Neurons

Authors: *J. PARK[1], J.-C. AHN[2];
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Abstract: Sensorineural hearing loss (SNHL) is a leading cause of permanent hearing impairment and is primarily attributed to the irreversible damage to inner ear hair cells (HCs). In this study, we established a co-culture system of LGR5+ inner ear organoids and spiral ganglion neuron (SGN) clusters to investigate the potential for functional synaptic integration and the formation of neural networks.LGR5+ cells were isolated from the cochlear sensory epithelium of postnatal day 1 C57BL/6 mice, while SGN clusters were dissected from the modiolus. Organoid cultures were initiated under Matrigel-based 3D conditions, and HC differentiation was promoted through the Wnt and Notch signaling pathways, supplemented by the administration of a Sonic Hedgehog (SHH) agonist on day 18. SGN clusters were introduced into the organoid cultures on day 7 to mimic the cellular environment of the inner ear. This combination is determined as 'Assembloid'.At week 4, adeno-associated viruses (AAVs) encoding Channelrhodopsin-2 and Halorhodopsin were used to transduce the organoids, enabling precise optical stimulation and inhibition. The functional connectivity of the co-culture system was evaluated using a multi-electrode array (MEA), which revealed light-evoked, temporally synchronized spiking activity in neurons. This suggests the formation of functional synapses between SGNs and organoid-derived sensory cells.This study demonstrates that LGR5+ inner ear organoids are capable of forming physiologically relevant interactions with auditory neurons and that their neuronal activity can be modulated using optogenetic techniques. The co-culture system serves as a valuable in vitro model for investigating inner ear development and regenerative mechanisms, while also holding promise as a preclinical platform for advancing cell-based therapies for the SNHL. Notably, optogenetic modulation may offer a therapeutic strategy for restoring and controlling auditory circuit function in sensorineural hearing loss.

Disclosures: J. Park: None. **J. Ahn:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

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Program #/Poster #: PSTR449.04/P5

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R15 DC020327-01

Title: Melatonin regulation of dopamine synthesis and D2a receptor expression in the auditory system of a vocal fish

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Abstract: Plainfin midshipman fish undergo a robust enhancement of hearing at the level of the inner ear during the summer, reproductive months to better detect and localize the mating call of males. Seasonal changes in dopamine innervation of the inner ear coupled with changes in inhibitory dopamine D2a receptor expression partially drive the seasonal change in hearing in females. However, the mechanisms that seasonally regulate catecholamines and D2a receptor expression in the peripheral and central auditory system are less understood. Melatonin production changes seasonally and its receptors are expressed in a forebrain region that contains auditory-projecting dopamine neurons, thereby supporting melatonin as a candidate hormone responsible for driving seasonal changes in catecholamine innervation of the auditory system. Here, we investigated the role of melatonin in regulating catecholamine innervation and synthesis in the central and peripheral auditory system, as well as changes in D2a receptor expression of the forebrain auditory-projecting dopamine neurons. Summer females were given either a control (N=8) or 2-Iodomelatonin (N=9) intraperitoneal implant and sacrificed after one week. Brains and saccules, the main end organs of hearing, were collected and processed for immunohistochemical analysis for markers of catecholaminergic innervation (tyrosine hydroxylase) and synthesis (phosphorylated tyrosine hydroxylase) in auditory nuclei and the saccule. Furthermore, we used fluorescence in situ hybridization (HCR RNA-FISH) on an alternate series to characterize changes in D2a receptor expression in auditory-projecting forebrain dopamine neurons. Our preliminary data suggest that melatonin increases both catecholamine synthesis and D2a receptor expression in the forebrain dopamine neurons that project to central and peripheral auditory areas. Furthermore, melatonin downregulates both catecholamine synthesis and dopamine neuron number in the preoptic area. Lastly, melatonin decreases catecholaminergic innervation in a diencephalic auditory nucleus. These results support melatonin regulation of dopamine neurons and their projections, expression of inhibitory dopamine D2a receptors, and catecholamine synthesis , which may contribute to the seasonal changes in hearing.

Disclosures: K. Kobi: None. **J.A. Sisneros:** None. **P.M. Forlano:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

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Program #/Poster #: PSTR449.05/P6

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R15 DC020327
NIH R25 NS114326

Title: Seasonal changes in catecholamine innervation of the auditory system in a vocal fish

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Abstract: In seasonal breeding vertebrates, hormone regulation of catecholamines, which include dopamine and noradrenaline, may function, in part, to modulate behavioral responses to conspecific vocalizations. During the early summer reproductive season, male plainfin midshipman fish produce advertisement calls that females detect and localize to mate as well as agonistic calls used during male competition for nests. While the mechanisms driving the seasonal change in hearing in female midshipman have been well documented, males also undergo a similar seasonal increase in hearing sensitivity, which is far less understood. To address this gap, here, we investigated seasonal changes in catecholamine innervation of the auditory system in male midshipman fish. Non-reproductive (N=8) and reproductive (N=9) were collected in winter and summer months respectively, brain and saccules, the main end organs of hearing, were collected and processed for immunohistochemical analysis for a marker of catecholamines (tyrosine hydroxylase). Summer reproductive males show greater catecholaminergic innervation of the auditory thalamus, and the hind brain cholinergic auditory efferent nucleus that project to the inner ear. These preliminary results parallel seasonal changes in catecholaminergic innervation of auditory nuclei found in females and suggests catecholamines as important modulators of auditory-driven reproductive behaviors.

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Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant NIDCD R56DC016054
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Title: Activation of group I mGluRs enhances the excitability and spike output of semilunar nucleus neurons which send an ipsilateral non-calyceal excitatory input to the mouse MNTB

Authors: H. WANG[1,2], X. WANG[3], Y. WANG[4], A. SUMSER[5], O. MARKKULA[5], C. KOPP-SCHEINPFLUG[5], *Y. LU[1,2];
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Abstract: The medial nucleus of the trapezoid body (MNTB) receives one of the largest synapses in the mammalian brain, the calyx of Held. Additional non-calyceal inputs have been reported, but their functions and origins are largely unknown. Recently, a non-calyceal input originating from the semilunar nucleus (SLN) to the ipsilateral MNTB was identified in the rat (Gómez-Martínez et al. 2023, Front Neuroanat). To understand the function of this novel neural circuit, we investigated the physiology, morphology, and connectivity of the SLN in mice, with a focus on neuromodulation mediated by group I metabotropic glutamate receptors (mGluRs). We conducted whole-cell patch clamp at 35 °C in brainstem slices from mice of two age groups (before hearing onset, P7-P12; after hearing onset P13-P39). Electrical stimulation of the area likely containing ipsilateral SLN to MNTB axons (dorsal and lateral to the MNTB) evoked AMPA receptor-dependent EPSCs in MNTB neurons, indicating glutamatergic input, putatively from SLN. Next, we recorded from SLN neurons, identified by anatomical landmarks, or as calbindin1-expressing neurons (by crossing calbindin1-Cre mouse to Ai9 reporter mouse). SLN neurons were highly excitable, with the current threshold at about 20 pA in a prolonged (200 ms) current injection protocol. Some SLN neurons exhibited spontaneous spike activity at their resting membrane potentials. Electrical stimulation of the area dorsal to the SLN evoked EPSCs in SLN neurons, which was blocked by AMPA receptor antagonist DNQX (20 μM). Immunohistochemistry staining identified the presence of group I mGluRs (mGluR1 and mGluR5) in the SLN at both ages. Activation of group I mGluRs with 3,5-DHPG (200 μM) enhanced the excitability of SLN neurons and increased their spontaneous spike activity in acute slice recordings. The enhancement was partially blocked by an antagonist for mGluR5 (MPEP, 1 μM) but not by mGluR1 blocker (JNJ16259685, 10 nM). The modulatory effect seemed long-lasting before hearing onset and shorter after hearing onset. In ongoing viral tracing experiments, we aim to define the anatomical layout of the SLN to MNTB pathway and its input sources, e.g. from auditory cortex. In summary, neurons in the mouse SLN were intrinsically highly excitable and received a glutamatergic input likely via a descending pathway. Neurons in the MNTB received a non-calyceal glutamatergic projection originating from the ipsilateral side. Group I mGluRs enhanced the SLN excitatory output, potentially forming a tonic excitation in MNTB neurons, which is hypothesized to improve their temporal processing.

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Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

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Program #/Poster #: PSTR449.07/P8

Topic: E.05. Auditory and Vestibular Systems

Support: FAPESP 2019/13458-1
FAPESP 2025/07250-0

Title: Glutamatergic neurotransmission in Dorsal Cochlear Nucleus Fusiform Neurons During Pre and Postnatal Development

Authors: N. BOARETTO[1], *R. M. LEAO[2];
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Abstract: The dorsal cochlear nucleus (DCN) integrates acoustic inputs from the cochlear nerve with multimodal inputs conveyed through parallel fibers (PF). Fusiform cells (FUS) are the principal neurons in the DCN, receiving glutamatergic synapses from both inputs, and are the primary output from the DCN to the inferior colliculus. Hearing onset in mice occurs at postnatal day 14, by the opening of the auditory meatus, and is accompanied by changes in the electrophysiological properties of FUS. We aimed to study the development of glutamatergic PF neurotransmission onto FUS during the developmental window, including the pre- and post-hearing periods. Brainstem slices containing the DCN of Swiss mice from pre-hearing (p6-13) and post-hearing (p14-21) groups were used to perform electrophysiological recordings of excitatory postsynaptic currents (EPSCs) in whole-cell patch clamp. EPSCs were evoked either by stimulation of parallel fibers (PF) or elicited by l-glutamate (1mM), applied through 20 ms puff applications (20 µm from the soma), targeting the molecular layer (ML) to reach the apical dendrites of FUS. We also performed immunofluorescence labeling for presynaptic markers VGLUT2, mainly associated with PF terminals, and the general synaptic marker SV2A. The strength of EPSCs evoked by PF stimulation was significantly greater in the post-hearing group, with increases in EPSC amplitude and area. However, no changes in EPSC kinetics were observed. The exogenous glutamate-evoked synaptic response showed that the current area was larger after hearing onset, along with its duration, including half-width and decay time constant. A decrease in the VGLUT2 to SV2A ratio in the ML was noted in the post-hearing group, which can be attributed to an increase only in SV2A puncta density, with no changes in VGLUT2 puncta density between groups. Our results indicate that the glutamatergic neurotransmission from PF to FUS change after hearing onset, increasing synaptic strength. Since the density of glutamatergic presynaptic terminals (VGLUT2) did not vary between groups, we suggest that

these changes predominantly occur postsynaptically, such as through increased dendritic arborization during development, resulting in a higher number of synaptic sites, evidenced by the increased area of glutamate induced currents.

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Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC019348
NSF Grant IOS1652432

Title: Neuromodulatory Regulation of Auditory Brainstem Responses: Neurochemical Interactions and Pharmacological Implications

Authors: *T. VAUGHN[1], J. A. KARA[2], C. C. LEE[3];
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Abstract: Neuromodulatory Regulation of Auditory Brainstem Responses: Neurochemical Interactions and Pharmacological ImplicationsTashonda Vaughn[1], John Kara[1], and Charles Lee[1]*.[1]Department of Comparative Biomedical Science, Louisiana State University School of Veterinary Medicine Baton Rouge, LA 70803*Corresponding authoremail: cclee@lsu.eduemail: tvaug12@lsu.eduAbstract: Precise auditory processing in the brainstem is critically shaped by several neuromodulatory systems, e.g. serotonergic, cholinergic, dopaminergic, noradrenergic, and histaminergic systems. Individually, these neuromodulators can influence the transmission and processing of acoustic signals. For instance, serotonin (5-HT) regulates auditory brainstem responses (ABRs) via receptor-specific pathways. However, the interaction among these systems remains under explored. In this study, we examined how interactions of such neuromodulatory systems influence ABR waveform morphology and latency in vivo, using pharmacological manipulations in rodent models. Among these neuromodulators, we found that systemic administration of selective 5-HT receptor agonists and antagonists (targeting 5-HT1A, 5-HT2A/2C, and 5-HT3 subtypes) revealed receptor-specific shifts in ABR amplitude, suggesting modulation of excitability across auditory nuclei. Furthermore, co-administration of AChE inhibitors (e.g., donepezil and physostigmine) potentiated serotonergic effects on ABRs, implicating a synergistic role of elevated acetylcholine in shaping serotonergic tone. Additionally, unique interactions occur with other combinations. Neurochemical assays confirmed region-specific changes in neurotransmitter levels across the cochlear nucleus and inferior colliculus. These findings highlight the dynamic neurochemical regulation of auditory brainstem function and suggest novel therapeutic targets for auditory disorders such as tinnitus,

hyperacusis, and central auditory processing deficits. This work provides new insights into how neuromodulatory systems jointly modulate early auditory processing and how targeted pharmacology may enhance auditory perception.Keywords: Auditory Brainstem Response (ABR), Serotonin, Acetylcholine, Histamine, Acetylcholinesterase, Neuromodulation, 5-HT Receptors, Auditory Pathway, Pharmacology, Tinnitus

Disclosures: T. Vaughn: None. **J.A. Kara:** None. **C.C. Lee:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01 DC 019348
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Title: Histamine Receptors in the Auditory Midbrain and Thalamus of the Mouse

Authors: *J. A. KARA[1], T. VAUGHN[2], C. C. LEE[3];
[1]Louisiana state university, Baton Rouge, LA; [2]Comparative biomedical science, Louisiana State Univ., Baton Rouge, LA; [3]Comparative Biomed. Sci., LSU Sch. of Vet. Med., Baton Rouge, LA

Abstract: The central histaminergic nervous system, originating from the tuberomammillary nucleus (TMN) of the hypothalamus, widely innervates almost the whole brain including the midbrain and thalamus. Brain histamine regulates diverse physiological functions, including wake and arousal states, forming part of the ascending reticular activating system. While the modulatory role of histamine in the brain, particularly in the cerebral cortex, is widely explored, very little is known about its function in the auditory system; in particular, histamine's role in the auditory midbrain (inferior colliculus: IC) and auditory thalamus (medial geniculate body: MGB) has been largely unexplored. Therefore, to assess histaminergic innervation of these auditory structures, we neuroanatomically and physiologically assessed IC and MGB neurons for functional histamine receptors. We immunohistochemically stained for histamine receptor subtypes (H1R, H2R, H3R) in both the IC and MGB. In addition, we employed *in vitro* whole-cell patch-clamp to record from IC and MGB neurons in response to bath application of histaminergic agonists. From our studies, we find a unique distribution of histamine receptors in the IC and MGB of the mouse that correlates with the responsiveness of neurons to histaminergic agonists, which in general act to depolarize auditory neurons. Overall, our data suggests that histamine can selectively heighten the responsiveness of auditory thalamic and midbrain structures to acoustic signals and highlights the overlooked role of histamine in these structures of central auditory processing.

Disclosures: J.A. Kara: None. **T. Vaughn:** None. **C.C. Lee:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

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Program #/Poster #: PSTR449.10/P11

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC020887

Title: Functions of different cell types in the lemniscal and non-lemniscal inferior colliculus

Authors: *J. WEI[1], C. XIAO[2], G. ZHANG[3], C. TAO[4], H. LI[5], H. W. TAO[6], L. I. ZHANG[5]; [2]Neurosci., [1]USC, Los angeles, CA; [3]Dept. of Neurosci. and Physiol., [4]Dept. of physiology and neuroscience, [5]USC, Los Angeles, CA; [6]Physiol. and Neurosci., USC Keck Sch. Med., Los Angeles, CA

Abstract: The inferior colliculus (IC) is a central hub for auditory and multimodal integration in the midbrain. Despite extensive previous research, the cell-type-specific circuit mechanisms underlying its functional roles remain poorly understood. Using single-nucleus RNA sequencing and multiplexed *in situ* hybridization in mice, we identified several distinct excitatory neuron subtypes in the IC shell (ICx). By exploiting the transgenic Cre lines of these cell types, we further characterized their anatomy, auditory response properties, and their contributions to central auditory processing and behavior. The study combines several approaches, including anterograde and retrograde tracing with viral vectors or chemical tracer, optrode recording of specifically tagged neurons in awake state, as well as optogenetic manipulation of neuronal activity under specific behavioral paradigms. The study likely generates additional understanding on the interactions between lemniscal and non-lemniscal auditory pathways.

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Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

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Program #/Poster #: PSTR449.11/P12

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant K99DC021582

Title: The representation of somato-motor signals in the inferior colliculus

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[3]Otorhinolaryngology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Real-world auditory behaviors, such as vocalization, sound-driven defense behavior, and orienting movements, often extend beyond passive listening and involve complex audio-motor and multisensory integration. Within the central auditory system, the inferior colliculus (IC) serves as an obligatory relay station and massive convergence center for auditory information. In addition to its role in sound processing, the IC receives input from diverse multisensory and neuromodulatory structures and is implicated in a variety of such acoustico-motor behaviors. However, little is known about the representation of somato-motor signals within the IC and their functional role in auditory behavior. In this study, we performed two-photon imaging in the IC while recording the spontaneous movements of head-fixed mice and presenting a variety of sound stimuli. Video recordings were analyzed using FaceMap and DeepLabCut and neurons that were responsive to either sound, movement, or both were parsed using a generalized linear model. We found that movement was robustly encoded across the dorsal surface of the IC, with movement-responsive neurons surprisingly outnumbering sound-responsive neurons. Neurons that encoded facial or ear movements were less common than neurons that encoded movements of the limbs or trunk, and many neurons encoded movement from multiple body regions. Movement led to a decrease in sound-driven responses in IC neurons and activation of somato-motor inputs to the IC led to a decrease in performance accuracy in mice trained on a sound detection task, suggesting a net suppressive effect of somato-motor inputs on auditory processing in the IC.

Disclosures: A.M. Lesicko: None. **K. Adeaga:** None. **E. Michel:** None. **A. Soots:** None. **M.N. Geffen:** None.

Poster

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Topic: E.05. Auditory and Vestibular Systems

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Title: A disinhibitory incerto-cortical circuit for integration of motivational and sensory signaling during natural behavior.

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Abstract: Producing adaptive natural behavior requires the integration of information from multiple sensory systems in the brain along with information about the organism's current motivational state; yet it remains unclear how this integration of information occurs between regions. Traditionally, studies of sensory encoding have focused on a single brain region or sensory system in isolation, using artificial and reduced behavioral tasks. Understanding how the brain accomplishes this during real-world operation requires natural behavioral paradigms and investigation of key brain regions that might be involved. Prey capture in mice is one such complex natural behavior well-suited to reveal the dynamic interactions of motivation and sensory information. Here we studied the interactions between the motivational region zona incerta (ZI) and the sensory region auditory cortex (AC). Previous studies have suggested that AC is critical for auditory scene analysis, which is likely necessary for auditory prey capture. The subthalamic structure ZI is not directly involved in auditory processing, but is involved in motivation and reinforcement, and has been shown to promote prey capture. In addition, ZI sends direct inhibitory projections to much of neocortex, in particular to several areas of AC. We therefore wondered if motivational signals provided by the ZI-AC projections might enhance the processing of salient sounds, such as the prey's movement, during nocturnal hunting. To test the impact of these ZI-AC projections, we first used a head-fixed prep with high-density silicon probes to gain insight into the effects of activation of the projections across cortical layers. For these experiments, mice expressing ChR2 in GAD2+ projections were presented with pure tones and white noise while superficial optic fibers were used for photoactivation. These recordings showed that activation of ZI projections modestly enhanced sound responses of a subset of cells in a frequency-specific manner. This enhancement suggests that integration of motivation and sensory information may involve the operation of a disinhibitory circuit in auditory cortex. To understand the role of these projections during prey capture, we used tetrode arrays to record from AC while mice performed auditory prey capture and, on some trials, optogenetically activated the terminals. Neuronal responses to pure tones and white noise showed modest enhancement of sound responses, similar to that seen with silicon probes in head-fixed mice. We are currently investigating the effect of optogenetic stimulation on the behavior during prey capture and on spiking of cells in auditory cortex.

Disclosures: M. Shallow: None. **A. Weible:** None. **M. Wehr:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.13/Q2

Topic: E.05. Auditory and Vestibular Systems

Support: SyNergy
IMPRS-BI

Title: Behavioral relevance shapes spatial tuning in the auditory cortex

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Abstract: The ability to localize sounds is critical for the survival of many species. Since spatial information is not directly encoded at the level of the auditory sensory epithelium, the brain has a complex task of reconstructing the auditory spatial world. Furthermore, beyond the initial stages of sensory processing, auditory input is combined with higher-order contextual signals in the auditory cortex (AC). Early AC studies in anesthetized animals showed that neurons are generally tuned to sounds originating from the contralateral hemifield. Yet, it remains unclear whether the auditory spatial tuning of AC neurons can shift depending on whether a specific location is behaviorally relevant to an awake animal. To investigate this, we performed longitudinal two-photon calcium imaging of the same neurons in the layer 2/3 of the AC while mice learned a sound localization task over the period of more than one month. Sound stimuli were presented from loudspeakers positioned at various azimuthal locations. Each mouse was trained to associate one predefined target location (either at the midline or contralateral to the imaged AC) with a water reward upon licking and to withhold licking for all other locations. We imaged ~450 neurons at each of the 10 sites in the AC of 7 mice. The behavioral paradigm and analysis were designed to primarily capture the sound-evoked component of the calcium responses. On average, ~7% of neurons per site exhibited spatial tuning. Although the proportion of spatially tuned neurons remained stable across training, individual neurons showed highly dynamic tuning, often changing their spatial preference. Importantly, as the behavioral performance improved, we observed a consistent increase in the percentage of spatial neurons tuned to the rewarded location. We also noted a consistent decrease in the percentage of spatial neurons preferring the ipsilateral side, possibly reflecting the initial prominence of the microscope (ipsilaterally located) to the animal. These results reveal experience-dependent reorganization of spatial representations in the auditory cortex, emphasizing the role of behavioral relevance in sensory cortical plasticity.

Disclosures: V. Kello: None. **D. Amaro:** None. **M.H. Myoga:** None. **W.F. Mlynarski:** None. **B. Grothe:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.14/Q3

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01DC012557

Title: Behavioral timescale synaptic plasticity in the mouse auditory cortex

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Abstract: Learning at the behavioral level can sometimes be 'one-shot' or almost instantaneous, but most studies of long-term plasticity such as long-term potentiation (LTP) seem to require dozens or hundreds of induction events yet measure outcomes minutes afterwards. However, recent studies of behavioral timescale synaptic plasticity (BTSP) show that enduring hippocampal plasticity can be induced in just a few trials in vivo and in vitro (Bittner et al. Nat Neurosci 2015, Bittner et al. Science 2017, Liao & Losonczy Annu Rev Neurosci 2024). Here we examine the potential for BTSP to occur in the mouse auditory cortex. For in vivo experiments, adult mice were head-fixed and trained on a 2-alternative forced-choice task to distinguish pure tones of one frequency (e.g., 13 kHz) from tones of other nearby frequencies (Martin et al. Nat Neurosci 2024). We performed 2-photon imaging during behavior and observed sudden, sometimes trial-to-trial changes in frequency tuning curves. For some responsive cells, new peaks to behaviorally relevant stimuli could emerge or be suppressed, shifting overall tuning curve structure. In some cases, unresponsive cells suddenly became responsive to tones during behavioral training. Many of these sudden and enduring changes happened during the earliest phases of training. We also examined BTSP in brain slices of adult mouse auditory cortex. We made whole-cell recordings from layer 5 pyramidal neurons in current-clamp mode, monitoring EPSP amplitudes before and after pairing events with strong postsynaptic depolarization ~500 ms on 2-10 pairing trials. ~25% of recordings showed BTSP post-pairing when inhibition was intact; this increased to ~50% of recordings with inhibition blocked. This also led to a change in spike output probability after pairing- 3.8% of trials before pairing evoked 1 or more postsynaptic spikes that increased to 27.3% of trials after pairing ($p=0.02$ in paired t-test, $n=6$ cells), without significant changes to resting membrane potential or input resistance. Finally, we pharmacologically blocked L-type calcium channels (LTCCs) and, as with hippocampal BTSP (Bittner et al. Science 2017) determined that LTCCs are required for cortical BTSP induction.

Disclosures: M. Wollet: None. **C.J. Bair-Marshall:** None. **K.A. Martin:** None. **R.C. Froemke:** None.

Poster

PSTR449: Auditory Circuits, Synapses, and Neurotransmitters

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.15/Q4

Topic: E.05. Auditory and Vestibular Systems

Support: FRAXA Research Foundation

Title: Can adult gene re-activation alone or combined with controlled sound exposure normalize EEG and behaviors in mouse model of FXS?

Authors: *A. NORMAN[1], N. FAROOQ[1], K. TAPIA[2], A. GOEL[5], K. A. RAZAK[3], I. M. ETHELL[4];
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Abstract: Fragile X Syndrome (FXS) is a neurodevelopmental disorder with no known cure, that is associated with epigenetic silencing of Fragile X Messenger Ribonucleoprotein 1 (*Fmr1*) gene. The most common symptoms of FXS include hyperactivity, repetitive behaviors, social communication deficits, and sensory hypersensitivity. These behaviors can stem from hyperexcitable cortical circuits manifesting in electroencephalogram (EEG) phenotypes that are remarkably similar between the mouse model of FXS and the human condition across different brain areas. Gene re-activation represents an attractive therapeutic strategy. However, a fundamental unanswered question for the current population of humans with FXS, is if the treatments can restore circuit function in adulthood, past the critical developmental period. Therefore, the main goal of this study was to test if gene re-activation alone or combined with sensory manipulations can lead to positive functional outcomes in adult mice. *Fmr1*^{FloxNeo}CAG-CreERT2 mice were treated with tamoxifen to achieve gene re-activation. In addition, a subset of mice were exposed to14 kHz pure tones (5 Hz repetition rate, 70 dB SPL) alone or combined with tamoxifen treatment. We further studied cortical activity using clinically relevant EEG recordings as well as locomotor and exploratory behaviors using open field test. We found that gamma synchronization to frequency-modulated sound, chirp, was significantly improved in the frontal cortex of KO mice following gene re-activation, however, there was no effect of sound exposure. Analysis of event-related potentials (ERP) showed that gene re-activation and sound exposure had similar effects in reducing power of ongoing responses to broadband sound trains. Finally, behavior testing revealed similar significant improvements in exploratory behaviors but not hyperactivity following both adult gene-reactivation and sound exposure. No enhanced effects of combined gene re-activation and controlled sound exposure were observed for cortical activity and behaviors in adult KO mice. Summarizing, our results show that adult gene re-activation as well as adult controlled acoustic exposure had positive effects on functional cortical responses and behaviors in KO mice. These findings prove that therapeutic and sensory interventions in adulthood can result at least in partial improvements of functional outcomes and open new possibilities for treatments of adult humans with FXS.

Disclosures: A. Norman: None. **N. Farooq:** None. **K. Tapia:** None. **A. Goel:** None. **K.A. Razak:** None. **I.M. Ethell:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.01/Q5

Topic: E.06. Vision

Support: NEI: 1R01EY032101 (j. l. h.)
NIGMS: P20GM103650 (Celluar and Molecular Imaging core facility)
NIH: GM103440 (Nevada INBRE)

Title: Metabolic Control of Visual Processing for Appetitive Stimuli

Authors: *T. FENG[1], G. JANUARY[2], J. HOY[3];
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Abstract: Metabolic states, specifically hunger, can bias visual processing to optimize food search by enhancing attention toward relevant environmental cues in humans and animals. However, the mechanisms underlying how internal states such as hunger influence visual pathways to enhance receptivity to appetitive stimuli remain unclear. The few existing studies on this topic point to the hormone ghrelin, its well-known ability to induce hunger perception and feeding behavior, and its control over higher-order areas that process food-associated sensory stimuli. In contrast, increasing circulating leptin consistently decreases food-seeking behavior across species and is therefore hypothesized as a counteracting stimulus to ghrelin, providing an overall dampening signal that might impair processing of food-related cues.
Our work aims to investigate how metabolic states regulate animals' orientation toward salient visual objects in the environment by examining prey-capture behavior in laboratory mice. We have observed that exogenous leptin reduced motivation of mice to prey on insects under food restriction but selectively increased their visual orienting (head and eyes) toward specific motion cues. Meanwhile, freezing behavior is notably increased under the same conditions after leptin treatment. Surprisingly, acute ghrelin administration in mice did not enhance approach responses towards moving live prey or small moving ellipses traversing a computer screen, but increased the time to first approach toward naturally appetitive stimuli, though only in female mice. Intriguingly, male mice also showed remarkably suppressed freezing behavior in response to certain types of visual stimulation following ghrelin treatment. Our ongoing work is investigating how leptin and ghrelin directly influence visual information processing in the mouse midbrain. Collectively, our data demonstrate that hunger states dynamically regulate visual orienting behaviors linked to food-seeking, providing insights into the neural circuitry underlying the interaction between visual processing and motivational states.

Disclosures: T. Feng: None. **G. January:** None. **J. Hoy:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.02/Q6

Topic: E.06. Vision

Support: 5T32NS007224-38
5T32GM136651-03
5T32GM136651-02
1F30EY037573-01

Title: Experience-dependent adaptation and orientation tuning plasticity across cortical layers in mouse visual cortex

Authors: *V. H. FAN, M. J. HIGLEY;
Neurosci., Yale Sch. of Med., New Haven, CT

Abstract: Experience-dependent adaptation in the mouse primary visual cortex (V1) is characterized by reduced response magnitudes following repeated visual stimulation. Although thalamocortical inputs have been shown to remain stable, the extent of these functional changes within cortex, particularly across layers, remains poorly understood. Moreover, it is unclear whether adaptation is selective for specific visual stimulus features such as orientation, which might suggest activity-dependent plasticity of specific synaptic subpopulations. To address these questions, we performed chronic in vivo two-photon calcium imaging in awake, head-fixed mice on a freely moving running wheel. We tracked the same individual GCaMP6s- and GCaMP8m-expressing pyramidal neurons in layers 2/3 and 4 of V1 across multiple days of imaging. Retinotopic mapping was performed via widefield imaging to identify V1 boundaries, followed by receptive field mapping to establish optimal stimulus position for each neuron. Neuronal orientation preferences were assessed on baseline (Day 1) and final (Day 7) imaging days using 0° and 90° drifting gratings. Between these sessions, mice received daily presentations of the 0° stimulus. Control experiments involved imaging neurons only on the first and last days, with daily stimulus presentations. We observed significant experience-dependent decreases in response amplitudes across both layer 2/3 and layer 4 pyramidal neurons, with neurons preferentially adapting to the adapted orientation. Furthermore, orientation tuning curves exhibited smaller amplitudes and shifts in preference away from the adapting stimulus. By Day 4, response amplitudes were reduced by ~50%, with further declines through Day 7, indicating robust long-term plasticity. Our results suggest that adaptation is driven by plasticity within layer 4, with thalamocortical synaptic depression or reduced layer 4 excitability as candidate mechanisms that we are currently exploring experimentally. Together, these results demonstrate that repeated visual experience induces orientation-specific adaptation and refinement of neuronal tuning in V1 neurons, likely through activity-dependent plasticity of stimulus-specific circuits within the cortex. Our findings also provide novel insights into how sustained visual experience shapes cortical function and the representation of external cues.

Disclosures: V.H. Fan: None. **M.J. Higley:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.03/Q7

Topic: E.06. Vision

Support: This work was performed under a FPI pre-doctoral contract, PREP2022-000645
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Project (PCI 2022-134995-2) funded by the Agencia Estatal de Investigación

Title: Neuronal dynamics during binocularly conflicting stimulus presentation in mouse V1

Authors: M. TIMPLALEXI[1,2], **R. F. CORREIA**[2], A. ESTOP[2], *A. RANSON[3];
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Abstract: Binocular rivalry occurs when the two eyes receive conflicting visual input, leading to bistable perceptual alternations rather than a fused image. While extensively studied in humans and non-human primates, methodological constraints have limited circuit-level understanding, and its presence in rodents remains unclear. Here, we implement an experimental framework to investigate binocular rivalry in mice, enabling detailed examination of neural circuits during interocular conflict. Using a mirror-based setup, awake head-fixed mice were presented with congruent and incongruent stimuli, including drifting gratings and naturalistic movies, while neuronal activity in primary visual cortex (V1) was recorded with two-photon calcium imaging. We observed increased trial-to-trial variability of V1 neuronal responses under incongruent conditions compared to monocular viewing, suggestive of rivalry-like dynamics. This variability increased when the contrast of the normally dominant contralateral input was reduced. A support vector machine (SVM) classifier trained on congruent responses decoded fluctuating stimulus representations during incongruent stimulation, with contralateral contrast reduction biasing the decoder toward ipsilateral stimuli. During extended (30-second) incongruent presentations, decoded stimulus identity fluctuated over time, reflecting alternating dominance, consistent across both artificial and naturalistic stimuli. We further examined input from the retrosplenial cortex (RSC) as a potential top-down modulator. RSC axonal boutons in V1 exhibited eye-specific activity, suggesting that eye-specific signals persist in higher-order association areas. Decoder analysis revealed that RSC boutons, like V1 neurons, showed dominant encoding of one stimulus during incongruent conditions, and were similarly influenced by contralateral contrast manipulations. Overall, our findings demonstrate that mice exhibit neural signatures consistent with binocular rivalry in V1 and highlight the contributions of both local circuits and long-range feedback during interocular mismatch.

Disclosures: M. Timplalexi: None. **R.F. Correia:** None. **A. Estop:** None. **A. Ranson:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.04/Q8

Topic: E.06. Vision

Support: NSERC Grant 2022-04632
CFI Grant 42263
CIHR Scholarship BESC M
Réseau de recherche en science de la vision Scholarchip
Université de Montréal Scholarship

Title: Acetylcholine release dynamics in the cortex of a mouse engaged in a virtual reality environment

Authors: *A. DRIOUICH[1], S. MEJIA ROMERO[2], E. VAUCHER[2];
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Abstract: Acetylcholine (ACh) is a neuromodulator involved in input processing and attention. However, the intricacies of its effect on the visual cortex have yet to be understood. To this end, we can now rely on virtual reality (VR) as a powerful tool to investigate complex information processing in a well-controlled environment. This work showcases the spatiotemporal dynamics of the release of ACh in head-fixed mice placed in a VR system. C57Bl/6 mice aged 3 to 4 months received a bilateral 2 µL ICV injection of AAV9-hSYN-ACh4.3 (gACh3.0, WZ Bioscience, from Dr. Y. Li, Peking University). This sensor allowed the recording of ACh release using mesoscopic fluorescence imaging while the mice were head-fixed in a VR environment displayed on 2 monitors in front. They were then shown videos simulating a journey in their cage with different shelters. A salient stimulus (horizontal sinusoidal grating at the top of the binocular visual field) was displayed during a stationary phase. The simulations were first divided into 4 groups: with or without the salient stimulus in a normal background (stim and sham, respectively), and with or without the salient stimulus in a dimmed background (grey filter application, stim/fg and sham/fg). Using the umIToolbox on MATLAB, the variation of fluorescence (ΔF/F) was extracted for different areas across the cortex and analyzed using a 1-way repeated measure ANOVA, i.e. in the primary visual cortex (V1), extrastriate visual areas (AM, LM, PM, AL), posterior parietal cortex (RL), retrospenial (RS) and anterior cingulate (ACA) cortical areas. Our analysis showed a significant increase of ACh release when the cage environment was moving, compared to the stationary phase, in the videos stim and sham for most cortical areas. For stim/fg and sham/fg, the ACh release was increased only by the salient stimulus in the RL cortex. These results suggest that ACh release might be more closely linked to dynamic visual stimulation rather than a static one, but is probably involved in salient stimulus processing in both cases.

Disclosures: A. Driouich: None. **S. Mejia Romero:** None. **E. Vaucher:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.05/Q9

Topic: E.06. Vision

Support: HHMI

Title: Spatial or temporal prediction in mouse visual cortex

Authors: *Q. ZHANG[1], A. L. GRACIAS[2], C. STRINGER[4], M. PACHITARIU[3];
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Abstract: Predictive coding is a framework that explains how animals build internal models of their sensory environments. Predictive coding may either capture spatial or temporal relationships between sensory objects. While the original theory by Rao and Ballard described spatial predictive coding, most of the experimental data so far has been interpreted as evidence for temporal predictive coding. Here we directly tested whether the "surprise" neural response to a novel stimulus in the sensory cortex is due to a spatial or a temporal internal model. We adopted two previously-used paradigms to study predictive coding: one based on virtual-reality and one based on flashed static stimuli. In both cases, mice were trained with a fixed sequence of stimuli for several days. After training, we made several manipulations: 1) we replaced a stimulus with a gray wall, 2) we introduced a novel stimulus, 3) we altered the order of the stimuli or 4) we repeated a trained stimulus. The first and second manipulations induced a substantial "surprise" neural response, while the third and fourth ones did not. Thus, a surprise response only occurred if a new spatial, not temporal, pattern was introduced. We further found evidence of spatial pattern-based adaptation as the mice became familiar with each stimulus set. We conclude that primary sensory areas in mice represent spatial rather than temporal models of sensory environments. A temporal model may exist elsewhere, such as in the hippocampus or frontal cortex.

Disclosures: Q. Zhang: None. **A.L. Gracias:** None. **C. Stringer:** None. **M. Pachitariu:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Topic: E.06. Vision

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Vanderbilt Brain Institute Faculty Fellow Award
NARSAD Young Investigator Award from the Brain and Behavior Research Foundation
National Science Foundation (NSF) Faculty Early Career Development Program (CAREER) grant 2339210

Title: Predictive Routing in the Visual Hierarchy

Authors: *E. Z. SENNESH[1], J. A. WESTERBERG[3], A. M. BASTOS[2];
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Abstract: Converging behavioral and neuroanatomical evidence suggest that the neocortex implements a probabilistic internal model of the sensorimotor environment (McNamee & Wolpert, 2019). The appearance at an anatomical level of a canonical laminar microcircuit (Douglas et al., 1989; Mumford, 1992) suggests that each six-layer column of granular cortex may subserve a canonical computation, perhaps in the form of predictive coding (Bastos et al., 2012; Friston & Kiebel, 2009; Rao & Ballard, 1999) or routing (Bastos et al., 2020), to represent and update this internal model. Predictive coding hypothesizes that matched populations of representation and error neurons encode feedback predictions and feedforward errors. Predictive routing assigns these roles to oscillatory bands: α/β for predictions and ɣ for errors. Based on previous experiments, predictive routing hypothesizes that these bands engage in a push-pull during stimulus processing, with ɣ feeding forward through laminar layers 2/3 to convey stimuli and α/β feeding back through laminar layers 1/6 and 5/6 to suppress predicted stimuli.
Recent experiments (Gabhart et al., 2025; Westerberg et al., 2025) have found evidence against the coding of prediction errors in spike rates, but these leave open both the question of why non-invasive recordings have supported predictive processing (Walsh et al., 2020) and of the predictive routing hypothesis. As part of the Allen Institute's OpenScope project, N=14 mice performed a visual oddball task (Bekinschtein et al., 2009) during multi-area laminar recording (Neuropixels (Jun et al., 2017)) to test predictive processing hypotheses. Histological labeling of the cortical laminae enabled a fine-grained examination of their roles in the task, and six areas up the visual hierarchy (V1, RL, LM, AL, PM, AM) were recorded in order to capture both feedforward and feedback effects.
ɣ-band local-field potential (LFP) oscillations conveyed feedforward prediction errors ubiquitously throughout the cortex; α/β-band oscillations weakened in unpredictable conditions compared to predictable ones; and θ-band oscillations additionally played a role in signaling slower, longer-scale temporal prediction errors. Current-source density analysis on LFPs re-epoched to the troughs of these oscillations demonstrated a laminar flow consistent with feedforward (θ), feedback (α/β), and feedforward (ɣ) laminar signaling, respectively. Predictive routing explains these findings better than rival spike-based predictive processing hypotheses, as well as better than simple feedforward stimulus representation/adaptation.

Disclosures: E.Z. Sennesh: None. **J.A. Westerberg:** None. **A.M. Bastos:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.07/Q11

Topic: B.07. Network Interactions

Title: Adaptation induces formation of new neuronal networks in adult brain

Authors: E. JAIN[1], A. ZADOUD[2], H. AJROUCHE[2], I. MAHIEDDINE[2], *S. MOLOTCHNIKOFF[3];
[1]UNIVERSITY OF MONTREAL, MONTREAL, QC, Canada; [2]Univ. of Montreal, Montréal, QC, Canada; [3]Biol. Sci., Univ. de Montreal, Montreal, QC, Canada

Abstract: Synaptic modifications within the connectome, the brain's map of functional neural circuits and inter neuronal connections, can occur in adulthood through visual adaptation. These experience-dependent changes reflect the ability of the connectome to reorganize its functional architecture in response to sensory input which is a sign of restructuring the neural network. Neuronal orientation selectivity, a key feature of the visual cortex, refers to the tendency of neurons to respond strongly to a specific stimulus angle called the preferred orientation. This study aims at exploring the effects of adaptation on connections between neurons. For this study 6 female CD-1 mice (30-35 g, aged 9-11 weeks) were used. The animals were anesthetized with Urethane and locally with Xylocaine and placed in a stereotaxic frame. A multi-electrode array was positioned over the visual cortex. Neuronal responses were recorded during repeated presentations (25 trials) of oriented drifting gratings shown for 4 seconds, with interstimulus intervals of 1.5 to 3 seconds. To induce adaptation, a single grating orientation was displayed continuously for 12 minutes. Functional connections were inferred through cross-correlogram analysis between simultaneously recorded neurons, allowing us to disclose functional relationships between the cells between their respective spike trains before and after adaptation. The analysis was performed on 44 neurons per condition (10 connectome pairs pre- and post-adaptation each). Under control conditions, adaptation increased the number of connections across the neurons leading to formation of a new neural network. Moreover, the connected neurons developed similar orientation preferences post adaptation while the cell that lost its connection showed no shift of preferred orientation, indicating that adaptation drives clustering of tuning properties within functional networks. These findings highlight the adaptive potential of the adult brain connections and identifies it as a necessary mechanism for its experience-driven reorganization. This constitution of a link between the cells may induce attractive shifts making neuron change its preferred orientation, the mechanism of which can be explored further. By linking orientation selectivity to connectome-level remodeling, this study contributes to a deeper understanding of adult cortical plasticity and network-level dynamics.

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Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Program #/Poster #: PSTR450.08/Q12

Topic: E.06. Vision

Support: NSERC/CRSNG

Title: Cross-modal adaptation reshapes visual cortical tuning beyond sensory borders

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Abstract: Although sensory cortices display modular selectivity for their primary inputs, they are far from isolated in function. Growing evidence indicates that regions like the visual cortex can undergo dynamic reconfiguration in response to stimuli from other modalities. To investigate the mechanisms underlying such cross-modal plasticity, we examined how 12 minutes of sustained adaptation to either visual or auditory stimuli modulated neuronal responses in the primary visual cortex (V1) of the cat (Felis catus), focusing on infra- (IF) and supra-granular (SG) layers.In line with previous findings (Chanauria et al., 2016, 2019), both adaptation protocols induced orientation tuning shifts. However, our neuron-by-neuron analysis (Visual Adaptation: IF = 45 neurons, SG = 46; Sound Adaptation: IF = 78, SG = 80) revealed that auditory adaptation significantly increased the area under the tuning curve [AUC (computed over neural responses across all orientations); permutation t-test, $p < 0.05$], indicating broader and more ambiguous tuning. Moreover, the overall shape of the population tuning curve differed significantly following auditory adaptation (Kolmogorov-Smirnov test, $p < 0.05$) and was accompanied by higher firing rates across orientations (permutation t-test, $p < 0.05$). Notably, only auditory adaptation led to a significant increase in response variability, as measured by the Fano factor (permutation t-test, $p < 0.05$), across both layers—regardless of whether neurons showed significantly modulated firing rates.These results suggest that distinct sensory adaptation pathways leave divergent functional imprints on cortical circuits. Specifically, sound adaptation appears to induce a more variable and flexible coding regime in V1, potentially broadening its representational scope and enhancing preparedness for complex or abstract visual inputs.
References : Chanauria, N., Bharmauria, V., Bachatene, L., Cattan, S., Rouat, J., and Molotchnikoff,S. (2016). Comparative effects of adaptation on layers II-III and V-VI neurons incat V1. European Journal of Neuroscience 44. doi: 10.1111/ejn.13439 Chanauria, N., Bharmauria, V., Bachatene, L., Cattan, S., Rouat, J., and Molotchnikoff,S. (2019). Sound Induces Change in Orientation Preference of V1 Neurons:Audio-Visual Cross-Influence. Neuroscience 404, 48-61. doi:10.1016/j.neuroscience.2019.01.039

Disclosures: Y. Belkacemi: None. **E. Mokhtarinejad:** None. **N. Chanauria:** None. **O. Flouty:** None. **S. Molotchnikoff:** None. **V. Bharmauria:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.09/Q13

Topic: E.06. Vision

Support: NEI R010005911

Title: Increases of cortical neuron spike rate guide behavior more effectively than equivalent spike rate decreases

Authors: *L. WEI[1,2], J. H. R. MAUNSELL[1,2];
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Abstract: How the brain translates changes in cortical spike rates into behavior remains a fundamental question in systems neuroscience. Although increases and decreases in spike rate can, in theory, convey equivalent amounts of information, recent optogenetic studies in mouse V1 have revealed a striking asymmetry: mice readily detect spike rate increases but are insensitive to equivalent decreases (Cone et al., 2020). To test whether this asymmetry extends to primates, we trained rhesus monkeys to detect changes in the motion coherence of dynamic random dot stimuli. While the monkeys performed the task, we recorded from individual neurons in the middle temporal visual area (MT), a key region for motion processing. Stimulus parameters (location, size, speed, and drift direction) were tailored to each neuron's preferences. MT neurons responded more strongly to high coherence than to low coherence when the dots drifted in their preferred direction. We compared behavioral sensitivity to coherence steps with neuronal sensitivity, using receiver operating characteristic (ROC) analysis of spike rate changes. For coherence increments in the preferred direction, the neurometric sensitivity of MT neurons aligned with the monkey's psychometric thresholds (neurometric threshold: 23.8% (1.7%) coherence, psychometric threshold 20.8% (0.5%) coherence; mean (SEM), n = 35 neurons). For coherence decrements, however, behavioral performance was markedly worse than neurometric performance (neurometric threshold: -29.6% (1.9%) coherence, psychometric threshold -38.9% (1.2%) coherence). Instead, the monkey's performance matched the neurometric sensitivity of neurons that preferred the opposite direction (threshold -37.8% (2.8%) coherence). These neurons increased their firing in response to coherence decrements, although their response modulations were always smaller than those of neurons that preferred the dot drift direction. These findings suggest that perception depends predominantly on increases in spike rate, even when other neurons show larger spike rate decreases. This asymmetric readout highlights a fundamental constraint on how cortical signals are used to guide behavior.

Disclosures: L. Wei: None. **J.H.R. Maunsell:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Program #/Poster #: PSTR450.10/Q14

Topic: E.06. Vision

Support: Simons Collaboration on the Global Brain award 542961SPI
NIH Grant R01EY022930
NIH Grant R01EY034723
NIH Grant RF1NS121913

Title: Behaviorally relevant modulations of visual cortical responses to image fragments after viewing the entire image

Authors: *C. XUE[1], M. CZARNIK[2], M. R. COHEN[1];
[1]Dept. of Neurobio. and Neurosci. Inst., Univ. of Chicago, Chicago, IL; [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Our perception of a visual scene emerges from visual cortical neurons that each respond to a fragment of it. Meanwhile, visual cortical responses to the fragments may also be modulated by perception of the entire scene. Here, we designed an experiment to tease the two processes apart, and tested the hypothesis that the responses of visual neurons to fragments of an image are modulated by exposure to the entire image in a behaviorally relevant fashion. We compared the responses of populations of simultaneously recorded macaque V1 and V4 neurons to image fragments before and after the monkey viewed the entire image. We first measured neuronal responses to image fragments flashed within the joint receptive fields of the recorded neurons while the animals passively fixated. The animals then free viewed the entire image while we recorded gaze position and neuronal responses. After extensive experience free viewing the image, we repeated the measurements of neuronal responses to the fragments. Our data are consistent with the hypothesis that viewing the entire image modulates neuronal responses in ways that reflect knowledge of how the fragment fits into the whole. In particular, neuronal responses after viewing the image better reflected the monkeys' gaze fixation patterns during free viewing, suggesting that the neuronal responses reflected the behavioral relevance of each image fragment. Adaptation or repetition suppression could not explain the changes because the modulation of responses to fragments was more correlated with the saliency of a fragment than the amount of time it was in the receptive field. To speculate how these modulations might impact perception, we compared responses to a pretrained convolutional neural network. We demonstrated that V1 and V4 neurons reflect higher-level features after exposure to the full image. These results show that early and intermediate visual cortex does not passively relay local signals but flexibly incorporates global context, likely through rapid feedback from higher stages. These modulations may underlie efficient encoding of visual scenes by aligning local representations with their statistical and behavioral relevance in the context of the global scene.

Disclosures: C. Xue: None. **M. Czarnik:** None. **M.R. Cohen:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.11/Q15

Topic: E.06. Vision

Title: Natural retinal statistics: How the optics and cones shape visual input

Authors: *D. BANNAI[1], A. BELSTEN[2], B. A. OLSHAUSEN[3], J. YATES[4];
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Abstract: In visual neuroscience, the statistics of natural scenes have been well-characterized with spectral power and spatial frequency related by a power law, typically 1/f^2. These statistics are hypothesized to constrain, and therefore shape, the organization and function of the early visual system. However, it is known that both the optics of the human eye (Artal 2012) and cone spectral sensitivities (Osorio and Bossomaier 1992) transform the visual stimulus even before it is processed by the retina. In this work, we analyze the change in statistics of hyperspectral images as they are processed by the (1) optical system of the human eye and (2) cone spectral sampling. Fifty hyperspectral natural scenes, sampled at 10nm intervals between 400-700nm, were utilized (Foster and Reeves 2022). Optical images were produced by running the hyperspectral data through an optical model of the human eye (Cottaris et al. 2019). From there, images representing L, M and S cone absorptions were calculated using each cone type's spectral sensitivity function. We then quantified the power spectra for each raw hyperspectral, optical and cone-absorption image (Fig.1). We found significant reductions in total power as well as attenuation of higher spatial frequency content after the optics and cone spectral sampling. The optics significantly changed the power distribution across spatial frequency, and this varied by wavelength band. We see similar results reflected in the power spectra of the cones. This work highlights the transformation of image statistics and characterizes the visual signal that is projected onto the retina. These changes may provide greater insight into the constraints placed upon the early visual system and context for how the retina may take advantage of these constraints when efficiently encoding natural scenes. Future work aims to analyze how cone mosaic patterns may arise from these retinal projections.

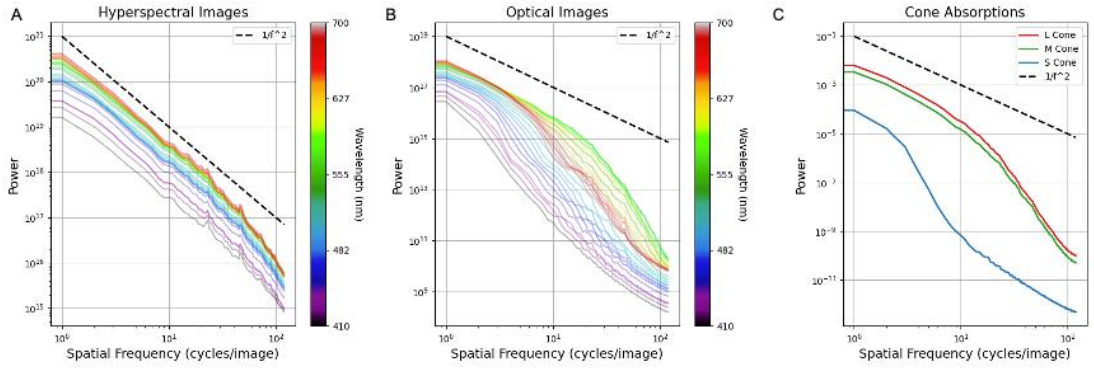


Figure 1. Power spectra of (A) raw hyperspectral, (B) optical and (C) cone images averaged over all radial orientations. The plots demonstrate the average power spectrum across 50 images. Colors of each plotted line in (A) and (B) describe the wavelength band of the data. In total, 31 wavelength bands from 400-700nm, spaced by 10nm, were used.

Disclosures: D. Bannai: None. **B.A. Olshausen:** None. **J. Yates:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.12/Q16

Topic: E.06. Vision

Title: Standard models fail to capture positional invariances in marmoset foveal V1

Authors: *T. KOTHAPALLI[1], R. RESSMEYER[2], J. F. MITCHELL[3], J. YATES[4]; [1]Univ. of California, Berkeley, Berkeley, CA; [2]Univ. of Washington, Seattle, WA; [3]Ctr. of Visual Sci., Univ. of Rochester, Rochester, NY; [4]Optometry, UC Berkeley, Oakland, CA

Abstract: Neurons in the primary visual cortex (V1) vary in their sensitivity to the precise position - or phase - of oriented stimuli. This phase sensitivity is used to classify cells along a spectrum from simple (highly phase-sensitive) to complex (phase-invariant). A prominent idea is that complex cells achieve some degree of positional invariance through pooling over phase, and this idea is formalized in the energy model. But it remains unclear whether such phase-based invariance is sufficient to explain tolerance to small shifts in the retinal image during natural fixational eye movements. In this work, we investigated both how sensitive foveal V1 neurons are to fixational eye movements and whether standard models capture their sensitivity.We fitted linear, energy, and combined (linear-energy) models to neuronal responses elicited by a full-field Gabor noise stimulus. As expected, the stimulus filters of the fitted models showed localized, oriented spatial structure. We then used these fitted models to predict responses of the same neurons to repeated presentations of natural image patches during fixation. The positional invariance of both the model and neural responses were then quantified by computing response variance as a function of inter-trial eye position differences. Foveal neurons were highly

sensitive to eye position displacements during fixation. However, standard models consistently over-estimated the sensitivity to small image displacements (< 0.6 degrees) and underestimated sensitivity to large displacements (> 0.6 degrees). Our analysis reveals that the phase invariance inherent in the energy model alone is insufficient to explain the full extent of observed positional invariance. These findings suggest that standard V1 models inadequately capture the true degree of positional invariance in foveal neural coding, implying that additional mechanisms for positional invariance are present during fixational eye movements on naturalistic stimuli.

Disclosures: T. Kothapalli: None. **R. Ressmeyer:** None. **J.F. Mitchell:** None. **J. Yates:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Program #/Poster #: PSTR450.13/R1

Topic: E.06. Vision

Support: NIH EY030998
Del Monte Institute for Neuroscience

Title: Optogenetic Inhibition of Direct-Projecting V1-to-Area MT Cells During Marmoset Free Viewing

Authors: *L. SHAW[1], K. H. WANG[2], J. F. MITCHELL[3];
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Abstract: Marmoset monkeys scan visual scenes with saccadic eye movements to strategically place high acuity foveal vision. Each eye movement produces a strong transient in neural activity within primary visual cortex that typically includes activity suppression followed by a positive post-saccadic rebound. Across the population, the amplitude of suppression and the latency of the rebound vary considerably in form and timing (Parker et al., Nature Neuroscience, 2023). These saccadic modulation profiles vary in relation to different cell types and cortical layers in V1. In particular, a subset of neurons shows a lack of suppression with an early response latency to saccades that is direction selective. These neurons are largely narrow spiking and reside in layers 4 and 6. It is possible that this population is consistent with direction selective neurons in the magnocellular pathway that directly project to dorsal stream areas like middle temporal (MT) area. Anatomical studies have shown that two populations of V1 cells project directly to area MT, including layer 4B stellate neurons (or layer 3C in marmoset) and also a population of layer 6 pyramidal cells (Meynert cells). Given their projection target, it is likely that these populations have unique motion tuning properties and roles in the saccadic suppression system. However, previous experiments have lacked the ability to determine the circuit anatomy of recorded neurons using electrophysiological signals alone. We investigated this circuit using a projection-specific optogenetic labeling method, which involves using a double adeno-associated virus

(AAV) intersection and optogenetic tagging with the inhibitory opsin Jaws. We recorded well-isolated single units across laminar depths as marmosets freely viewed natural images, a blank screen, or full field moving gratings. During these recordings, light pulses were delivered to the cortical surface to tag and inhibit area MT projecting V1 cells. We found a subpopulation of saccade modulated cells whose post-saccadic rebounds were suppressed by ~20% during optogenetic stimulation. We here describe the motion tuning properties, laminar placement, electrophysiological profiles, and saccade modulation profiles of these area MT-projecting cells and compare their properties to the rest of the population of V1 saccade-modulated cells.

Disclosures: L. Shaw: None. **K.H. Wang:** None. **J.F. Mitchell:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Program #/Poster #: PSTR450.14/R2

Topic: E.06. Vision

Support: Department of Veterans Affairs: Veteran Readiness and Employment (Chapter 31) Funding

Title: Ocular Drift Transforms Retinal Image Statistics and Spatiotemporal Receptive Field Dynamics

Authors: *D. PEREZ, Jr.[1], A. BELSTEN[2], J. YATES[3];
[1]Vision Sci., Univ. of California, Berkeley, Berkeley, CA; [2]Univ. of California, Berkeley Vision Sci. Phd Program, Berkeley, CA; [3]Optometry, UC Berkeley, Berkeley, CA

Abstract: Efficient coding is a foundational theory in visual neuroscience, offering normative explanations for representations learned in early sensory systems. In the retina, efficient coding objectives predict center-surround receptive fields as a strategy to decorrelate spatial input, effectively whitening natural scene statistics. However, recent work has proposed that eye movements themselves, particularly the Brownian motion-like ocular drift during fixation, also serve to whiten visual inputs (Kuang et al., 2012). By converting spatial correlations into temporal modulations, drift flattens the power spectrum of natural scenes, effectively whitening input to the retina. This finding raises a potential tension: if spatial redundancy reduction is already achieved, does center-surround organization still emerge, and would this persistence reveal alternative roles that reframe retinal design principles? This possibility aligns with empirical observations that spatial tuning in primate ganglion cells is often less sharply bandpass than classical models predict (Croner & Kaplan, 1995) and with psychophysical evidence that fixational drift fundamentally contributes to contrast sensitivity (Casile et al., 2019). To test whether fixational drift shifts encoding strategies, we adapted an efficient coding model (Karklin and Simoncelli, 2011; Jun et al., 2022) trained on spatiotemporal segments drawn from natural movies (NM) and from the same movies sampled along Brownian motion (BM) trajectories

simulating ocular drift. We compared the resulting spatial, temporal, and spectral properties of learned receptive fields across conditions. We report three key findings. First, while NM training produced stronger absolute surround responses, when normalized to center strength, surround influence remained comparable. Second, BM training yielded diffuse receptive fields with lower spatial frequency selectivity (spatial centroids 0.07-0.12 cycles/pixel), while NM training produced more compact receptive fields with higher spatial frequency selectivity (centroids up to 0.22 cycles/pixel).Third, temporal tuning shifted: BM training yielded consistently fast, biphasic filters spanning higher frequencies (1-11 Hz), while NM training produced more diverse responses, with a notable convergence toward slow, monophasic filters (1-2 Hz). These results suggest that while center-surround organization persists despite pre-whitened inputs, retinal encoding shifts emphasis from spatial to temporal processing, demonstrating that center-surround mechanisms serve broader computational purposes beyond classical redundancy reduction.

Disclosures: D. Perez: None. **A. Belsten:** None. **J. Yates:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Program #/Poster #: PSTR450.15/R3

Topic: E.06. Vision

Support: STI2030-Major Projects Grant 2022ZD0204600

Title: Representational geometry of contrast responses and the effects of adaptation in macaque V1

Authors: *C. CHEN, S. GUAN, N. JU, S. ZHANG, X. WANG, S. TANG, C. YU;
Peking Univ., Beijing City, China

Abstract: We used two-photon calcium imaging and multidimensional scaling (MDS) to investigate contrast response functions and their representational geometries in macaque V1 neurons. Individual neurons were first classified based on their contrast responses to Gabor gratings at various orientations. Hierarchical clustering of contrast response functions revealed three distinct neuron types: (1) neurons showing response saturation at higher contrasts, resembling the Naka-Rushton function (30%); (2) neurons displaying linear contrast response functions (20%); and (3) neurons exhibiting steep increases at high contrasts without saturation (33%). At the population level, MDS revealed that the orientation manifolds expanded with increasing contrast in the representational space, radiating outward from a central origin and forming a cone-like structure where each orientation followed a distinct trajectory. The inter-centroid distance increased with contrast, and for each neuron type, the rate of distance increase paralleled the corresponding contrast response function. These results indicate enhanced orientation discriminability at higher contrasts, in contrast to previous reports that orientation

tuning functions of individual neurons were contrast-invariant. We further examined how adaptation reshapes the geometry of orientation and contrast representations. In the orientation adaptation experiment, the adaptor orientation appeared eight times as often as each of the other seven orientations. This led to response suppression at the adaptor orientation and a concave distortion in the circular orientation manifold. In the contrast adaptation experiment, the 0.5 adaptor contrast was presented six times as often as each of the other five contrasts, resulting in compression of the contrast response function—particularly at the adaptor and higher contrast levels (0.5 and 1). At the population level, the maximum representational distances shifted from low-low to mid-high contrast levels, consistent with the idea that neuronal populations dynamically adjust their sensitivity to the most prevalent contrast in the environment. Together, these findings demonstrate that the contrast not only modulates response gain at the single-neuron level but also reshapes the geometry of feature representations. These geometric transformations are further modulated by adaptation, reflecting the population's dynamic tuning to recent environmental statistics.

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Poster

PSTR450: Visual System: Response Modulation and Adaptation

Location: SDCC Halls B-H

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Program #/Poster #: PSTR450.16/R4

Topic: E.06. Vision

Title: Image-dependent temporal filter characteristics in primary visual cortex but not superior colliculus neurons

Authors: *Y. YU[1], B. GÜLBAHÇE[2], Z. M. HAFED[3];
[1]Univ. of Tuebingen, Tuebingen, Germany; [2]Grad. Training Centre, Univ. of Tübingen, Tuebingen, Germany; [3]Ctr. for Integrative Neurosci., Tuebingen, Germany

Abstract: Stimulus-driven neuronal responses are often characterized by an initial spike burst followed by a gradual reduction towards lower steady-state activity. Such temporal adaptation is mathematically equivalent to high pass filtering, suggesting that different adaptation dynamics translate into different abilities to faithfully track time varying stimuli. Here, motivated by the idea that luminance polarity (dark versus bright contrasts) and spatial frequency may not be equally likely at all possible temporal frequencies in natural dynamic scenes, we asked whether primary visual cortex (V1) and superior colliculus (SC) neurons exhibit different adaptation time constants along these feature dimensions. For luminance polarity, we recorded from 350 V1 (two male macaque monkeys) and 248 SC (three monkeys) neurons. In each trial, a disc (0.51 deg radius and variable dark or bright Weber contrast) appeared within the neurons' response fields. For spatial frequency, we recorded from 251 V1 and 108 SC neurons (two monkeys) while presenting a static Gabor grating. SC neurons exhibited much faster adaptation dynamics than

V1 neurons for the luminance polarity stimuli, and this effect was particularly strong in SC visual-motor neurons. However, there was no SC dependence of adaptation rate on luminance polarity. V1 neurons, on the other hand, exhibited clear feature-dependence. These neurons' temporal dynamics were slower for low contrast (10%) bright than dark stimuli, whereas they were considerably faster for 100% contrast bright than dark stimuli. For spatial frequency, SC neurons again showed no image dependence in their temporal dynamics, whereas V1 neurons always exhibited the fastest adaptation, which was surprisingly faster than in the SC, at intermediate (4 cycles/deg) spatial frequencies. All of these effects were not explained by the individual feature preferences of the neurons. We hypothesized that the generally fast SC adaptation allows visual-motor SC neurons to quickly recruit saccade-related bursts after the sensory responses. Instead, V1 neurons need to track scene dynamics. Consistent with this, we found that the darkest parts of natural dynamic scenes generally have the slowest temporal modulations, consistent with the slow V1 adaptation time constants for very dark stimuli. On the other hand, luminance edges in natural dynamic scenes have the largest temporal bandwidths of luminance modulations at a given retinotopic location, which can also be the case in static scenes shifted on the retina via fixational eye movements; this is consistent with the increasingly fast V1 adaptation rates as a function of increasing spatial frequency.

Disclosures: Y. Yu: None. **B. Gülbahçe:** None. **Z.M. Hafed:** None.

Poster

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Title: Omission responses reveal the functional role of neuronal oscillations in predictive routing

Authors: *H. NEJAT[1], Y. S. XIONG[1], J. A. WESTERBERG[3], A. M. BASTOS[2];
[1]Psychology, [2]Psychology and Vanderbilt Brain Inst., Vanderbilt Univ., Nashville, TN; [3]Dept. of Vision and Cognition, Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: Predictive coding (PC) is one of the widely studied theories to explain hierarchical processing in the mammalian cortex. PC states that the brain computes internal models of expected events and responds to unexpected deviances in its observations with prediction errors. It also has been proposed that the PC is implemented in the brain via predictive routing (PR). PR states that slow oscillations in alpha/beta (8-30Hz) represent internally processed top-down

signals, and inhibit bottom-up spiking and fast oscillations in gamma (40Hz+), which represents prediction error. Causal elimination of top-down alpha/beta oscillations via propofol has shown enhanced gamma and spiking, supporting the function of top-down oscillatory signals in PR. Here, we use a sequential omission paradigm in order to eliminate the bottom-up inputs and test the PR model. We recorded dense laminar electrophysiologic signals from eleven areas (V1,V2,V3d,V3a,V4,MT,MST,TEO,FST,FEF,PFC) across the cortical hierarchy in two awake macaques over 16 sessions. Using dense 128-channel laminar probes (Diagnostic Biochips, Glen Burnie, MD) we recorded a total of 5,760 Local Field Potentials (LFP) channels and 3,213 neurons distributed across these areas. Our omission paradigm consists of two contexts: (1) a common and expected sequence of stimuli, and (2) an uncommon sequence of stimuli in which one of them is omitted, while monkeys continue to fixate so that any omission responses are not affected by sensory/motor confounds. This omission paradigm is well-suited to test PC and PR, because the omission should reflect internally generated activity where neuronal responses are entirely decoupled from sensory evoked activity. We found a strong dissociation between LFP and single unit spiking. Omission specific single neuron spiking was only found at top of the hierarchy in prefrontal areas PFC/FEF. In contrast, there was widespread modulation in the LFP predominantly in the theta (2-7Hz), alpha (8-12Hz) and beta (13-30Hz) bands. Collectively, our findings suggest that while omission involves higher-order cognitive processing mediated by sparse, specialized neuronal populations, it also elicits a global top-down response on the LFP across diverse cortical areas in an area-specific manner, supporting the PR hypothesis that internally generated signals in the cortex are represented via low-frequency oscillations. In addition, we propose that the observed decrease in low-frequency power during omission functions to prepare the sensory cortex for future bottom-up signals, setting up a hyper-vigilant state.

Disclosures: H. Nejat: None. **Y.S. Xiong:** None. **J.A. Westerberg:** None. **A.M. Bastos:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Program #/Poster #: PSTR450.18/R6

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Title: Fading of perceptions elicited by repeated electrical microstimulation and its recovery for cortical visual prostheses

Authors: *M. VAN DER GRINTEN[1], F. GRANI[2], G. BOUWMAN[3], M. VALE-CALVO[2], F. WANG[1], A. LOZANO[2], R. LÓPEZ-PECO[2], M. VILLAMARÍN ORTIZ[2], C. SOTO SANCHEZ[2], P. C. KLINK[1], R. VAN WEZEL[3], P. R. ROELFSEMA[1], E. FERNANDEZ[2]; [1]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [2]Bioengineering Inst., Univ. Miguel Hernández de Elche, Elche, Spain; [3]Donders Ctr. for Neurosci., Donders Inst. For Brain, Cognition and Behaviour, Radboud Univ., Nijmegen, Netherlands

Abstract: Visual prosthetics are a promising solution for millions of blind people worldwide. Electrical stimulation of the primary visual cortex has been found to produce dots of light in the subject's vision, called phosphenes. By converting camera input to electrical stimulation of the visual system, part of the impaired pathway can be bypassed in blind people, allowing for restoration of a rudimentary form of vision through patterned phosphenes.
To develop a functionally useful prosthesis that allows for interaction with the world, it is important that the prosthesis wearer can see moving, continuous patterns. However, there are indications that repeated stimulation of the same electrodes leads to habituation or fading of the phosphene percept. In this work, we investigate these temporal effects of electrical microstimulation on phosphene perception. We combine behavioral reports and neural recordings from 3 blind volunteers implanted with one 96-channel Utah array in V1, with 1024-channel recordings from 2 non-human primates implanted in V1, V4 and IT.
Our results show that repeated stimulation induces both neural and perceptual habituation, and that this effect is strongly dependent on the interval between consecutive stimulation events as well as the stimulation amplitude. We quantify the spatial spread of the habituation effect, showing that the effect is locally restricted around the stimulation electrode in V1, and that the effect is propagated along the ventral visual pathway. We demonstrate that these neural correlates can be used to detect fading of phosphenes, paving the way for closed-loop interventions to allow for continuous prosthetic vision.

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Poster

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SNSF 31NE30_203974 ERA-net
Carigest Foundation

Title: Comparing Optogenetic and Electrical Stimulation of Macaque Primary Visual Cortex for Visual Prosthesis Development

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Abstract: Optogenetic stimulation of primary visual cortex (V1) has been proposed as a more spatially specific alternative to electrical stimulation for future visual cortical prostheses. However, translating optogenetic methods from rodents to primates remains a major challenge. Here, we present preliminary data directly comparing the perceptual and neural effects of optogenetic and electrical stimulation of macaque V1.
Two macaques received injections of optogenetic constructs into their V1, guided by laminar-resolved electrophysiological recordings. Both optogenetic and electrical stimulation were applied across cortical depths. Monkeys performed a forced-choice phosphene detection task (50% stimulation, 50% catch trials) and underwent perimetry testing following training under visual stimulation conditions.
Electrophysiological recordings confirmed reliable neural activation with optogenetic stimulation. Behaviorally, monkeys consistently reported phosphenes in response to electrical, but not optogenetic, stimulation. Phosphene detection thresholds varied linearly with electrical current strength and closely resembled visual contrast-response functions. The highest efficacy for phosphene induction was observed with stimulation of granular and supragranular layers, while infragranular stimulation was less effective. In contrast, optogenetic stimulation failed to elicit reliable percepts regardless of stimulation layer or intensity. Interestingly, preliminary testing with surface LED stimulation above the V1 dura appeared to yield weak but detectable phosphenes.
These findings confirm the robustness of electrical stimulation for eliciting visual percepts in macaque V1. Our results highlight key challenges in achieving perceptual effects with optogenetics at this stage and underscore the importance of understanding how either of these methods affects laminar and lateral cortical circuit dynamics for successful prosthetic vision development.

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Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Program #/Poster #: PSTR450.20/R8

Topic: E.06. Vision

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Title: Human-in-the-loop optimisation for efficient intracortical microstimulation temporal patterns in visual cortex

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Abstract: Biomimetic intracortical stimulation has shown promising effects on energy efficiency and perceptual quality for BCI applications like evoking tactile sensations. However, stimulation temporal patterns are often handcrafted, and their use in visual neural implants remains underexplored. We present preliminary first-in-human and in-silico evidence that Human-in-the-Loop (HILO) Preferential Bayesian Optimisation (PBO) can identify energy-efficient temporal amplitude-modulation patterns for intracortical microstimulation (ICMS) in the blind visual cortex. Specifically, we (1) optimise single-train temporal profiles of ICMS in a blind volunteer implanted with a Utah array; (2) compare optimised patterns with constant, ramped, and biomimetic baselines; and (3) validate the strategy on simulated data, asking whether HILO can recover ground-truth temporal kernels embedded in a noisy phosphene generator. The participant received 50-pulse trains parametrised by ten amplitude values (α_1-α_{10}), each controlling five successive pulses, and then indicated in a two-alternative forced-choice task which stimulus appeared brighter. To isolate temporal effects from current level, total charge per train was fixed. Choices updated a Gaussian-process surrogate, whose acquisition function proposed subsequent profiles. After convergence, psychometric functions were measured for optimised and baseline patterns. In-silico, synthetic phosphene trials with realistic noise assessed optimisation accuracy via root-mean-square deviation between true and estimated kernels. HILO consistently lowered stimulation thresholds versus constant-current baselines across electrodes and sessions. Simulations recovered kernels near the noise floor, confirming the efficiency of PBO and the HILO approach. Preliminary data suggest that temporal dynamics are key to improving visual neuroprosthesis interactions with the blind cortex, and that patient-driven optimisation can tailor ICMS dynamics for better perceptual efficacy. Our framework also accurately identifies temporal kernels in silico, promising more efficient visual neuroprostheses.

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Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Program #/Poster #: PSTR450.21/R9

Topic: E.06. Vision

Title: Alpha-band phase modulates perceptual sensitivity by changing internal noise and sensory tuning

Authors: *A. PILIPENKO[1], A. MCGOWAN[2], J. CHAUDHRY[3], V. NUKALA[2], E. LINCOLN[2], A. NARAYANAN[2], J. SAMAHA[4];
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Abstract: Trial-to-trial variability in alpha-band neural oscillations (8-13 Hz) have previously been linked to variability in conscious visual perception. However, the functional role of alpha phase in visual perception remains debated, with prior studies reporting effects of pre-stimulus phase on detection (i.e., hit rates) but also null results. Methodological differences such as stimulus properties (e.g., duration, size, location) and low trial counts may contribute to these inconsistencies. Additionally, previous studies have not distinguished whether alpha phase modulates perceptual sensitivity (d') or criterion, using signal detection theory (SDT). To address these gaps, we used a Yes/No detection paradigm with an 8ms vertical Gabor target (2 cycles per degree) embedded in filtered noise. Participants reported whether they perceived the target in the noise or only the noise (target presence = 50%). Each participant (n=6) completed 6,020 trials across 4-5 EEG sessions. We observed a significant effect of pre-stimulus alpha phase on d' at the group level with no accompanying effect on criterion. Examining detection across the alpha cycle indicates that these sensitivity modulations arise from an inverse phasic relationship between hit and false alarm rates, consistent with a reduction in internal noise during optimal alpha phases. This contrasts with a multiplicative gain model, which would predict a constant false alarm rate across phases and only a boost in hits. Moreover, participants were more consistent in their response to two identical stimuli when both had been presented during their optimal phase. These findings suggest that alpha phase enhances perceptual sensitivity by decreasing internal noise, rather than amplifying the signal. Lastly, we created classification images of the optimal and suboptimal phases. These images showed small boosts in the sharpness of spatial frequency and orientation tuning during the optimal alpha phase, suggesting that alpha phase may modulate sensory tuning towards relevant stimulus properties.

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Poster

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Topic: E.06. Vision

Support: STI2030-Major Projects 2022ZD0204600

Title: Is blindsight qualitatively degraded conscious vision? A TMS study on awareness and visuomotor performance

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Abstract: Blindsight, residual vision after V1 damage without conscious awareness, poses a key debate: Is it simply degraded conscious vision (linked to the ventral pathway and correlated with awareness) or a distinct unconscious process (mediated by the dorsal pathway or subcortical nuclei, often assessed via visuomotor or saccade tasks)?We used TMS to induce blindsight-like behavior in healthy participants, employing a novel “consciousness-gating” design with two groups. The 2-Alternative-Voluntary-Choice (2-AVC) group responded via saccade and key-press only if they perceived a stimulus, otherwise they fixated (reporting "no stimulus"). The 2-Alternative-Forced-Choice (2-AFC) group always guessed the stimulus location, even without perception. Both groups rated awareness trial by trial. We hypothesized that saccade tasks would be less affected by V1 disruption due to subcortical engagement, but that conscious perception would gate saccade initiation in 2-AVC, a gate bypassed in 2-AFC. Results (N = 34) confirmed our hypotheses. In the 2-AFC group, V1 TMS (80 ms SOA) significantly decreased key-press accuracy ($p = 0.007$) and awareness ($p = 0.038$), but saccade accuracy was unaffected ($p = 0.38$). Key-press accuracy and awareness correlated strongly ($r = 0.87$, $p = 0.005$), while saccade accuracy and awareness did not ($r = 0.56$, $p = 0.15$), showing a dissociation between eye movement performance and visual consciousness. This dissociation was absent in the 2-AVC group, where conscious perception gated saccade initiation. Both key-press accuracy and awareness decreased significantly at 100 ms SOA ($p = 0.003$; $p = 0.018$). Saccade accuracy also decreased ($p = 0.007$) when participants were required to maintain fixation for "unseen" trials. All measures (saccade accuracy, key-press accuracy, self-rated awareness) correlated strongly (e.g., saccade vs. awareness: $r = 0.92$, $p = 0.001$). We replicated correlations suggesting blindsight resembles degraded conscious vision. However, the saccade method in 2-AFC revealed preserved blindsight-like behavior: V1 disruption suppressed awareness but not saccade accuracy. Crucially, in 2-AVC, V1 suppression impaired saccade initiation when conscious perception was required for response. This demonstrates a fundamental dissociation between non-conscious visual processing and conscious awareness, showing that conscious awareness actively gates behavioral performance based on task demands. This research is supported by STI2030-Major Project*s 2022ZD0204600*.

Disclosures: Y. Wang: None. **W. Li:** None.

Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Topic: E.06. Vision

Support: National Natural Science Foundation of China Grant 61876222
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Title: An anti-Hebbian model for binocular visual plasticity and its attentional modulation

Authors: *Z. CHEN, Y.-C. CAI;
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Abstract: Monocular deprivation during the critical period impairs both the cortical structure and visual function of the deprived eye. In contrast, brief occlusion of one eye for minutes to hours in adults paradoxically enhances the predominance of that eye. This counter-intuitive effect of short-term monocular deprivation is considered a form of homeostatic plasticity, serving to stabilize visual cortical activity during deprivation. However, whether this sensory plasticity requires attention, and the underlying neural mechanisms remain unclear. We employed a newly designed paradigm—monocular flash deprivation—to investigate short-term binocular visual plasticity, enabling precise control over both the deprivation process and attention levels. Changes in ocular dominance were measured using binocular rivalry tasks before and immediately after deprivation. Twelve male and ten female observers (mean age: 20.6 years; range: 18-24 years) participated in the psychophysical experiment. We found that the deprivation effect was dramatically reduced in the absence of attention (two-way repeated measures ANOVA, $F_{attention}(2,42) = 12.72$, $p < 0.001$, $\eta_p^2 = 0.377$), indicating that attention plays a critical modulatory role in short-term binocular visual plasticity. We developed a neural computational model incorporating the Hebbian learning rule at interocular inhibitory synapses (i.e., anti-Hebbian learning) to explain the deprivation effect. During monocular deprivation, the non-deprived eye receives normal visual input and exhibits stronger neural activity, whereas the deprived eye lacks visual input and shows weaker activity. The model posits that this interocular asynchrony in neural activity drives Hebbian learning at inhibitory synapses, thereby weakening the inhibitory connections from the non-deprived eye to the deprived eye. Consequently, inhibition of the deprived eye is substantially reduced following deprivation, leading to a marked enhancement of its ocular dominance. Our model predicts both the boosting of the deprived eye and its dependence on attention. Moreover, it accounts for other forms of binocular plasticity, including those observed in prolonged binocular rivalry and those induced by eye-based attention. We suggest that short-term binocular plasticity arises from the plasticity in inhibitory

connections between the two monocular pathways, with anti-Hebbian learning playing a fundamental role in its underlying neural mechanisms.

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Poster

PSTR450: Visual System: Response Modulation and Adaptation

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Topic: E.06. Vision

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Title: Modulation of experience-dependent visual cortical plasticity: The roles of attention and contrast gain in contrast response function sensitivity

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Abstract: Stimulus-specific response potentiation (SSRP) is a form of cortical plasticity observed in the visual system, characterized by enhanced visual evoked potentials (VEPs) following the passive viewing of a high-contrast visual stimulus. SSRP enables noninvasive investigation of experience-dependent neuroplasticity in vivo. While attention is known to modulate both learning and plasticity, its influence on SSRP remains largely unexplored. Additionally, individual differences in visual processing such as contrast gain control may contribute to variability in SSRP effects across individuals. In this study, we investigate how attentional state and gain control mechanisms shape SSRP. We hypothesized that directing spatial attention toward an SSRP-induction stimulus would enhance response potentiation within its retinotopic extent, while diverting attention would diminish it. In parallel, we hypothesized that different contrast response function phenotypes (reflecting differences in contrast gain control) may predict the extent of SSRP potentiation. Pre-Post SSRP stimuli consisted of 2 semicircular hemifield checkerboards, each frequency-tagged to measure EEG steady-state VEPs (128-channel EGI system). Participants (n=54) observed contrast-sweeps of the checkerboards before and after SSRP-induction, with sign-reversal rates of 6 Hz and 7.5 Hz (non-plasticity inducing), maintaining fixation via a letter-detection task. During SSRP-induction, the left checkerboard (100% contrast, 2 Hz reversal) served as the potentiation stimulus, while the right checkerboard (2% contrast, 3 Hz reversal) was the non-potentiated control. Participants performed a task to deploy covert attention to either the potentiating stimulus or the non-potentiated control hemifield. Participants were categorized into linear (n=16), saturating (n=24) and supersaturating (n=14) groups based on the best CRF model fit derived from the lowest Akaike Information Criterion score. Strikingly, we observed that participants with saturating

CRFs showed more pronounced post-induction response potentiation compared to participants with non-saturating (i.e. more linear) CRFs, suggesting that SSRP depends on the engagement of contrast gain control mechanisms. This group-specific SSRP did not depend on the attention condition and moreover was not retinotopic, i.e. potentiation occurred in both hemifields. These findings suggest that contrast gain control mechanisms may gate visual cortical plasticity in SSRP, while visual spatial attention has a modest if any role in SSRP.

Disclosures: P.N. Limon: None. **A.M. Norcia:** None. **R.T. Ash:** None.

Poster

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Title: Cross-modal semantic processing and predictive coding in the human visual cortex revealed by a large-scale vision-language fMRI dataset

Authors: *Y. LI[1], S. LI[1], R.-Y. ZHANG[2], S. GU[3];
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Abstract: Understanding how the human brain integrates vision and language at the semantic level requires both ecologically valid experimental paradigms and large-scale multimodal datasets. We introduce the Caption Scene Dataset (CSD), a high-resolution fMRI dataset in which 8 participants each viewed over 4,400 paired stimuli consisting of a text caption followed by a naturalistic image, judging their semantic congruence. In addition to fMRI scans, the dataset includes T1, T2, diffusion MRI, eye-tracking, and ECG data, along with localized functional ROIs. Using this dataset, we investigated the neural basis of semantic expectation and prediction error in the visual cortex. Guided by predictive coding theory, we found that early visual areas (V1-V3) showed reduced responses when visual inputs matched semantic expectations derived from prior text cues. Deep neural encoding models leveraging language and vision features successfully predicted cortical responses, revealing that early visual areas represent cross-modal semantic priors. Furthermore, a gradient of prediction error coding was observed, progressing from low- to high-level visual areas, with response suppression strength reflecting the magnitude of semantic congruence. Together, this work provides a robust resource for vision-language research and reveals mechanistic insights into how the visual system encodes and updates

semantic predictions, highlighting the dynamic interplay between feedforward sensory input and top-down semantic inference.

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Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

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Program #/Poster #: PSTR451.02/R14

Topic: E.07. Visual Sensory-Motor Processing

Support: Swiss SNF grant (310030_212516)

Title: Imitation learning of dexterous hand control reveals muscle-level encoding in primate motor and somatosensory cortex

Authors: *A. MARIN VARGAS, A. PEREZ ROTONDO, A. CHIAPPA, M. W. MATHIS, A. MATHIS;
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Abstract: Dexterous behavior, such as grasping, relies on the integration of proprioceptive feedback with adaptive motor commands. Here, we develop a neural network policy that is trained via deep reinforcement learning. We are able to train this policy to achieve muscle-based control while receiving continuous proprioceptive feedback to reproduce primate grasping with a high-dimensional, musculoskeletal hand model (39 muscles). The learned representations better captured the neural activity in primary motor (M1) and somatosensory (S1) cortices than high-dimensional muscle states and control signals. Indeed, the highest neural predictability is achieved from the network layer that nonlinearly combined afferent and efferent information. Recurrent architectures further enhance predictability of single-unit cortical activity. Importantly, models trained to control muscles rather than joints, show better alignment with cortical dynamics, suggesting that the cortex processes muscle states. Cortex also contains high-level signals, and we show that S1/M1 can directly drive a neural network policy to generate dexterous movements closely matching primate hand kinematics. These findings underscore the potential for combining reinforcement learning and biomechanics (embodiment) for elucidating sensorimotor processing and lay the groundwork for advanced brain-machine interfaces.

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Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

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Topic: E.07. Visual Sensory-Motor Processing

Title: Selective suppression of bright, but not dark, visual stimulus information in the primary visual cortex by saccades

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Abstract: Saccade generation is accompanied by a marked reduction in perceptual sensitivity to stimuli that appear around the time of eye movement onset. This phenomenon, known as saccadic suppression, not only alters perception but also affects subsequent oculomotor behavior. Neural correlates of saccadic suppression have been observed in multiple brain areas, including the retina, superior colliculus (SC), and primary visual cortex (V1). However, the relative contributions of each area to the overall perceptual effect remain poorly understood. Motivated by previous findings that perisaccadic detectability is similarly impaired for both dark and bright stimuli in perception (Baumann et al., Journal of Vision, 2021), as well as by matching observations in the visual sensitivity of SC neurons for both dark and bright contrasts (Wu & Hafed, Scientific Reports, 2025), we asked whether this was a general property of other brain areas experiencing saccadic suppression, or whether the SC might play a uniquely central role in dictating perisaccadic perceptual detection abilities. Our approach was to conduct experiments in different brain areas within the same animals and with the same visual stimuli and eye movement behaviors. We recorded from 204 SC neurons (three monkeys) and 140 V1 neurons (two monkeys). In each trial, a small disc (0.51° radius; either dark or bright) appeared within the neurons' receptive fields, and we measured visual response strength as a function of stimulus onset time relative to microsaccades. In the SC, we replicated our earlier findings of (similarly) strong suppression for both dark and bright visual stimuli. Surprisingly, V1 responses exhibited a drastically different pattern: dark stimuli were clearly immune to saccadic suppression, whereas bright stimuli were not. These results suggest that V1 does not mediate perisaccadic perceptual detectability, since the latter is similarly suppressed for darks and brights. However, this does not necessarily mean a complete lack of V1 contribution to perisaccadic vision. To explore this further, we conducted psychophysical experiments in five human subjects using supra-threshold oriented bars (either dark or bright; 20% contrast). The task required orientation discrimination for brief perisaccadic stimuli, rather than perceptual detection. Although the brief, supra-threshold bars were perisaccadically detected in all trials, orientation discrimination thresholds were slightly elevated for bright relative to dark stimuli, reflecting the V1 asymmetry. Our results document a highly selective suppression of ON processing pathways in the primary visual cortex.

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Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

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Program #/Poster #: PSTR451.04/R16

Topic: E.07. Visual Sensory-Motor Processing

Support: AMX-20-CE-06
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Title: Combined vestibular and visuo-motor mismatch modulates neuronal activity and serotonin levels in mouse visual cortex

Authors: *E. AMBRAD GIOVANNETTI[1], I. KHARITONOV[1], H. TEIGEN[1,2], J. LE LIVEC[1], E. RANCZ[1];
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Abstract: The predictive processing framework posits that perception arises from comparisons between sensory input and internally generated predictions, with prediction error (PE) signals guiding internal model updates. PE signals have been identified in layer 2/3 (L2/3) pyramidal neurons of the mouse primary visual cortex (V1). Here, we hypothesise that layer 5 extratelencephalically projecting (L5ET) neurons also contribute to PE computations, particularly in active inference. Within the visual hierarchy, medial secondary visual cortex (V2M) responds strongly to vestibular input and is implicated in optic flow processing during navigation. We previously showed that V2M L5ET neurons receive both visual and vestibular inputs and project to subcortical structures such as the superior colliculus (SCm), positioning them ideally to influence eye movements. In addition, we show that V2M receives dense serotonergic innervation, which may affect local computations and modulate the balance between predictive and sensory inputs. We hypothesise that L5ET neurons carry out PE computations for active inference by comparing self-motion predicted and sensory vestibular and optic flow signals, and may direct corrective eye movements. Here, we examined how such mismatches are encoded in V2M and how they relate to serotonergic signalling.
To investigate this, we used a custom-built rotation platform that restores vestibular input in yaw to head-fixed mice, allowing animal driven navigation in rotational space and systematic manipulation of visual and vestibular sensory environment. We recorded neuronal activity using fibre photometry from L2/3 neurons or L5ET neurons expressing red-shifted Ca^{2+} indicators, and monitored serotonergic tone using the GRAB-5HT3.0 sensor. We also simultaneously tracked running and turning of the animal, as well as pupil dynamics and eye movements, and found differential correlations between behaviour, neuronal activity and serotonin levels.
Due to the reinstatement of vestibular inputs, mice displayed rich gaze-shifting and gaze-stabilising eye movements during self-initiated turns. Both L2/3 and L5ET neurons responded to increased optic flow during turns, introduced as perturbation, with L5ET activity often persisting after the perturbation. Serotonergic tone, in contrast, showed an anti-correlated profile, decreasing upon sensory-motor mismatch.
In summary, we have developed a novel approach to study visuo-vestibulo-motor interactions in head-fixed mice. Preliminary data suggest that both the superficial and deep layers of V2M respond to mismatch events, and that serotonergic tone is modulated during these episodes.

Disclosures: E. Ambrad Giovannetti: None. **I. Kharitonov:** None. **H. Teigen:** None. **J. Le Livec:** None. **E. Rancz:** None.

Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

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Program #/Poster #: PSTR451.05/S1

Topic: E.07. Visual Sensory-Motor Processing

Support: Henry Dale Fellowship 224156/Z/21/Z
Blakemore-Magdalen College Scholarship

Title: Striatal sensory potentiation precedes frontal cortical activation and sensorimotor learning

Authors: *A.-M. MARICA, A. J. PETERS;
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Abstract: The cortex and basal ganglia cooperate to drive the acquisition and execution of sensorimotor associations. A key step in learning new sensorimotor associations is thought to be re-routing of sensory information across these structures. In support of this, we have previously shown that learning drives increased stimulus responses in both the striatum (Peters et al., Nature 2021) and medial prefrontal cortex (Peters et al., Cell Reports 2022). However, it is not clear where learning is initiated. We addressed this question by examining stimulus-driven activity in the cortex and striatum of mice across sensorimotor learning. We used widefield calcium imaging to record from the whole dorsal surface of the cortex, and simultaneously recorded from a Neuropixels probe inserted diagonally into the striatum acutely on each recording. We trained mice in a simple task that required moving a visual stimulus from a peripheral starting position to a central target position by turning a wheel with their forelimbs. Mice typically learned this task within four days. In order to record stimulus-driven activity without movement, after training on each day, mice passively viewed stimuli in the starting, target, and non-task positions. We defined distinct regions in the striatum based on correlated cortical regions, including visual-recipient, medial prefrontal-recipient, and orofacial-recipient domains. Cortical areas associated with each domain were consistent across learning, suggesting fixed regional correlations between the cortex and striatum. We found that visual responses increased in the visual-recipient striatum, medial prefrontal-recipient striatum, and medial prefrontal cortex after learning. Notably, the visual-recipient striatum was the first structure to show increased visual responses, which preceded learning. The medial prefrontal cortex and medial prefrontal-recipient striatum then increased visual responses from the first day of learned behavior. These results indicate striatal changes initiate and precede learning, which lead to subsequent changes in the medial prefrontal cortex to execute learned behavior.

Disclosures: A. Marica: None. **A.J. Peters:** None.

Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

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Program #/Poster #: PSTR451.06/S2

Topic: E.07. Visual Sensory-Motor Processing

Support: Henry Dale Fellowship 224156/Z/21/Z (AJP)

Title: Cortical and striatal activity dissociate across modality and learning order in cross-modal learning

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Abstract: Sensorimotor associations are supported by both cortical and striatal activity. It has been established that the prefrontal cortex (PFC) and striatum exhibit sensory-evoked responses at well-trained stages of learning. However, it remains unclear whether these learning-evoked sensory responses are modality-specific, or if they are instead related to more generalized sensorimotor learning. We used widefield calcium imaging to record cortical activity while mice were trained on visual and auditory sensorimotor tasks presented in counterbalanced order. We found that the anterior PFC (aPFC) was activated bilaterally by both visual and auditory stimuli during the well-trained stages of both tasks, whereas the medial PFC (mPFC) was activated only by contralateral visual stimuli after learning. Mice learned both modalities successfully, but visually trained mice learned the auditory task immediately, while auditory trained mice required days of visual training before learning. Despite the differences in learning time, cortical activity patterns were dependent only on learning and not modality order. In contrast, electrophysiological recordings in the anterior striatum revealed that visually responsive neurons became co-responsive to auditory stimuli more frequently in mice trained on the visual task first compared to those trained in the auditory task first. These co-responsive neurons were primarily located in a central region of the anterior striatum. These findings reveal a modality- and order-dependent divergence in cortical and striatal encoding during sensorimotor learning. While cortical representations tend to generalize across learning sequences, striatal activity remains sensitive to the order of sensory experience.

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Poster

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Program #/Poster #: PSTR451.07/S3

Topic: E.07. Visual Sensory-Motor Processing

Title: Top-down feedback from retrosplenial cortex shapes prediction-error dynamics in the visual cortex

Authors: *S. ELNOZAHY, S. FURUTACHI, S. B. HOFER;
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Abstract: The ability of animals to rapidly generate predictions about their surroundings using prior knowledge and experience is a fundamental aspect of learning and cognition. According to the predictive processing framework, cortical circuits compare top-down-driven internal models of prior expectations with incoming sensory input to generate sensory prediction errors that can in turn update incorrect predictions. While different types of prediction-error signals have been found in many cortical areas, how prediction errors are computed, and the neural circuit mechanisms by which top-down signals contribute to their generation remains unknown. To investigate this, we use two-photon calcium imaging to monitor retrosplenial cortex (RSC) axons projecting to layer 1 of primary visual cortex (V1), as well as local V1 population activity, while mice traverse a virtual corridor containing expected and unexpected visual stimuli. We confirmed that unexpected visual stimuli robustly activated a subset of V1 neurons via VIP-interneuron-mediated disinhibition (Furutachi et al. 2024). Optogenetic silencing of RSC axons modulated prediction-error-related signals in V1, suggesting that top-down feedback is involved in the generation of prediction-error signals. However, V1 prediction errors do not appear to be simply inherited from RSC, because the population activity of RSC axons to V1 did not itself encode prediction-errors. Instead, these projections carried largely visually-evoked, mixed-selective signals modulated by spatial context, indicating that they provide high-dimensional contextual information to V1. Population analyses reveal that responses to expected stimuli in RSC axons in V1 remain stable over time, whereas responses to unexpected stimuli evolve gradually and dynamically as animals learn to expect them. Initially, RSC representations of unexpected inputs are biased toward prior expectations, but with repeated exposures they diverge to form distinct and increasingly stable representations as the stimulus becomes familiar. Together, our data suggest that top-down input from RSC does not convey prediction-errors but instead provides context-driven sensory representations that are shaped by the animals' expectations.

Disclosures: S. Elnozahy: None. **S. Furutachi:** None. **S.B. Hofer:** None.

Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.08/S4

Topic: E.07. Visual Sensory-Motor Processing

Title: Brain region differences in adaptation to repeated visual and auditory stimuli in zebrafish larvae

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Abstract: Non-associative learning (habituation and sensitization) depends on plasticity in sensory and motor brain areas. We used fluorescent calcium imaging across brain regions in zebrafish larvae to map activity correlated with adaptation to visual and auditory stimuli. The visual stimulus was sudden dimming of ambient light (dark-flash), which elicits behavioral escape responses and activation of retinorecipient brain areas. The auditory stimulus was a buzzer producing a 400Hz, 75dB tone. Previous research has shown behavioral and neural adaptations to dark flash in zebrafish, revealing circuit-level mechanisms of visuomotor learning. We aimed to extend this work by analyzing multiple brain areas and sensory modalities during non-associative learning. Larvae were immobilized on the stage of a confocal microscope adjacent to a stimulus light and buzzer. A horizontal optical section of the brain spanning the habenula to the medulla, bilaterally, was imaged at 1Hz for 3min, and triggers activating a 4sec sensory stimulus occurred every 10 sec for 16 total trials. Each larva (N=6) experienced both stimuli with order counterbalanced across subjects. Regions within habenula, tectum, cerebellum, and hindbrain, on each side, were analyzed in a repeated measures ANOVA with stimulus modality (visual or auditory), stimulus phase (on or off), brain area, and trial number, as within subjects factors. Results showed a main effect of stimulus phase, indicating increased brain activity overall during visual and auditory stimulation relative to pre-stimulus baseline. There was a significant interaction effect between stimulus phase and brain area, showing that evoked responses differed across brain regions, and an interaction among stimulus phase, brain area, and trial number, showing that adaptation (change in neural responses across trials) depended on brain region and sensory modality. Notably, left habenula showed habituation, and right habenula showed sensitization, across visual and auditory trials, while tectum showed habituation only on visual trials. Hindbrain showed sensitization across both visual and auditory trials. Planned studies will seek to replicate these results and examine response diversity across individual neurons within these brain regions.

Disclosures: E.B. Gahtan: None. **Y.M. Wang:** None. **J. Mellett:** None. **T. Colegrove:** None.

Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

Location: SDCC Halls B-H

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Program #/Poster #: PSTR451.09/S5

Topic: E.07. Visual Sensory-Motor Processing

Support: NIH Grant EY037507-01
NIH BRAIN Initiative RF1NS12885-01

Title: Dissecting neural circuits underlying visuomotor transformations in larval zebrafish

Authors: *K. E. FOUKE[1], J. MORRA[2], Z. HE[1], O. TRAUBERT[1], J. A. ATKINSON[2], E. A. NAUMANN[2];
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Abstract: Brain-scale neural circuits transform visual inputs into discrete movements with appropriate speed, vigor, and duration. Yet, single-cell resolution and mechanistic characterization of such circuits in vertebrates have been elusive, largely due to the vast number of neurons and complexity of the mammalian brain. The translucent larval zebrafish offers unique opportunities to study brain-wide cellular-level neural computations during vertebrate visuomotor transformations. One such transformation is the optomotor response (OMR), where fish execute discrete locomotion bouts to stabilize their body position in response to optic flow. Previous studies have functionally characterized OMR neural circuits across the brain, including the retinorecipient pretectum (*Pt*) and motor command neurons in the midbrain nucleus of the longitudinal fasciculus (*nMLF*) and ventral spinal projection neurons (*vSPNs*). Direction and eye-specific visual motion elicit specific neural activation in *Pt*, *nMLF*, and *vSPN* populations, ultimately generating unique swimming and turning behaviors. However, it remains unknown how these visually responsive *Pt* neurons causally link to *nMLF* neurons and *vSPNs* to produce forward and turning movement. To investigate how *Pt* neurons influence motor command neurons, we combined volumetric two-photon calcium imaging with 3D holographic optogenetic photostimulation, visual stimulation, and high-speed behavioral tail tracking in larval zebrafish, expressing cytosolic GCaMP7f and the red-shifted opsin rsChRmine. Using these all-optical methods, we mapped the functional connectivity between *Pt*, *nMLF*, and *vSPN* populations, revealing how visually characterized *Pt* neurons recruit downstream motor command neurons. Specifically, we measured the causal connections of monocular, forward motion responsive *Pt* neurons to medial *nMLF* neurons and *vSPN*s, recording their excitatory or inhibitory influence and network dynamics throughout the entire circuit. We demonstrate that photostimulation of critical *Pt* ensembles induce directed tail movements, confirming their role in behavior. Our results yielded *Pt-nMLF-vSPN* functional connectomes generating population-level models of how visual motion is decoded onto motor commands. Together, we demonstrate how all-optical methods at cellular resolution can empirically map functional connectivity, offering insights into how single neurons transform sensory information into motor commands and general principles of vertebrate visuomotor control.

Disclosures: K.E. Fouke: None. **J. Morra:** None. **Z. He:** None. **O. Traubert:** None. **J.A. Atkinson:** None. **E.A. Naumann:** None.

Poster

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Program #/Poster #: PSTR451.10/S6

Topic: E.07. Visual Sensory-Motor Processing

Support: NIH U19NS123716

Title: Realignment of communication subspaces between regions to support stimulus-driven context-dependent behavior

Authors: *N. L. MACKENZIE[1], J. PEMBERTON[2], K. E. MILLER[3], M. TUCKER[3], I. BRAIN LAB[4], M. D. GOLUB[2], N. A. STEINMETZ[3];
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Abstract: How does the brain generate different behaviors from identical visual inputs depending on context? To explore this, we analyzed communication subspaces across the brain — low-dimensional subspaces within one region's neural population activity that selectively drive activity in another region. We hypothesize that communication subspace properties, such as dimensionality and magnitude, vary systematically across region pairs, and that their selective reconfiguration supports flexible behavior. To test this, we simultaneously recorded neural activity from pairs of brain regions in mice during a context-dependent visual decision-making task. We targeted 48 anatomically connected source-target pairs from 16 task-activated brain regions spanning sensory and frontal cortex, thalamus, basal ganglia, midbrain, hindbrain, and cerebellum. We quantified communication subspace dimensionality (complexity), magnitude (strength), and orientation (alignment with behaviorally relevant stimulus dimensions). Preliminary results supported our hypotheses. First, comparing primary visual cortex (VISp) to five of its targets — secondary visual cortex (VISam), secondary motor cortex (MOs), lateral posterior nucleus (LP) in thalamus, caudoputamen (CP) in basal ganglia, and superior colliculus (SC) in midbrain — we find target-dependent differences: VISp-CP communication exhibits greater magnitude and dimensionality than to other target regions. Second, analyzing left-hemisphere VISp-LP communication, we observe significant context-dependent changes in subspace orientation: during right-biased blocks, subspaces align more strongly with right-stimulus activity, predicting rightward choices. Significantly, this ongoing project is generating an unprecedented dataset. Our current recordings cover 40 of 48 targeted brain region pairs, with over half having at least five recording sessions each, totaling 371 probe insertions across 28 subjects. Regardless of the specific subspace properties ultimately identified, this large-scale study offers unique insights. It extends prior communication subspace work, often limited to fewer, predominantly cortical interactions, to many distributed brain region pairs. Importantly, this is the first study to investigate communication subspaces during a flexible, context-dependent behavioral task. This extensive open dataset will be a valuable community resource, advancing understanding of brain-wide communication during context-dependent behavior.

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Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.11/S7

Topic: E.07. Visual Sensory-Motor Processing

Title: Characterization of motion preferences of macaque MSTd neurons using transformer models and closed-loop electrophysiology

Authors: *A. EDATHODATHIL[1], V. IVANOV[1], F. H. SINZ[3], S. TREUE[2];
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Abstract: The dorsal Medial Superior Temporal area (MSTd) in primate visual cortex plays a crucial role in the processing and perception of complex motion. Neurons in MSTd are tuned to the direction of linear motion as well as spiral motion patterns within their large receptive fields. Efforts to map the local direction selectivity of MSTd receptive fields, aiming to account for these motion preferences, have been of mixed success.To address this, we developed a novel stimulus, tessellating hexagonal patches of random dot patterns, moving coherently in a linear direction. By independently setting the direction and speed of each pattern, this stimulus allows the generation of arbitrarily complex motion patterns. However, using such stimuli to map the spatial distribution of motion preferences within MSTd receptive fields encounters the “curse of dimensionality”, given the large number of possible combinations of local motion.Applying deep learning approaches, recent studies have attempted to determine the Most Exciting Images (MEIs) for neurons in mouse and monkey primary visual cortex (V1) and in monkey extrastriate cortical area V4. We adapted this approach to non-parametrically search for MEIs for individual MSTd neurons. To achieve this, we utilized a Transformer neural network to model the receptive field profiles of MSTd neurons and predict their corresponding complex motion MEIs.During an experimental session, we collected responses from a single MSTd neuron to a quick succession of briefly presented random and structured motion patterns. We then used this data to train the neural network, and have it predict MEIs. Completing our closed-loop electrophysiology approach, we presented the presumed MEIs (pMEIs) and recorded the neuron’s responses. This allowed us to directly compare the responses to pMEIs and to traditional linear and spiral motion stimuli.Most of those pMEIs that evoked the largest responses combined linear and spiral motion preferences. In addition, we observed MEIs with a combined representation of pure linear or spiral motion preferences. Correspondingly, in 64% of the neurons, responses to the predicted MEIs were not statistically different from the best traditional linear or spiral motion patterns, suggesting an invariant global motion encoding that was not sensitive to minor tweaks in the flow field.In 7% of the cells, however, the MEIs evoked significantly stronger responses than the preferred linear or spiral stimulus. A vector decomposition of MEIs revealed clusters involved in linear, spiral, a mixture of both, and more abstract representations.Our data indicate an invariant, flexible encoding of motion patterns in MSTd neurons.

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Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

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Program #/Poster #: PSTR451.12/S8

Topic: E.07. Visual Sensory-Motor Processing

Support: Howard Hughes Medical Institute

Title: A critical initialization for biological neural networks

Authors: *M. PACHITARIU, L. ZHONG, A. L. GRACIAS, C. LOPEZ, C. STRINGER; HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Artificial neural networks learn faster if they are initialized well. Good initializations can generate high-dimensional macroscopic dynamics with long timescales. It is not known if biological neural networks have similar properties. Here we show that the eigenvalue spectrum and dynamical properties of large-scale neural recordings in mice (two-photon and electrophysiology) are similar to those produced by linear dynamics governed by a random symmetric matrix that is critically normalized. An exception was hippocampal area CA1: population activity in this area resembled an efficient, uncorrelated neural code, which may be optimized for information storage capacity. Global emergent activity modes persisted in simulations with sparse, clustered or spatial connectivity. We hypothesize that the spontaneous neural activity reflects a critical initialization of whole-brain neural circuits that is optimized for learning time-dependent tasks.

Disclosures: M. Pachitariu: None. **L. Zhong:** None. **A.L. Gracias:** None. **C. Lopez:** None. **C. Stringer:** None.

Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

Location: SDCC Halls B-H

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Topic: E.07. Visual Sensory-Motor Processing

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Title: Simulations of cortical circuits across the cortical hierarchy

Authors: *L. GREEN[1], K. DAIE[3], M. ROZSA[2], S. ITO[1], D. HAUFLER[1], A. ARKHIPOV[1]; [2]Allen Inst. for Neural Dynamics, [1]Allen Inst., Seattle, WA; [3]Allen Inst. for Neural Dynamics, Seattle, WA

Abstract: The mammalian neocortex is a complex structure with many interacting regions and cell types. It is increasingly popular to generate large datasets that record data from multiple cortical regions to determine generalizing principles of cortical organization and activity. One such generalizing principle for mammalian cortex is the concept of a cortical hierarchy - low-

dimensional macroscopic gradients of biological properties across cortical areas and a hierarchy of timescales for information processing. Such gradients in properties along a cortical hierarchy may explain how different cortical regions serve different computational roles (i.e. sensory processing versus motor control). We set out to investigate such principles using biologically realistic simulations. Starting from our previously published model of the mouse primary visual cortex (V1), we generate multiple versions of the cortical circuit model with increased connectivity as measured along the cortical hierarchy. We then measure the resulting neural activity in response to a simulated single-cell photostimulation paradigm and thalamocortical inputs. We find that the models that are higher along the cortical hierarchy better replicate activity patterns (noise correlations and cell-type specific responses to photostimulation) experimentally recorded in M1 relative to the original V1 model. We also find that increasing circuit connectivity is sufficient to generate longer timescales and differential activity in inhibitory cell types in models along the cortical hierarchy. Our results shed light on the mechanisms that determine distinct activity patterns of cortical regions and, thus, likely facilitate their distinct computational roles. Our findings also link population activity to cell type and circuit properties, generating insight into potential perturbation mechanisms to produce desired neural activity.

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Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

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Topic: E.07. Visual Sensory-Motor Processing

Support: Fiona and Sanjay Jha Chair in Neuroscience (J.H.R)

Title: Saccade vector micromaps in the marmoset monkey frontal cortex

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Abstract: The cortical column has been proposed as a basic unit of processing in the cortex. For example, in macaque V1, orientation columns tile the cortex to create an orientation selectivity map. It is not known if columnar coding exists in frontal oculomotor cortical areas (termed FEF+) because the frontal eye fields (FEF) and the immediately adjacent premotor eye fields (PMEF) in the macaque monkey are located in the anterior and posterior banks of the arcuate sulcus, making it challenging to record neurons from within a putative column. To overcome this limitation of the macaque, we utilized the marmoset, which has a smooth cortex lacking prominent sulci. To test for a columnar organization in FEF+, we used Neuropixels probes to map visual receptive fields and saccade motor fields in the frontal cortex of marmosets (n=2).

Visual receptive fields were mapped using briefly flashed 2dva stimuli covering a 22dva by 22dva area of the visual field. Monkeys were allowed to saccade freely during the mapping procedure. Stimuli were only used if the eye position was stable around the time of stimulus presentation, and the location of stimuli relative to eye position was used for analysis. We then utilized their natural saccadic behavior to map saccade motor fields. We recorded from a total of 39 sites within frontal areas 8aV, 6Va, 8C, 6DC, 6DR, and 8aD, resulting in 4,221 well-isolated units. We used Spatial Information Analysis to identify neurons with visual and/or saccade fields, finding a high incidence only within the FEF+ region. Field locations were quantified in polar coordinates (angle and eccentricity). Due to the chamber's position relative to the cortex, penetrations were made at a slight angle (~15 deg.), leading to a horizontal offset of ~500 microns going from superficial to deep. Within a single penetration, the preferred angles of both visual and motor fields typically changed smoothly as a function of depth, often covering over 180 degrees and extending into the ipsilateral hemifield. The eccentricity also changed smoothly, and in some cases, the eccentricity decreased and then increased as the preferred angle rotated, suggesting that the probe is moving across a small radially oriented map. These findings indicate that patches of cortex that span only a few 100 microns (micromaps) code for large continuous regions of visual space, shifting our understanding from coarse, inferred topography to a fine-scale, columnar organization in FEF+. Whether there are multiple maps, potentially one for each region of FEF+, and how they function to select saccade targets will be the focus of future work.

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Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

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Topic: E.07. Visual Sensory-Motor Processing

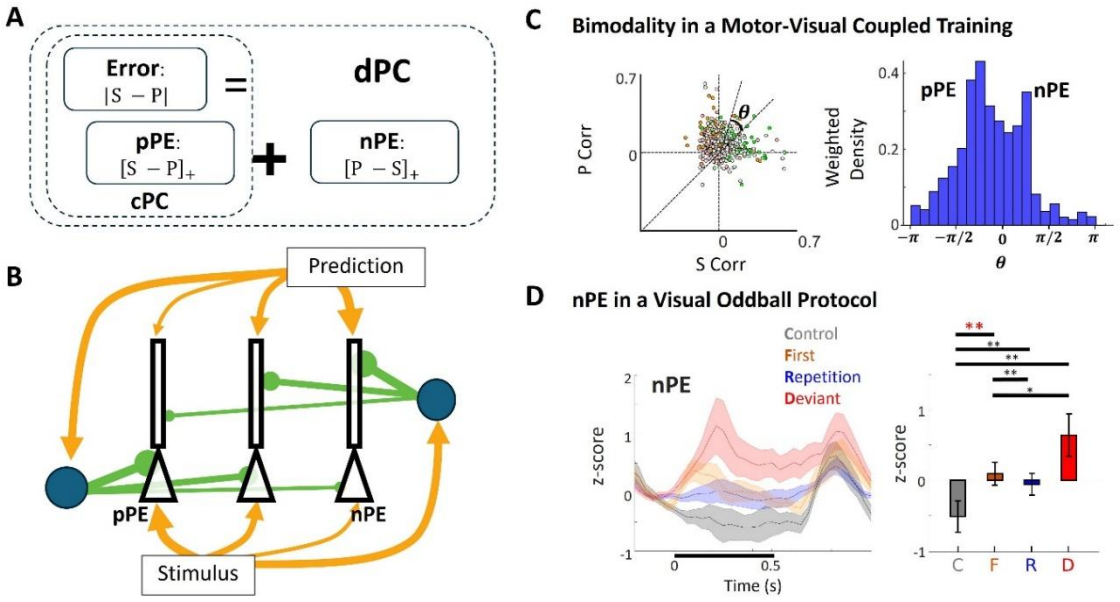
Support: ONR grant N00014-23-1-2040
NIH grant R01MH062349
NIH grant R01EY033950

Title: Duet Predictive Coding Unifies Mismatch Response and Deviant Detection: Theoretical Predictions and Data Validation

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Abstract: The brain, far from being a passive receiver of sensory input, actively generates predictions about the external world. These predictions prioritize surprise signals over familiar ones, such as a mistuned piano note or a bus arriving late. Generating a surprise signal requires

comparing internal predictions with incoming sensory input (Fig. 1A). Classical predictive coding (cPC) suggests that the brain learns to cancel expected sensory consequences. Yet, it models top-down effects as purely inhibitory and permits negative firing rates, raising concerns about biological plausibility. Here, we propose Duet Predictive Coding (dPC), a biologically plausible framework in which neurons encode both positive and negative prediction errors. Building on the idea that a global neuromodulatory signal, such as noradrenaline, guides local learning, we show how optimal connectivity emerges to compute prediction errors (Fig. 1B). This circuit model reproduces mismatch responses in motor-visual coupling, selective suppression in motor-modulated auditory tasks, auditory omission responses, mismatch negativity, and deviance detection in visual oddball protocols, offering a unified framework for studying predictive coding. Furthermore, our theory pinpoints predictions that are validated by experimental data. In coupled training, the model predicts that neurons split into populations correlating more with either the stimulus or the prediction signal (Fig. 1C). In the oddball protocol, neurons encoding negative prediction errors should respond more strongly to the first stimulus repetition than to a random control (Fig. 1D). Experimental data support both predictions. Together, our dPC framework unifies mismatch and deviance detection, addresses prior theoretical limitations, yields testable predictions, and highlights the broad applicability of predictive coding across brain systems.



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Poster

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Topic: E.07. Visual Sensory-Motor Processing

Support: NIH EY029438
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Title: Sensorimotor associations at the parieto-occipital junction are experience dependent

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Abstract: Learning sports or other activities requires the formation of new sensorimotor associations. For instance, catching a frisbee requires practice to map the disc's movements to interceptive actions. Experience drives the transition from novice to expert, strengthening sensorimotor associations for more efficient execution. The basal ganglia, through connections to sensory- and motor-related cortical structures, is important for forming sensorimotor associations and motor learning. Parietal cortex also plays an important role in implementing sensorimotor transformations through the multiplexing of sensory and motor signals. However, how those representations change with learning to enable the transformation from novice to expert remains unclear. Here we use a visuomotor paradigm to contrast the effects of training on sensory and motor representations in cortex.

Neurons in macaque area V3A and its downstream target, the caudal intraparietal area located at the parieto-occipital junction, multiplex visual and saccade-related activity. We previously trained monkeys to associate the three-dimensional orientation of planar surfaces with a saccade to a target at the near side of the plane. In those monkeys, neurons in both areas showed a strong alignment between their preferred surface orientation and saccade direction. This association may have arisen through the task training or existed naturally, reflecting the behavioral relevance of closer stimuli. To evaluate these alternatives, here we assessed if a sensorimotor association is found in monkeys prior to sensorimotor training. In two untrained monkeys, neurons again showed multiplexed surface orientation and saccade direction selectivity. Critically, however, there was no systematic association between the two preferences. This supports that the sensorimotor associations previously observed were a result of task training.

This observation raises the question "who maps onto whom?", sensory onto motor, vice versa, or both. Further comparisons revealed that the saccade preferences tended to align with the receptive field locations in both trained and untrained animals. This finding implies that during task training, sensory representations are remapped to align with the learned motor response. It further suggests that the topographical map of visual space across cortex serves as a scaffold for mapping high-dimensional visual inputs onto the lower-dimensional space of oculomotor responses. Together, these findings implicate the parieto-occipital junction as an important site of sensorimotor associative learning through a reorganization of sensory representations.

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Poster

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NIH EY029438
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NIH NS128586

Title: Manifolds for the neural representation of 3D spatial experience

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Abstract: Navigating and interacting with objects are fundamental three-dimensional (3D) sensorimotor processes, both relying on the precise determination of orientation and position (i.e., pose) information. A rigorous understanding of how the brains of animals—from fruit flies to humans—encode spatial pose remains elusive. Neural activity can be represented on a *manifold*, the space of possible values that a set of variables (e.g., firing rates) can take. One approach to defining such a representation is to infer low-dimensional manifolds from neural and behavioral measurements. A complementary approach taken here uses the manifold structure of 3D movement as a prior to guide experimentation. Using object and head direction as examples, we show how a first-principles characterization of the geometry of manifolds facilitates the development of rigorous analytical and computational tools.

The manifold of 3D spatial orientation comprises three degrees of freedom (DOF). We examine how an object's shape, texture, and symmetries can reduce the manifold's dimensionality and constrain its geometry. For planes with rotationally invariant textures, a Bingham function over slant and tilt parameterizes neuronal orientation tuning functions. This is demonstrated through an analysis of 3D orientation tuning curves measured in the caudal intraparietal area of macaque monkeys. Using the same data, we further show how the alternative approach of manifold inference from neuronal firing rates converges to a structure similar to that from our first-principles analysis.

Like 3D object pose, head direction has three rotational DOF. For example, single neurons in the dorsal presubiculum of Egyptian fruit bats encode combinations of azimuth and pitch, and their 3D head orientation is represented on a toroidal manifold of azimuth and pitch (Finkelstein et al., 2015). Here we provide a mathematical proof to validate this representation, then parameterize neuronal firing rate in a form where the rotation matrix representing "roll-free" head direction appears explicitly, inspired by Koditschek (1988). Finally, we verify that the model accurately describes the tuning curves of bat head direction cells.

We present a theoretical framework for modeling the configuration spaces of 3D object pose and head direction. By selectively constraining degrees of freedom and leveraging geometric structure, our approach enables compact, interpretable representations and supports the development of powerful tools for tuning function parameterization. This framework offers a principled roadmap for future research on manifold representations in neural systems.

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Poster

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Topic: E.07. Visual Sensory-Motor Processing

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Title: Multiple visual features in naturalistic visual environments shape steering responses in flying Drosophila

Authors: *K. KIM[1], A. J. KIM[2];
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Abstract: Neuroscientists studying vision have traditionally focused on how neural circuits respond to individual visual patterns. In Drosophila melanogaster, circuits tuned to specific patterns—such as moving bars, spots, and gratings—have been identified. However, in naturalistic environments—especially during flight—flies are exposed to rich visual scenes that include optic flow, a whole-field motion cue driven by self-motion, object motion with distinct dynamics, or both occurring simultaneously. To understand visual processing in response to naturalistic scenes, we measured both behavioral and physiological responses of Drosophila to naturalistic videos and developed computational models that are designed to capture the underlying neural computations. First, we constructed a cylindrical flight arena surrounded by a flexible display and recorded wing responses of tethered flies to panoramic, naturalistic videos. We carefully chose three different videos: one dominated by optic flow ("OF-only"), one featuring moving objects without optic flow ("object-only"), and one combining both ("OF+object"). In response to these videos, we assessed the reproducibility of steering behavior across trials and flies and found that wing responses were more consistent for videos containing optic flow. This raised a key question: does optic flow play a dominant role in shaping steering behavior in Drosophila? To address this, we built a phenomenological model to predict wing signals based on the optic flow in the videos. The model successfully predicted wing responses, with normalized cross-covariance (n-xcov) values of 0.40 for OF-only, 0.32 for object-only, and 0.49 for OF+object, indicating significant, but varying contributions of optic flow. To identify

the physiological basis of this processing, we performed whole-cell patch-clamp recordings from Horizontal System cells, a well-known class of optic flow detectors. The neural responses aligned with our model's predictions, showing that lateral asymmetries in optic flow strongly correlated with steering signals. To account for visual features beyond optic flow, we extracted the positions of moving objects in the videos—such as pedestrians, vehicles, and birds. Incorporating both object motion and optic flow as inputs improved model performance in predicting wing steering responses (n-xcov: 0.60 for OF+object). Additional experiments and analyses are underway to further examine the role of different types of object motion. Together, our study represents an important step toward understanding how multiple visual features orchestrate steering behavior in natural environments.

Disclosures: K. Kim: None. **A.J. Kim:** None.

Poster

PSTR451: Sensorimotor Transformation: Neuroprocessing

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.19/T3

Topic: E.07. Visual Sensory-Motor Processing

Support: Canada First First Research Excellence Fund, Grant #CFREF-2022-00010

Title: Spatiotemporal dynamics of sensory memory and reference frame transformation during memory-guided reach - a recurrent neural network model

Authors: *K. PABST[1], G. BLOHM[3], J. CRAWFORD[2];
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Abstract: Delayed reach tasks require both the retention of spatial target information in working memory and the transformation of eye-centred sensory signals into shoulder-centred motor outputs. Prior work has examined these components separately: computational models have explored memory mechanisms in saccade tasks (Xing et al., 2000 *J. Neurophys.*; Mitchell & Zipser, 2001 *Vis. Res.*; Keith et al., 2010 *J. Neurophys.*) or reference frame transformations (Blohm et al., 2009 *Cereb. Cortex*). Likewise, behavioural and neurophysiological studies have investigated sensory-motor dynamics during memory delays (Sajad et al., 2016 *eNeuro*; Sadeh et al., 2018 *Front. Neural Circuits*) or gain-field mechanisms supporting coordinate transformations (Chang et al., 2009 *Neuron*; Brayanov et al., 2012 *J. Neurosci.*). However, to our knowledge, no prior network modelling study has jointly investigated how spatial sensory information is retained and transformed through time and transformed into motor codes. Here, we address this gap using a recurrent neural network trained on a delayed reach task to probe the spatiotemporal dynamics of candidate cortical computations. We trained a 4-layer recurrent neural network to generate a reach vector based on retinal target position and proprioceptive gaze and hand positions. Simulations followed an experimental design employed in our lab: in each

trial, gaze and hand were placed at one of nine grid locations, a visual target appeared briefly, followed by a memory delay and a Go-signal. We analysed unit properties across intermediate network layers, focusing on spatial tuning over the course of a trial. Preliminary results show that the model's intermediate layers exhibit emergent properties resembling known neurophysiological motifs such as response fields and gain field-like modulations. Units in the earlier intermediate layer fell into three functional classes: (1) inactive units, (2) visual-memory units, spatially tuned during target presentation and/or delay but silent after the Go-signal, and (3) movement-related units, silent until the Go signal, then showing spatial tuning. Units in the later layer fell into two classes: (1) spatially untuned units with variable baseline activity, and (2) movement-related units, spatially tuned after the Go-signal. Both layers showed anti-correlated gaze and hand position modulations, similar to those reported by Chang et al. (2009). These findings suggest that our earlier intermediate units retain visual informationduring the delay period, whereas the Go signal causes this information to be transformedinto a motor format in the later intermediate units.

Disclosures: K. Pabst: None. **G. Blohm:** None. **J. Crawford:** None.

Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.01/T4

Topic: F.03. Basal Ganglia

Title: The application of magnetite nanodiscs for neuromodulation

Authors: *A. A. T. WOLTERS[1,3], L. SIGNORELLI[4], C. HERFF[1,3], G. KENIS[2,3], H. R. CLUSMANN[5], Y. TEMELY[1,3], D. GREGUREC[4], S. HESCHAM[1,3,6];
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Abstract: Deep Brain Stimulation (DBS) is a widely used neurosurgical technique that involves the stereotactic implantation of electrodes to deliver targeted electrical stimulation to subcortical brain structures. It is primarily used to alleviate symptoms associated with neurological disorders such as Parkinson's disease (PD). Despite its clinical benefits, conventional DBS faces several limitations, including the need for permanently implanted hardware, wired connections and periodic battery replacements. Innovative approaches have been explored to address these challenges, particularly those utilising nanotechnology to develop minimally invasive and wireless neuromodulation techniques. One such promising approach is magnetomechanical DBS (mDBS), which uses magnetite nanodiscs (MNDs) and a weak (5-10 Hz) alternating magnetic field (AMF) to induce neuronal excitation through torque. In this study, we demonstrate that the

torque generated by MNDs under an AMF can trigger Ca^{2+} influx *in vitro* across various cell types, including HEK293 cells, rat primary cortical neurons, and human embryonic stem-cell-derived cortical neurons. This effect was also observed *ex vivo* in human organotypic brain slice cultures through the activation of endogenous mechanosensitive ion channels. The stimulation evoked repeated calcium transients, suggesting the potential for generating in vivo action potentials. Piezo1, a mechanosensitive ion channel widely expressed in the brain, was selectively stimulated by MNDs, as confirmed by specific agonists and antagonists. Furthermore, we demonstrate that mDBS can provide similar therapeutic benefits to conventional DBS in a unilateral 6-hydroxydopamine (6-OHDA) mouse model of PD. We achieved magnetomechanical neuromodulation in freely moving mice by activating the endogenous expression of mechanosensitive ion channels by MNDs. Stimulation of the subthalamic nucleus (STN) using mDBS enabled remote modulation of motor behaviour in healthy mice and reversed motor deficits in a severe hemi Parkinsonian model. In conclusion, this study presents a magnetomechanical, MND-based method for wireless neuronal stimulation that does not require genetic manipulation, offering a minimally invasive and clinically relevant alternative to traditional DBS.

Disclosures: A.A.T. Wolters: None. **L. Signorelli:** None. **C. Herff:** None. **G. Kenis:** None. **H.R. Clusmann:** None. **Y. Temely:** None. **D. Gregurec:** None. **S. Hescham:** None.

Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.02/T5

Topic: F.03. Basal Ganglia

Support: 32130044
2021ZD0202500
T2241002
2024YFF0507601

Title: Pallidal deep brain stimulation desynchronizes GABA release and alleviates Parkinsonian motor deficits

Authors: *S. YUAN[1], Z. XU[2], S. DENG[3], W. DUAN[2], X. ZHANG[2], Y. SHU[2];
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Abstract: Globus pallidus pars interna (GPi) is one of the effective targets of deep brain stimulation (DBS) for treating Parkinson's disease (PD). However, it remains unclear what the underlying synaptic and circuit mechanisms of pallidal DBS are, and why high- (HFS), but not low-frequency stimulation (LFS), is required for the beneficial effects. We performed electrophysiological recording in basal ganglia slices, behavior test, together with DBS or

optogenetic stimulation in 6-OHDA-induced dopamine-depleted (DD) Parkinsonian mice. In slices, we observed strong inhibitory postsynaptic responses and a failure of spiking in entopeduncular nucleus (EP, homogenous to GPi in primate) neurons during the initial period (approximately 2 s) of local electric HFS at 130 Hz. However, during the late phases of stimulation, the spiking activity of EP neurons would restore to the baseline level before the stimulation, while the inter-spike-interval became irregular. Next, we performed electrophysiological and optogenetic experiments and revealed that two parallel GABAergic pathways, striatum —>EP and globus pallidus pars externa (GPe) —>EP, mediate the HFS-induced effects on spiking activity of EP neurons by releasing GABA in both synchronous release (SR) and asynchronous release (AR) modes, with a contribution of AR up to ~70% to the total inhibitory charge. Because AR dominated the late phases of HFS, it should play a predominant role in mediating the long-lasting beneficial effects on motor behaviors. Further genetic downregulation of fast Ca^{2+} sensor synaptotagmin-1 revealed that a decrease in the expression level of this Ca^{2+} sensor could enhance the strength of AR and thus the pallidal stimulation efficiency in DD mice. In addition, in comparison to a constant-frequency stimulation, a stimulation protocol with intermittent high and low frequencies but with the same charge size of stimulation maximized the strength of GABA AR and showed significantly greater improvement of the locomotion in DD mice. Together, our results reveal an important role of asynchronous GABA release at the inhibitory input synapses of EP neurons in alleviating Parkinsonian motor deficits, and demonstrate that an optimized AR strength with intermittent high-low frequencies can produce similar beneficial effect to that of HFS. Therefore, we reveal a novel synaptic and circuit mechanism for pallidal DBS, as well as a biomarker (i.e. AR strength) for optimizing DBS protocols in treating PD motor dysfunctions.

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Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.03/T6

Topic: F.03. Basal Ganglia

Support: NSFC, YSF, 32400814
NSFC, Major Program, 92368204
China Postdoctoral Science Foundation, 2022M723243

Title: The neural mechanism of endogenous neural circuits of mice by driving the release of dopamine from transplanted hESC-derived dopamine neurons to treat Parkinson`s disease

Authors: *Z. CHEN;
Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of science, Shanghai, China

Abstract: Parkinson's disease (PD), one of the most common neurodegenerative disorder, holds immense therapeutic promise through the transplantation of dopamine neurons. However, **the neural mechanisms underlying how grafted cells function in vivo remain incompletely understood**. In this study, human embryonic stem cell (hESC)-derived midbrain dopamine (mDA) neurons were transplanted into the striatum of PD model mice. We focused on investigating the activity of the grafted cells within the host. This included assessing resting-state dopamine release, neural activity during various mouse behaviors, and the corresponding neural circuit mechanisms. Our results demonstrate that HPLC measurements revealed significantly elevated dopamine levels in grafted mice under physiological conditions compared to PD mice. Furthermore, we found that grafted cells were activated and released dopamine during both motor and reward-related behaviors, a response markedly distinct from that observed in PD mice. These findings provide compelling evidence that **the host neural circuitry integrates the grafted cells and autonomously drives dopamine release**. We also investigated the interactions between grafted cells and the host's endogenous circuitry. We discovered that grafted cells are inhibited by striatal neurons. This result offers further insight into **how the grafted nucleus is specifically integrated by the host and how it is driven at the circuit level**. This project aims to elucidate the circuit mechanisms by which transplanted mDA neurons improve motor function in PD model animals, thereby **providing a theoretical foundation for PD cell therapy**.

Disclosures: Z. Chen: None.

Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

Location: SDCC Halls B-H

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Program #/Poster #: PSTR452.04/T7

Topic: F.03. Basal Ganglia

Support: NINDS Grant NS126816
NINDS Grant DA055166

Title: Region specific dopamine dynamics in the sensorimotor and limbic striatum during adaptive forelimb reaching

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Abstract: From simple movements to complex decision-making, the ability to translate intentions into action and adjust behavior based on expected outcomes is fundamental for survival and adaptive function. Dopamine neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) play a central role in this process by encoding prediction errors—signals that indicate whether outcomes are better or worse than expected. These prediction errors act as a key reinforcement mechanism, guiding behavioral adaptation over time.

Importantly, the diverse projections of dopamine neurons across the central nervous system suggest that prediction errors may serve distinct functions depending on their target circuits. The striatum, a major subcortical target of midbrain dopamine neurons, plays a key role in this process. Although the striatum is broadly organized, it can be further divided based on functionality and connectivity to distinct subregions. The dorsolateral striatum (DLS) integrates sensorimotor cortical input and dopaminergic signals from the SNc to support movement and habit formation. In contrast, the nucleus accumbens (NAc) integrates limbic cortical input with dopamine signaling from the VTA to support motivation and goal-directed behavior. To understand how these distinct striatal circuits support adaptive behavior, the present study characterizes region-specific dopamine release dynamics during motor performance and reward evaluation, uncovering how dopamine signaling in the DLS and NAc may differentially contribute to motor control and reinforcement learning. We pair in-vivo dopamine recordings with an isometric pull-bar task in which pull duration was adapted across training days, to test the temporal correlation of dopamine release during pull initiation, pull completion & performance feedback, and reward receipt. Our preliminary data suggest that phasic dopamine release in DLS increases during movement and peaks during performance feedback, suggesting a role for dopamine in both action execution and reinforcement of correctly performed movements. By contrast, we find that dopamine in the NAc ramps towards future rewards, peaking around feedback delivery and again around reward receipt, consistent with the large literature reporting reward and prediction error signaling in this region. Together, our data contributes to a growing understanding of the heterogeneity of striatal dopamine signaling.

Disclosures: C.D. Phillips: None. **C.A. Thorn:** None.

Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.05/T8

Topic: F.03. Basal Ganglia

Support: UF-NS108177
U19 NS113201
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Whitehead Institute Innovation Initiative
Whitehead Fellows Program

Title: Dopamine calibrates movement timing in response to internal and external constraints

Authors: *Q. DING[1], I. C. WIJSMAN[2], Z. OZCAN[1], E. NORRI[1], J. A. ASSAD[2,3], A. E. HAMILOS[1,2];
[1]Whitehead Inst., Cambridge, MA; [2]Neurobio., Harvard Med. Sch., Boston, MA; [3]Inst. Italiano di Tecnologia, Genoa, Italy

Abstract: Dopamine neurons (DANs) are poised to integrate information about internal and external constraints to influence movement. We recently showed DANs control trial-by-trial updates to movement timing in a self-timed movement task. Here, we show these updates exhibit striking differences in the face of different internal and external pressures. On each trial, headfixed, water-restricted mice earned a juice reward if the timing of their first lick occurred during a hidden rewarded time window (e.g., 3.3-7s after a cue), which had to be discovered through trial-and-error. This produced apparent exploratory behavior, with mice sampling a broad range of movement times before targeting the reward window. Mice exhibited trial-by-trial timing updates, which became progressively smaller as task performance improved, and these updates were proportional to the amplitude of reward-related striatal DA transients ("rrDA"), which also declined in tandem with performance (measured with fiber photometry in sex-balanced cohorts, dLight1.3/rdLight1, n=13). To quantify this apparent calibration process, we asked how the timing "set-point" evolved over experience (measured as the local median of the timing distribution). Mice adjusted their set-point in response to blocks of trials with different reward windows (e.g., from 7-12 to 2-3.3s), arguing set-point changes were related to the statistics of the environment. However, different internal and external constraints also influenced set-point. Manipulations that naturally increased endogenous rrDA amplitude (e.g., increased reward amount or thirst) caused surprisingly early-biased timing and delayed calibration—at the expense of reward—whereas manipulations that decreased rrDA (e.g., decreased reward or thirst) caused more rapid calibration and later-biased timing. Despite these differences, across all manipulations, rrDA dynamics remained highly anticorrelated with set-point (r = -0.64 to -0.89), explaining both early-to-late and late-to-early shifts. Abrupt changes in these constraints consistently reproduced these effects, which were robust to bleaching, optical artifacts, and spurious movements. Calibrated optogenetic DAN manipulation recapitulated these effects, with increases in rrDA causing rapid early-shifting (ChR2 in genetically defined DANs, n=4), and No Opsin control animals showing no effect (n=4). We conclude that internal and external constraints alter rrDA dynamics, which in turn control the set-point of motor timing. We propose that DANs serve as a common hub for integrating information pertaining to these pressures to drive changes in the propensity to move.

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Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.06/T9

Topic: F.03. Basal Ganglia

Support: NIH Grant R21NS137136
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American Parkinson's Disease Foundations

5T32NS086750
5TL1TR001447

Title: Uncovering striatal direct pathway hyper-responsiveness to dopamine in Parkinson's disease

Authors: *J. R. MARTIN[1], M. MALTESE[2], J. S. DASEN[3], N. X. TRITSCH[5,4];
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Abstract: Levodopa-induced-dyskinesia (LID) is a debilitating side effect of dopamine (DA) replacement therapy for patients with Parkinson's disease. LID is thought to be largely mediated by the aberrant hyperactivity of striatal direct pathway spiny projection neurons (dSPNs). It remains poorly understood what conditions render dSPNs hyper-responsive to DA, such that treatment with levodopa or D1 receptor (D1R) agonist induces hyperactivation. Here, using a combination of genetic, pharmacological, and lesion manipulations, we determined the precise threshold of DA axon loss required for dSPNs to become hyperactive with levodopa or D1R agonist treatment. We then demonstrate that loss of D1R is sufficient to render dSPNs hyper-responsive to Gs signaling and that maintaining continuous Gs signaling can protect dSPNs from hyper-responsiveness to D1R activation even when DA axons are totally lost. Our data suggest that the complete loss of DA axons renders dSPNs hyper-responsive through prolonged loss of D1R Gs signaling. Our findings suggest interventional targets that could combat DA replacement therapy from inducing dyskinesia.

Disclosures: J.R. Martin: None. **M. Maltese:** None. **J.S. Dasen:** None. **N.X. Tritsch:** None.

Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.07/T10

Topic: F.03. Basal Ganglia

Title: Pharmacologic activation of the muscarinic (M4) receptor modulates dorsal striatum neuronal activity before and after concurrent SSRI treatment

Authors: G. SØRENSEN[1], O. H. MILLER[2], L. BELLIER[2], P. BOTTA[1], K. ZITELLI[2], D. CHENG[2], S. NEUFELD[2], M. S. THOMSEN[1], J. J. NASSI[2], *B. J. HALL[1];
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Abstract: Longitudinal imaging of neural circuits in preclinical species provides a powerful approach to addressing variability and reducing risk when defining pharmacokinetic to pharmacodynamic relationships during therapeutic development. Using miniature microscopes

combined with genetically encoded calcium indicators (GCaMPs), we simultaneously recorded the activity of hundreds of individual and ensemble neurons in freely behaving mice and imaged the same populations across time and treatment. We investigated the effects of a muscarinic acetylcholine receptor subtype 4 (M4) positive allosteric modulator (PAM) on direct and indirect pathway spiny projection neurons (D1-SPNs and D2-SPNs, respectively) in dorsal striatum. We also compared dose-dependent effects of this M4 PAM (0.0, 0.45, 1.5, and 4.5 mg/kg) to the M4 agonist/PAM xanomeline (0.0, 0.3, 1.0, and 3.0 mg/kg) across behavioral and striatal functional endpoints. In naïve mice, the M4 PAM reduced spontaneous movement frequency and velocity. During states of rest, the M4 PAM dose-dependently suppressed D1-SPN activity, with less effect on D2-SPN activity. However, during movement, when dopaminergic tone and corticostriatal drive are elevated, the M4 PAM strongly facilitated D2-SPN activity. Interestingly, xanomeline reproduced behavioral and D2-SPN-driven effects of the M4 PAM but exhibited a distinct profile regarding D1-SPN activity across doses. Using rat microdialysis, we confirmed that the effects observed following M4 PAM or xanomeline administration were not mediated by direct dopaminergic mechanisms, as neither treatment caused a measurable change in dopamine levels within the striatum. Another critical variable often overlooked in translational research is the influence of standard-of-care (SoC) treatments, which may modify the efficacy of investigational drugs. To address this for the M4 PAM concept, we tested mice chronically treated with fluoxetine (20 mg/kg), a selective serotonin reuptake inhibitor (SSRI) commonly prescribed for obsessive-compulsive disorder. Chronic fluoxetine treatment prevented the hypolocomotive effects of the M4 PAM while largely recapitulating the state-dependent effects on neuronal activity, excepting the velocity encoding of D1-SPNs. This study highlights the utility of calcium imaging with miniature microscopes for assessing therapeutic-induced neural circuit alterations and the modulation of these effects by SoC treatments. Furthermore, they underscore the value of longitudinal imaging in differentiating the target engagement profiles of mechanistically similar yet distinct compounds.

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Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.08/T11

Topic: F.03. Basal Ganglia

Support: NIMH Grant R01 MH136354

Title: Striatal Neuromodulatory Dysfunction in Neurexin1-alpha Mutant Mice

Authors: *J. GALANAUGH[1], M. F. DAVATOLHAGH[2], W. TU[1], M. V. FUCCILLO[1];
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Abstract: Neurexin 1α (Nrxn1α) is a presynaptically-localized synaptic adhesion molecule that has region and cell-type specific function, including a presynaptic role in calcium channel regulation for synaptic transmission and a transsynaptic organizing function. Given these central function for Nrxn1α, it is unsurprising that mutations to this molecule are correlated with a range of neuropsychiatric disorders. Many of these disorders are characterized by abnormalities in how reward is used to guide behavior, with some leading hypotheses suggesting an etiology in neuromodulatory dysfunction. The striatum is a key integrator for sensorimotor and reward-related information. Striatal processing, which is heavily informed by neuromodulators such as Acetylcholine (ACh) and Dopamine (DA), is important for reinforcement behaviors that are disrupted in disease. Cholinergic interneurons (ChINs) are the main source of ACh in striatum, and dopaminergic neuron (DAN) terminals projected from VTA and SNc are the source of DA. Though Nrxn1α is expressed at striatal ChIN and DAN terminals, a role for Nrxn1α in the modulation of cholinergic or dopaminergic signals has not yet been described. Here, we demonstrate (1) a sex-dependent, cell-autonomous role for Nrxn1α in ChINs by altered spontaneous and evoked ACh levels in female ChAT conditional KOs and (2) a role for Nrxn1α in striatal dopamine release in vitro and outcome-related dynamics in vivo. Ongoing work seeks further clarification on loci, mechanisms, and consequences of these neuromodulatory abnormalities.

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Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

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Topic: F.03. Basal Ganglia

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National Defense Science and Engineering Graduate (NDSEG) Fellowship Program, sponsored by the Air Force Research Laboratory (AFRL), the Office of Naval Research (ONR), and the Army Research Office (ARO) (FA9550–21-F-0003)

Title: Characterization of dopamine dynamics in relation to motor performance in monkeys

Authors: *R. D. MURRAY, U. AMJAD, A. SOMICH, H. N. SCHWERDT;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Increasing evidence demonstrate dopamine signaling related to movement and action initiation and invigoration (Dodson et al. 2016). However, our knowledge of how these signals relate to distinct motor performance phases defined by the eye movement responses to task stimuli has yet to be resolved. Here, we investigated dopamine dynamics under various states of engagement as measured by motor performance in monkeys. We used a version of visually guided reward-biased task developed previously (Kawagoe et al. 2004) that required the monkey to saccade and maintain fixation to a peripheral visual stimulus before receiving reward. The location (left or right) of the peripheral stimulus was associated with the upcoming reward size (large or small). This location-reward contingency switched randomly with a block size ranging from 35 - 200 trials to dissociate reward size and movement direction variables. Movement time (MT) was defined as the duration between when the peripheral stimulus was displayed to when the saccade was made to the stimulus. We computed running averages of MT, along with success and failure over windows of consecutive trials to create a contextual metric of motor performance. Subsecond DA concentration changes with fast-scan cyclic voltammetry were recorded in the caudate nucleus (CN) and putamen using chronically implanted carbon fiber electrodes. We compared DA dynamics from high and low performance windows of trials. Early analysis indicates increased peak DA concentration changes for higher performance phases. These increases were measured during the trial period in which the monkey fixates on the peripheral stimulus. So far, these increases were mainly observed in the CN (4/6 sites in 15 sessions), but less present in the putamen (3/9 sites in 15 sessions). These results are in line with recent performance related dopamine measurements in songbirds (Kasdin et al. 2025, Qi et al. 2025), but further demonstrate possible region specificity. This trend was largely contingent on having a large reward condition and left (contralateral to implanted hemisphere) stimulus location. These movement contingencies are consistent with our earlier work (Schwerdt et al. 2020). Ongoing analysis is underway to investigate different trial periods, including the intertrial interval, as well as other metrics of motor performance.

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Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.10/T13

Topic: F.03. Basal Ganglia

Support: NIH MH113257

Title: Sex as a biological variable in the density of cholinergic interneurons in the NHP striatum

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Abstract: The NIH initiative to balance sex of animals in research has been pivotal to understanding fundamental biological differences between male (M) and female (F). This has direct consequences on the reproducibility of research and implementation of experimental designs more conducive to translational medicine. We continue our research of striatal cholinergic interneurons (SCI) and how their numbers and distributions change as a function of age and sex. Our interest in the striatum arises from its importance in motor, cognitive and motivational processes. Here we report our preliminary results on a comparison of n=6 naïve rhesus macaques (NHPs), 3 F and 3 M, all at 1 year of age. All the materials were drawn from Collection 6 of the MacBrain Resource Center and are publicly available at https://macbraingallery.yale.edu/collection6/. We used the web-based artificial intelligence platform Aiforia™ to expedite measuring and counting processes in an accurate, reproduceable, and unbiased manner. An in-house algorithm was trained to measure striatal area and to identify and count SCIs. Measurements and counts were conducted in one hemisphere on the whole rostro-caudal extent of the striatum (caudate + putamen). This encompassed 58 coronal sections in F and 61 in M. In F, n=43,579 SCIs were identified and counted; in M, n=44,728. The mean density of SCIs in F and M specimens were similar: ~224 SCI/mm^3 in F and ~207 SCI/mm^3 in M. Among F specimens, however, one displayed much higher density than the others (~260 SCI/mm^3). When this F is excluded, mean density in F was ~ 206 SCI/mm^3, basically matching density in M. Our preliminary results indicate possible sex related differences in the SCI populations of normal animals which warrant further exploration. This encourages future research to establish if the same trend persists at different developmental ages, including in elderly, and if the trend is also identified in other cholinergic territories such as the basal forebrain. Understanding these details may help us understand why the incidence of Alzheimer's disease is different in human males and females and why some cholinergic populations seem to be more vulnerable than others.

Disclosures: L. Greene: None. **P. Rakic:** None. **A. Duque:** None.

Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.11/T14

Topic: F.03. Basal Ganglia

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Whitehead Fellows Program
Whitehead Innovation Initiative

Title: Reward-related dopamine transients exert one-shot calibrating updates to motor timing.

Authors: *A. E. HAMILOS[1,2], I. C. WIJSMAN[2], Q. DING[1], P. ASSAWAPHADUNGSIT[1,2], J. A. ASSAD[2,3];
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Abstract: Reward-related dopamine (rrDA) transients are thought to promote gradual learning, with ongoing debate over what rrDA represents in the context of reinforcement learning (RL) models. Potentially in parallel, DA has also been shown to play an apparently distinct, "real-time" role in motor control and vigor, and it remains unknown whether these real-time effects are related to DA's role in reward signaling or gradual reinforcement. To study DA's dual roles in the same context, we trained headfixed mice to do a self-timed movement task: on each trial, mice received a cue and were rewarded if their next lick occurred during a hidden rewarded time window (3.3-7s after the cue), which mice had to discover through trial-and-error experience. Mice exhibited apparent exploratory behavior, sampling a broad range of movement times before eventually targeting the reward window. This allowed us to examine how rrDA transients were related to trial-by-trial updates to movement timing, which gradually led to improved task performance. To do so, we recorded DA signals with fiber photometry in sex-balanced cohorts (GCaMP6f in genetically defined DA neurons (DANs, n=4); the DA indicators DA2m (n=4) or rdLight1 (n=8) in striatal neurons). Single rrDA transients were associated with one-shot updates to movement timing—but in a surprising way. Rather than reinforce specific movement times, the amplitude of rrDA transients (which were highly variable) predicted a proportional, analog change to movement timing on the next trial, 10-20s in the future, with the highest transients associated with the largest early-shifts, and the lowest with the largest late-shifts. rrDA's one-shot timing adjustments accumulated over trials and were associated with changes in the median of the timing distribution that improved task performance. These effects were robust to behavioral non-stationarity, spurious movements and optical artifacts. Closed-loop optogenetic DAN stimulation recapitulated both single-trial (one-shot) updates and longer-term timing effects (n=4 ChR2; triggered on the timed movement and calibrated to mimic rrDA), whereas No Opsin control stimulation (n=4) did not affect timing updates. We conclude that rrDA transients drive proportional, one-shot calibrating updates to motor timing. The rapid timecourse of these effects is suggestive of a faster, more flexible mechanism than gradual synaptic plasticity, such as changes in striatal excitability, which may operate in parallel with and support slower DA-mediated RL through increasing the opportunity to repeat rewarded actions in reward-rich environments.

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Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

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Topic: F.03. Basal Ganglia

Support: NIH Grant NS138598
ASAP 020600

Title: Heterogeneous subthalamic regulation of substantia nigra circuitry

Authors: *A. GARCIA[1], M. XIA[1], L. C. HADJAS[2], L. LINDERHOF[1], G. J. KOLLMAN[1], T. S. HNASKO[2], N. G. HOLLON[3];
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Abstract: The subthalamic nucleus (STN) is an established target for deep-brain stimulation (DBS) for movement disorders such as Parkinson's disease (PD), and more medial domains are emerging targets for treating neuropsychiatric conditions such as obsessive-compulsive disorder (OCD). The STN and the adjacent parasubthalamic nucleus (pSTN) contain multiple heterogeneous neuronal subtypes, implicated in a range of functions including movement regulation, appetite suppression, and aversion, but the downstream circuit interactions of these distinct subpopulations remain poorly understood. Both these neighboring subthalamic regions contain predominantly glutamatergic neurons expressing the vesicular glutamate transporter VGLUT2. More specific markers for major neuronal subtypes within these regions include Pitx2 for STN and Tac1 for pSTN. We have recently shown that stimulation of glutamatergic projections spanning these subthalamic inputs drives sustained activation of GABA neurons in the substantia nigra pars reticulata (SNr), transient increase in dopamine release in the tail of the striatum (TS), and inhibition of dopamine in the dorsolateral striatum (DLS).
Here, we find that whereas Pitx2+ STN neurons project throughout the SNr, Tac1+ pSTN projections are largely restricted to the substantia nigra pars compacta (SNc). In ongoing experiments we combine optogenetic stimulation of these subthalamic inputs with fiber photometry recording of either GCaMP in SNr GABA or SNc dopamine neurons, or GRAB_DA dopamine sensor recordings in striatal subregions. Preliminary results are consistent with the hypothesis that the STN preferentially drives SNr GABA neurons whereas pSTN can transiently drive SNc dopamine neurons. The striatal dopamine sensor recordings reveal a striking dissociation where stimulating the Pitx2 STN input suppresses DLS dopamine, and in contrast the Tac1 pSTN selectively increases TS dopamine release. These findings reveal that heterogeneous cell types within neighboring subthalamic regions have divergent effects on substantia nigra neurons and distinct nigrostriatal dopamine pathways, with important implications for understanding basal ganglia circuitry and refining therapeutic interventions for conditions such as PD and OCD.

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Poster

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Program #/Poster #: PSTR452.13/T16

Topic: F.03. Basal Ganglia

Support: F32DA060556

Title: Different spatiotemporal modes of dopamine transmission drive motor output and motor learning

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Abstract: Striatal dopamine is critical for executing coordinated movements and motor learning, yet the subcellular mechanisms that drive these functions remain unclear. Within the dorsolateral striatum, sparse dopamine varicosities are thought to signal to postsynaptic receptors through volume transmission. This spatiotemporal mode is characterized by slow changes (>100 msec) in low concentrations of dopamine (<1 μM) that occur over a broad volume (>10 μm). Recently, emerging evidence suggests that dopamine transmission can also occur through a 'synaptic-like' mode (referred here as focal transmission), which is characterized by fast, localized changes in high concentrations of dopamine. Given dopamine's multiple behavioral functions and the potential existence of two spatiotemporal modes transmission, we test the hypothesis that different spatiotemporal modes of dopamine signaling drive distinct aspects of motor behavior. Using a combination of fast-scan cyclic photometry, slice electrophysiology, and two-photon imaging of fluorescent dopamine sensors, we first show that focal and volume dopamine transmission can be regulated independently of each other. Next, using a battery of manipulations to perturb dopamine release, we demonstrate that while volume transmission is necessary for healthy motor output, focal transmission is sufficient to support motor learning. Lastly, we use a combination of electrophysiology and imaging to examine how these spatiotemporal modes of dopamine transmission shape medium spiny neuron firing and plasticity—functions critical to their behavioral output. Our findings suggest that the spatiotemporal structure of dopamine transmission shapes both its physiological and behavioral function within the dorsolateral striatum.

Disclosures: M.M. McGregor: None. **C.P. Ford:** None.

Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

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Topic: F.03. Basal Ganglia

Support: ASAP-020600
NIH R01 NS138598
NIA P01AG084497

Title: Parkinson's Disease vulnerable dopamine neurons display opposite responses

Authors: *L. C. HADJAS[1], G. KOLLMAN[2], L. LINDERHOF[6], M. XIA[3], B. LIM[4], E. B. LEE[7], F. CICCHETTI[8], R. AWATRAMANI[9], N. G. HOLLON[5], T. S. HNASKO[10];
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Abstract: Dopamine (DA) neurons of the substantia nigra (SN) are essential for motor control and selectively degenerate in Parkinson's disease (PD). However, DA neurons are molecularly heterogeneous, with some showing greater vulnerability and others resilience. Here, we show that the DA subtype marker *Anxa1*, identified in mice, labels PD-vulnerable DA neurons in human SN. Using mice, we found that excitatory inputs from subthalamic (STN) and pedunculopontine (PPN) nuclei evoked frequency-dependent excitation in SN GABA neurons, but complex multiphasic DA neuron responses, suggesting heterogeneous DA subtype responses. Indeed, excitatory inputs evoked differential DA responses in striatal subregions, an increase in caudal striatum, but inhibition followed by rebound in dorsolateral striatum. Additionally, PD-resilient Vglut2+ DA neurons were excited by STN/PPN input, while vulnerable Anxa1+ DA neurons were inhibited. These findings demonstrate that DA subtypes are embedded in distinct functional networks, suggesting that some therapeutic interventions may differentially impact vulnerable and resilient DA subtypes.

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Poster

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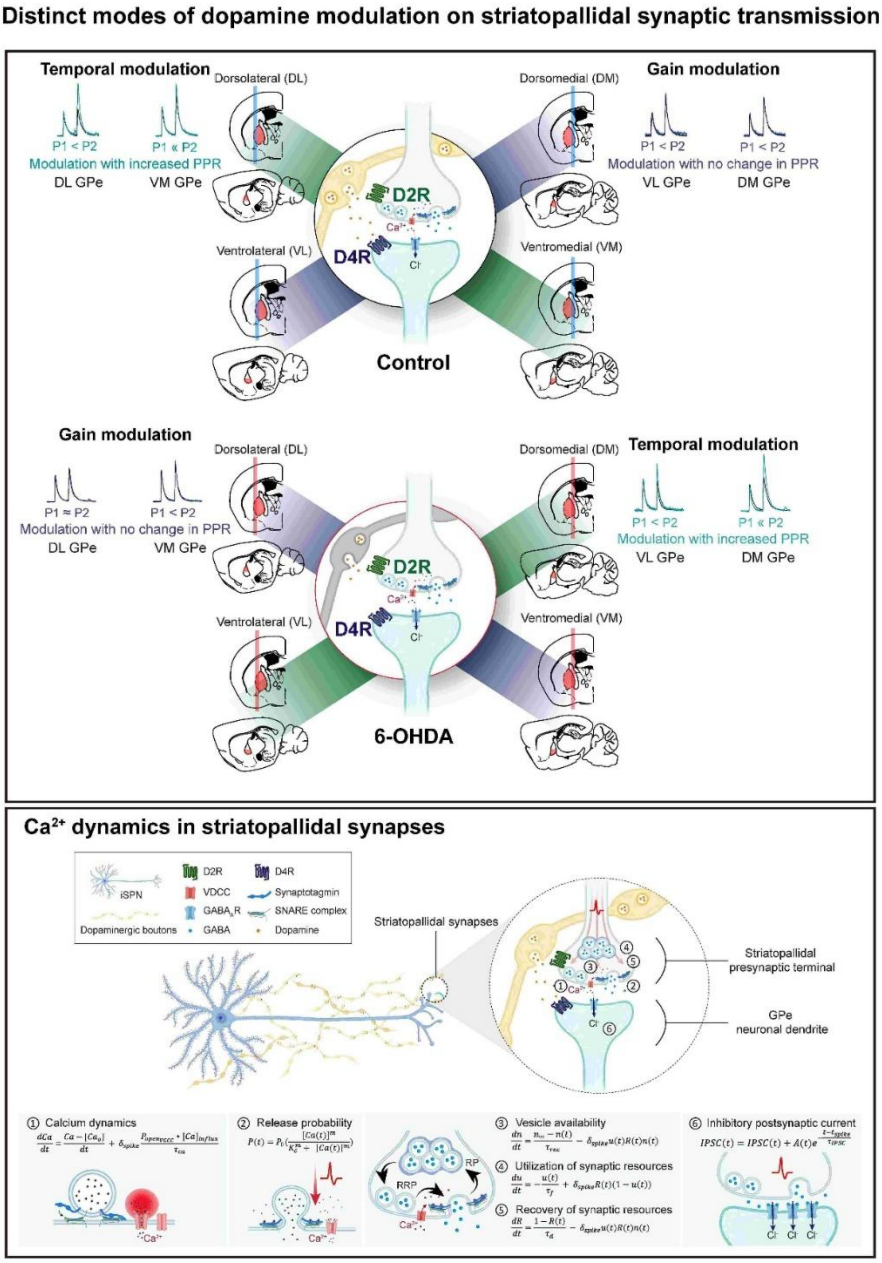
Title: Distinct modes of dopamine modulation on striatopallidal synaptic transmission

Authors: ***Y. LEE**[1], M. REVA[2], K. KIM[3], H.-J. KIM[4], Y. LI[5], C. LEE[6], C. LUSCHER[7];
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Abstract: Dopamine (DA) plays a crucial role in voluntary movement by modulating basal ganglia function. According to the classical model, DA depletion leads to overactivation of the indirect pathway, excessive thalamic inhibition, and ultimately hypokinesia. Although the striatopallidal synapse—linking the striatum to the external globus pallidus (GPe)—is a key node in this pathway, its dopaminergic modulation remains poorly understood due to sparse DA innervation.

To address this, we combined projection-specific optogenetics, whole-cell patch-clamp recordings in acute mouse brain slices, and computational modeling. We found that DA exerts region-specific effects through D2 and D4 receptors in the GPe. In dorsolateral (DL) and ventromedial (VM) GPe, D2 receptors mediate presynaptic inhibition by increasing paired-pulse ratio (PPR) and reducing GABA release. In contrast, in dorsomedial (DM) and ventrolateral (VL) GPe, D4 receptors mediate postsynaptic inhibition without affecting PPR. This reveals a spatially organized, pinwheel-like pattern of DA signaling across GPe subregions. Following 6-hydroxydopamine (6-OHDA)-induced DA depletion, this spatial pattern reverses: PPR increases in the VL and DM while diminishing in the DL and VM.

Together, our findings demonstrate that striatopallidal synapses are spatially organized and differentially modulated by dopamine across GPe subregions. This structured dopaminergic modulation enables selective gating of indirect pathway signals and may contribute to region-specific dysfunctions in Parkinsonian states. Understanding this spatial logic provides new insight into the functional architecture and pathological vulnerability of basal ganglia circuits.



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Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

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Program #/Poster #: PSTR452.16/U3

Topic: F.03. Basal Ganglia

Support: NIH Grant R01-NS95809
NIH Grant R01-DA35821
NIH Grant F32-DA51135

Title: Precise spatiotemporal encoding of striatal dopamine signals

Authors: *A. G. YEE, C. P. FORD;
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Abstract: Striatal dopamine (DA) signaling is traditionally thought to be mediated by a spatially broad mode of transmission, whereby low concentrations of DA non-selectively activate extra-synaptic receptors. However, this mode of signaling is not consistent with behaviors mediated by DA which require high spatiotemporal precision, as well as increasing evidence indicating that striatal DA transmission is more tightly organized than previously appreciated. Using two-photon imaging and whole-cell electrophysiology, we have directly defined the spatiotemporal properties of DA transmission onto indirect pathway spiny projection neurons in striatal brain slices. Sparse activation of DA release sites evoked highly localized DA signals which produced spatially-discrete, D2 receptor-mediated responses *via* Gβγ-mediated signaling. Membrane-delimited Gβγ signaling required higher concentrations of DA compared to downstream second messenger signaling (i.e. Δ[cAMP]). Spatially-restricted DA signals were diversely encoded at dendrites of striatal neurons, indicating that subcellular localization is critical for signal encoding. We propose that membrane-delimited Gβγ signaling occurs in parallel to classical second messenger pathways, providing a mechanism for precise spatiotemporal encoding of behaviors by striatal DA transmission.

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Poster

PSTR452: Basal Ganglia: Transmitters and Neuromodulation

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Program #/Poster #: PSTR452.17/U4

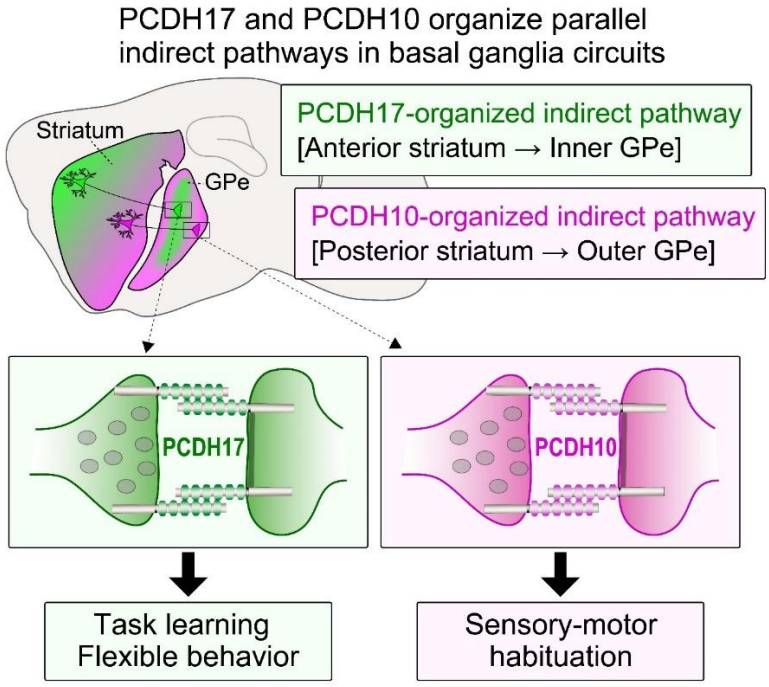
Topic: F.03. Basal Ganglia

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Title: Delta2-protocadherins organize parallel indirect basal ganglia circuits

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Abstract: The basal ganglia comprise multiple parallel neural circuits, each governing distinct behavioral functions. However, the molecular mechanisms organizing these circuits remain poorly understood. Here, we show that two delta2-protocadherins (PCDHs)-PCDH17 and PCDH10, homophilic cell adhesion molecules-define two distinct indirect basal ganglia circuits that regulate separate behavioral domains. Histological analyses revealed complementary expression patterns of PCDH17 and PCDH10 in the mouse basal ganglia around two weeks of age, anatomically delineating two parallel indirect pathways. PCDH17 is enriched in the anterior striatum and inner regions of the globus pallidus external (GPe), while PCDH10 is preferentially expressed in the posterior striatum and outer regions of the GPe. To investigate their roles, we generated indirect pathway-specific conditional knockout (cKO) mice for *Pcdh17* and *Pcdh10* by crossing with *A2A-Cre* line and conducted synaptic imaging in male and female mice at 2-3 weeks of age. Both *A2A-Cre;Pcdh17* and *A2A-Cre;Pcdh10* cKO lines exhibited regionally distinct impairments in circuit formation compared to controls. Blind behavioral analyses of adult male mice revealed that *A2A-Cre;Pcdh17* cKO mice showed deficits in task learning and behavioral flexibility, whereas *A2A-Cre;Pcdh10* cKO mice demonstrated reduced motor and sensory habituation. These results identify PCDH17 and PCDH10 as molecular organizers of distinct indirect basal ganglia circuits and provide insight into the molecular basis of parallel circuit organization.



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Poster

PSTR453: Basal Ganglia: Physiology and Plasticity

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Topic: F.03. Basal Ganglia

Support: NIH Grant R01NS125814

Title: Calcium currents shape PPN response to stimulation: A computational perspective

Authors: *A. K. THOMAS[1,2], J. E. RUBIN[1,2], M. FALLAH[3], R. C. EVANS[3], A. H. GITTIS[4,5]; [1]Mathematics, [2]Ctr. for the Neural Basis of Cognition, Univ. of Pittsburgh, Pittsburgh, PA; [3]Neurosci., Georgetown Univ. Med. Ctr., Washington, DC; [4]Biol. Sci., [5]Ctr. for the Neural Basis of Cognition, Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The pedunculopontine nucleus (PPN), a brainstem structure connected to the basal ganglia (BG), plays a key role in motor control and is increasingly recognized as critical in Parkinson's disease (PD) recovery. Recent studies suggest that stimulation to specific BG sites can promote long-term motor recovery in dopamine-depleted rodents, but only when the PPN is intact. Despite its importance, models of PD dynamics rarely consider the contributions of the PPN. We present a novel conductance-based model of PPN neurons that captures key features such as post-stimulus rebound activity and high-voltage oscillations observed in patch-clamp electrophysiology experiments. By incorporating two distinct types of voltage-activated calcium channels, our model demonstrates how differing channel kinetics support diverse firing responses under external stimulation. This work offers a foundation for understanding PPN single-cell activity and for exploring its contributions to PD-related motor circuits.

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Poster

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Support: NIH Grant R01 NS119520

Title: Model-based design of subthalamic nucleus neurons using hybrid optimization

Authors: *H. CHEN, C. C. MCINTYRE;
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Abstract: The subthalamic Nucleus (STN) is a primary target for Deep Brain Stimulation (DBS) in the treatment of advanced Parkinson's Disease (PD). Although DBS has proven therapeutic efficacy, the underlying mechanism remains poorly understood. Computational models of STN neurons are often used to study the neural response to DBS and simulate its effects on the basal ganglia circuitry. However, currently available STN models are limited by their biophysical realism in terms of firing characteristics and electrophysiological properties. Therefore, we present two complementary STN neuron models: a simplified four-compartment model (soma, proximal/distal dendrite, and axon initial segment) and a detailed model based on 3D anatomical reconstruction (Sato et al., 2000). Both models aim to better reproduce known STN firing characteristics. We also introduce a novel hybrid optimization framework that combines the genetic algorithm (GA) with simulation-based inference (SBI). The GA efficiently explores the parameter space, while SBI infers the underlying probabilistic distributions, offering insights on how individual parameters influence model behavior and improve our understanding of the biophysics. We benchmarked this hybrid approach against GA-only and SBI-only methods and found that it not only produced superior fits to experimental data but also reached optimized results faster and more efficiently. Additionally, the generated probabilistic distributions were used to examine how model parameters relate to known firing characteristics of STN neurons. Our results show that the inferred distributions reliably capture how parameter values shift in response to changes in target firing features in both basic biophysical relationships and STN-specific factors such as the critical role of sKCa channel conductance in shaping the frequency-current profile. In conclusion, the optimized STN model accurately reproduced key features observed in experimental recordings, including spontaneous firing, action potential shape, hyperpolarization response, frequency-current relationship, and phase response to simulated synaptic input. Our updated STN neuron models offer both improved realism and flexibility. In addition, the probabilistic parameter distributions enable the generation of realistic STN neuron populations with variability in electrophysiological profiles—an important step toward modeling network-level behaviors. Together, the improved models and hybrid optimization method provide powerful tools for future understanding of STN neurophysiology and for simulating and interpreting the effects of neuromodulation.

Disclosures: H. Chen: None. **C.C. McIntyre:** None.

Poster

PSTR453: Basal Ganglia: Physiology and Plasticity

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Moshinsky fellowship 2019 to F.T.

Title: Investigating target specific activity in the substantia nigra pars reticulata

Authors: *J. A. AGUILAR PALOMARES[1,2], J. RAMIREZ-JARQUIN[2], G. B. FLORAN[1], F. TECUAPETLA[2];
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Abstract: The substantia nigra pars reticulata (SNr), a major output nucleus of the basal ganglia, plays a central role in motor control and decision-making. Despite extensive GABAergic projections from SNr neurons to diverse downstream targets, including the thalamus and the mesencephalic locomotor region, it remains unclear whether these outputs convey overlapping or target-specific information during voluntary behavior. To investigate this, neural activity was recorded in vivo from SNr neurons in freely moving mice performing a two-alternative forced choice task. Recordings were synchronized with high-resolution kinematic tracking using DeepLabCut to capture behavioral dynamics across distinct task epochs, including stimulus processing, action selection and initiation, and reward evaluation. Task difficulty, movement parameters, and decision-related variables such as confidence were examined to determine their relationship to SNr firing patterns. Opto-tagging was employed to identify the projection targets of individual SNr neurons, allowing for the correlation of firing dynamics with downstream connectivity. Preliminary dimensionality reduction analyses using Uniform Manifold Approximation and Projection (UMAP) revealed distinct clusters of SNr neurons based on temporal activity profiles, supporting the hypothesis of functional heterogeneity within SNr output. These findings suggest that the SNr may transmit target-specific signals aligned with behavioral variables, rather than broadcasting a uniform motor command. By integrating electrophysiological, anatomical, and behavioral data, this study provides new insight into how basal ganglia outputs are organized to support adaptive behavior, with implications for understanding motor and cognitive dysfunction in basal ganglia-related disorders.

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Poster

PSTR453: Basal Ganglia: Physiology and Plasticity

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Program #/Poster #: PSTR453.04/U8

Topic: F.03. Basal Ganglia

Support: Leon Levy Fellowship
NIMH Grant R01MH130658

Title: Leveraging membrane potential recordings to dissect the actions of dopamine on cells and synapses in vivo

Authors: *M. DRUART[1], Y. C. YANG[1], N. X. TRITSCH[2], T. SIPPY[1];
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Abstract: Dopamine (DA) is a key neuromodulator that plays a central role in motivation and learning, and its dysregulation has been implicated in a range of neuropsychiatric conditions, including Parkinson's disease, mood disorders, and addiction. While phasic DA activity is associated with reward and movement and is believed to support learning, the mechanisms by which DA influences its target neurons to drive behavioral change remain poorly understood. A major limitation in elucidating DA's cellular actions is that the properties it modulates—such as neuronal excitability and synaptic strength—are typically measured ex vivo, under conditions that fail to capture the complex and dynamic nature of DA signaling in the intact brain. In this study, we address this gap by examining these properties in vivo, focusing on the principal postsynaptic targets of DA: D1- and D2-expressing striatal projection neurons (SPNs) in the dorsolateral striatum (DLS). To do this, we recorded membrane potential (Vm) dynamics in D1- and D2-SPNs in the dorsolateral striatum (DLS) using the optopatch method for cell-type identification. In a subset of animals, we expressed ChRimson in primary somatosensory cortex (S1) to isolate cortically evoked excitatory postsynaptic currents (eEPSCs). We trained mice to lick a reward spout to this stimulus, allowing us to measure the eEPSCs before and after learning. Finally, to isolate the contribution of DA to this process, we infected midbrain DA neurons with either excitatory or inhibitory opsins, allowing us to mimic positive and negative reward prediction errors (RPEs) that occur during learning. Our initial results demonstrate that optogenetic stimulation of dopamine neurons does not alter the intrinsic excitability of either D1- or D2-expressing SPNs over the time scale of seconds to minutes[NT1] . This contrasts with previous ex vivo findings suggesting that dopamine enhances excitability in D1-SPNs over these time scales. Over longer timescales consistent with learning, dopamine is thought to modulate synaptic strength, enabling lasting changes in circuit function. Supporting this, a single pairing of phasic optogenetic dopamine release with a cortically evoked eEPSC does not alter response amplitude over short timescales, suggesting that repeated pairings—such as those occurring during learning—are necessary to engage DA-dependent synaptic plasticity. Ongoing experiments aim to optimize stimulation protocols to reliably induce such plasticity in vivo, while concurrently assessing changes in eEPSC strength before and after learning.

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Poster

PSTR453: Basal Ganglia: Physiology and Plasticity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.05/U9

Topic: F.03. Basal Ganglia

Support: SNSF Grant 323630_214535

Title: Single-cell RNA sequencing reveals two distinct cell types in the Subthalamic Nucleus

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Abstract: The mechanism of action of deep brain stimulation remains elusive. Mounting evidence suggests that it is not merely a functional lesion, but rather a modulation of subthalamic nucleus (STN) circuits that conveys the beneficial effect. Stimulation of the hyperdirect pathway mimicks these beneficial effects on symptoms, yet optogenetic high-frequency stimulation of cells in the STN neurons only partially recreates these results. While the STN is generally considered a homogenous glutamatergic nucleus, in other parts of the basal ganglia, for example the external Globus pallidus (GPe), two populations of neurons with opposing effects for alleviating parkinsonian symptoms have been observed. We investigated the cellular diversity of the STN with single nuclei RNA sequencing and identified two distinct, glutamatergic cell populations. We confirmed their existance with immunohistochemistry (IHC) using markers from single cell sequencing, type 1 cells being Schip1+ and type 2 cells being Gabrg3+. Viral retrotracings reveal a distinct projection pattern onto spatially segregated cell types within the SNr. We combined this approach with IHC and could show that type 1 and type 2 project to the SNr in a cell-type specific manner. We then performed a cell-type specific rabies retrograde tracing from the STN to identify distinct neuronal input. Indeed, we found that input from prototypic GPe neurons project to the STN in a cell-type specific manner. Prototypic neurons projecting on type 1 STN neurons were Pv+, whereas those projecting onto the type 2 STN neurons were Lhx6+. The rabies tracing further revealed that predominantely the type 1 STN neurons receive hyperdirect input from cortex. Our findings provide molecular and anatomical proof for cellular diversity in the STN. The cell-type specific connectivity has far-reaching consequences for basal ganglia circuitry and the indirect pathway in general as it suggests the existence of two parallel indirect pathways. Further, these finding may help to better understand the mechanisms of deep brain stimulation, as Pv+ and Lhx6+ prototypic neurons have been implicated in opposing effects on parkinsonian mice. This could then serve as a blueprint for more refined stimulation protocols in the future.

Disclosures: A. Hoyningen: None. **C. Luscher:** None.

Poster

PSTR453: Basal Ganglia: Physiology and Plasticity

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Program #/Poster #: PSTR453.06/U10

Topic: F.03. Basal Ganglia

Support: NIH Grant T32NS0906050
ASAP-020572 Grant
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NIH Grant P51-OD011132

Title: Characterization of pyramidal tract (PT) corticospinal axon collateralization in basal ganglia-related structures in normal and parkinsonian monkeys

Authors: *K. SOUTH[1,2], N. N. MAGNUSSON[2,1], J. PRINCE JACOB[4], G. J. MASILAMONI[1], N. M. BOULIS[5], T. FEDERICI[5], R. RAHEB KHELO[5], A. GALVAN[3], Y. SMITH[3]; [1]Emory Natl. Primate Res. Ctr., [2]Neurosci. Grad. program, [3]Emory Natl. Primate Res. Ctr. and Dept. of Neurol., Emory Univ., Atlanta, GA; [4]Mercer Univ., Macon, GA; [5]Neurosurg., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: In Parkinson's disease (PD), striatal dopamine denervation leads to dysfunction of the basal ganglia-thalamo-cortical loops and pathophysiological changes in neurons of the primary motor cortex (M1) and supplementary motor area (SMA), which ultimately leads to the development of parkinsonian motor symptoms. Given that M1 and SMA are reciprocally connected to the basal ganglia-thalamo-cortical loop and responsible for the generation and control of movements, investigating alterations of corticofugal neurons in these regions is important to better understand PD pathophysiology. Pyramidal tract (PT) corticospinal neurons display both morphological alterations of their somatodendritic domain and physiological changes in severe parkinsonism. The main goal of this study is to investigate anatomical changes to the axonal domain of PT-corticospinal neurons between normal and parkinsonian monkeys. Following unilateral injections of AAV2-retro in the cervical spinal cord, the cell body, dendritic processes, and full axonal projectome of PT-corticospinal neurons in M1 and SMA are labeled in a Golgi-like fashion allowing for detailed analyses of the location and density of their axon collateral projections throughout the CNS. Our preliminary analysis from 3 control and 3 MPTP-treated parkinsonian monkeys indicates that PT-corticospinal cells send axon collaterals to several basal ganglia-related structures, including the post-commissural putamen, ventral motor thalamus, center median/parafascicular nucleus, subthalamic nucleus, zona incerta (ZI), and pedunculopontine nucleus (PPN). The PT-corticospinal axon collaterals differ in abundance and follow specific patterns of distribution within these regions. At the level of the ventral motor thalamus, they are confined to the pallidal-receiving territory and largely avoid the cerebellar afferent region, while in the PPN, they arborize profusely within the sensorimotor pallidal-receiving area with minimal input to the rest of the nucleus. Interestingly, among the target regions, the ZI receives the most massive proportional innervation from these collaterals. Comparative quantitative analysis of the relative density of PT-corticospinal axon collaterals between control and parkinsonian monkeys is in progress. Results of this study will lay the foundation for a deeper understanding of the corticospinal neurons' projectome and the neuroplastic changes it undergoes in parkinsonism, providing a basis for the design of cell type-specific antiparkinsonian therapies.

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Poster

PSTR453: Basal Ganglia: Physiology and Plasticity

Location: SDCC Halls B-H

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Topic: F.03. Basal Ganglia

Support: DOD w81xwh-22-1-0758
American Parkinson Disease Association
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Title: D1-msns acquire new epigenetic and transcriptional states during levodopa-induced dyskinesia development and persistence

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Abstract: Levodopa (L-DOPA)-induced dyskinesia (LID) is a side effect of prolonged L-DOPA therapy in Parkinson's disease, characterized by aberrant involuntary movements and postures. Upon its establishment, dyskinetic movements become persistent and progressively worsens, suggesting a "priming effect". We have previously identified a discrete subset of L-DOPA-responsive D1-medium spiny neurons (MSNs) that alter their transcriptional profile based on the duration of treatment. Initial L-DOPA led to increased expression of activity-related Immediate Early Genes (IEGs) in this subset, while prolonged exposure was associated with expression of synaptic plasticity-related genes. This profile was similar to that observed in hippocampal engram cells that encode behavioral responses to learning and memory tasks. It is likely that L-DOPA exposure induces a process of circuitry refinement and epigenetic remodeling, leading to lasting alterations in chromatin availability in specific neurons. Thus, we hypothesize that ensembles of D1-MSNs undergo persistent epigenetic and transcriptional sensitization that prime the system, thereby worsening LID upon each consecutive dose of L-DOPA. We performed single nucleus multiome sequencing (snRNA-seq and ATAC-seq) on striatal tissue from male hemiparkinsonian mice treated with vehicle or L-DOPA for 1, 5, or 10 d. Striatal nuclei were processed. The multiome data demonstrated that L-DOPA induced open chromatin regions on gene regulatory regions and increased the expression of differentially expressed genes. Initial L-DOPA treatment (1 d) increased the number of transcriptionally active D1-MSNs and enhanced the availability of open chromatin regions of IEGs. Prolonged exposure to L-DOPA (5 and 10 d) reduced the number of transcriptionally active D1-MSNs, suggesting a circuitry refinement process, and induced new open chromatin regions at enhancer regions and expression of synaptic plasticity-related genes. We utilized Fos-TRAP hemiparkinsonian mice to confirm this refinement process of transcriptionally active D1-MSNs across LID development. Overall, the results uncover the epigenetic and transcriptional processes underlying the development and

persistence of LID. Prospective experiments will characterize the structural and functional changes of D1-MSNs upon repeated exposure to L-DOPA.

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Poster

PSTR453: Basal Ganglia: Physiology and Plasticity

Location: SDCC Halls B-H

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Program #/Poster #: PSTR453.08/U12

Topic: F.03. Basal Ganglia

Title: In vivo Neuropixels recordings reveal movement-phase-specific activity of putative dopamine neurons in the substantia nigra

Authors: *Y. LU, P. VOGEL, J. ROEPER;
Inst. of Neurophysiol., Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: Dopamine (DA) neurons in the substantia nigra (SN) are essential for motor control and are profoundly affected in Parkinson's disease. To investigate their role in movement dynamics, we performed high-density extracellular recordings in awake, head-fixed mice (N = 11 male C57BL/6N) walking on a treadmill, using Neuropixels 1.0 probes alongside behavioral tracking (camera, position sensors). Approximately 3000 units were recorded across the span of the probe, with 48% (n = 1500) showing significant activity modulation around movement initiation (-2 to -1 s vs. 0 to +1 s), by either increasing (n = 882, +6.0 ± 6.3 Hz) or decreasing (n = 618, -3.8 ± 4.4 Hz) their firing rates. A similar proportion of neurons (42%, n = 1296) responded to movement termination (n = 579 increased, +4.8 ± 6.3 Hz; n = 717 decreased, -5.4 ± 6.0 Hz), and 64% (n = 1988) responded to both movement transitions. A subset of putative DA neurons (n = 251, ~8%) was identified based on low firing rate (≤10 Hz), broad spike waveform (half-width ≥200 μs), DiI labeling of the electrode tracks, and post hoc tyrosine hydroxylase staining to define which recording sites of the electrode crossed the substantia nigra. Among these, 44% (n = 110) exhibited activity changes during movement onset (n = 65 increased, +3.0 ± 3.5 Hz; n = 45 decreased, -1.4 ± 1.2 Hz), 34% (n = 85) during movement offset (n = 44 increased, +1.5 ± 1.0 Hz; n = 41 decreased, -2.9 ± 5.8 Hz), and 56% (n = 141) changed their firing rates during both phases. These findings demonstrate distinctive firing patterns of DA SN neurons in relation to self-paced movements. In recent experiments, we improved the spatial resolution of our recordings by using Neuropixels 2.0 probes with a four-shank configuration, enabling simultaneous recordings of medial and lateral regions within the SN. Additionally, we recorded neural activity from female mice (N = 3 female C57BL/6N), allowing exploration of potential sex differences in SN DA neuron activity. We are currently investigating these datasets.

Future work will focus on refining DA neuron identification using pharmacological tagging strategies to enable more precise classification of neurons within the SN.

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Poster

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Topic: F.03. Basal Ganglia

Support: NINDS Grant U01NS133760

Title: A ground truth dataset for electrophysiology-based cell type classification in the basal ganglia and midbrain

Authors: *A. A. LAKUNINA[1], V. ARORA[2], C. L. HURWITZ[3], M. OLSEN[4], S. NARAYAN[5], B. TASIC[5], E. L. DYER[2], K. SVOBODA[4], J. H. SIEGLE[4];
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Abstract: Recently developed cell type taxonomies for the mouse brain, based on single-cell RNA sequencing, organize neuronal and non-neuronal cells into 338 "subclasses," encompassing populations such as cortical layer 2/3 intratelencephalic neurons and striatal ‘direct’ and ‘indirect’ pathway medium spiny neurons (dMSN. iMSN). Understanding the function of each subclass requires identifying them in vivo, such that their activity can be monitored in the context of behavior. The standard method in electrophysiology is via "optotagging," but this technique suffers from low yield and the need for complex genetic manipulations. Alternative approaches that classify cells based on waveform and spiking patterns have shown promise for a small number of neuron types, but validated ground truth datasets required for robust training are lacking. To date, publicly available optotagging data only exists for three neocortical inhibitory interneuron subclasses and four cerebellar/pontine subclasses. To fill this gap, we performed optotagging across a range of subcortical regions, including dorsal and ventral striatum, globus pallidus, and midbrain reticular nucleus. We used Neuropixels Opto probes with integrated light emission sites (Lakunina et al., 2025 bioRxiv), which enabled optotagging of two cell types in parallel: one expressing a red-shifted opsin and one expressing a blue-shifted opsin. Distinguishing cell types in the striatum is of particular interest to the field, as the dMSNs and iMSNs have proven difficult to distinguish based on electrophysiological features alone, despite their divergent projection patterns and effects on behavior. Our dorsal striatum dataset consists of at least 172 opto-tagged dMSNs and 161 iMSNs, as well as 36 cholinergic cells and 10 parvalbumin-expressing interneurons, all passing stringent quality control and registered to the mouse common coordinate framework (CCF). This dataset allows iterative testing of automated

classifiers tailored to each brain region. We are evaluating a spatiotemporal transformer model that captures both within-neuron dynamics and between-neuron interactions—an approach well suited to distinguishing dMSNs and iMSNs, whose waveforms and inter-spike interval distributions are nearly identical. By extending ground-truth electrophysiology datasets to new regions and developing advanced classification models, our goal is to build a “lookup table” linking neuron types and electrophysiological signatures. Such a resource would empower the neuroscience community to more readily identify neuronal subclasses in vivo, advancing our understanding of their role in behavior.

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Poster

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Topic: F.03. Basal Ganglia

Support: NIH Grant R01NS125814

Title: Reduction in TRPC3 conductance is a key factor in altered substantia nigra pars reticulata (SNr) activity under dopamine depletion

Authors: *J. E. RUBIN[1], J. E. PARKER[1], A. ARISTIETA[2], A. H. GITTIS[3];
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Abstract: The standard view of Parkinson's disease asserts that reduced dopamine levels cause a variety of alterations in firing throughout the basal ganglia, which in turn manifest as motor symptoms. Reported activity changes include alterations in firing rate, in correlation structure and synchrony, and in firing patterns including spike timing variability and prevalence of bursting. A detailed evaluation of activity changes under dopamine depletion is significantly more subtle than this general picture would suggest, however, because activity within basal ganglia neuronal populations is heterogeneous, with diverse firing patterns occurring across neurons within the same region. To better understand effects of dopamine depletion on basal ganglia outputs, we recorded from neurons in the mouse substantia nigra pars reticulata (SNr) under control and dopamine depleted conditions, capturing and providing a detailed characterization both of spontaneous firing and of responses to optogenetic stimulation of synaptic terminals from globus pallidus and striatum that project to SNr. Our data exhibited distributions of a range of firing properties, with significant overlap across the control and dopamine depleted cases. We then turned to computational modeling to generate predictions about which changes in SNr neuron properties under dopamine depletion underlie the alterations in SNr firing that we recorded. To derive a computational model that reproduces the

experimentally observed firing heterogeneity, we adopted a novel approach that included (1) generating a large set of model neurons and building a base network from those that best aligned with individual recordings and (2) sequentially spawning offspring networks from previously successful ones and then selecting the subset that best matched additional constraints. Our modeling predicts that, while various factors including changes in inputs and in KCC2 conductance may contribute, reduced TRPC3 conductance in SNr dendrites is the critical determinant of altered SNr activity in the dopamine depleted state.

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Poster

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Title: Learning improves the temporal precision of dopaminergic reward omission dips

Authors: *R. LI[1], T. B. DAW[1], A. SÁNCHEZ-FUENTES[4], C. LONG[2], D. V. BUONOMANO[3], S. C. MASMANIDIS[1];
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Abstract: Dopaminergic reward prediction error signals are critical for reinforcement learning and contain information about reward timing. However, their temporal properties as a function of learning are not fully characterized. This work examines an understudied signature of timing in dopaminergic signals: the transient dip in dopaminergic activity that occurs when predicted rewards are omitted. These dips, a form of negative reward prediction error, provide a powerful teaching signal for reinforcement learning. We present novel experimental evidence showing that omission dips also provide an effective neurophysiological readout of predicted reward timing. We used dopamine sensor dLight1.2 and fiber photometry to measure ventral striatal dopaminergic dynamics in mice undergoing Pavlovian reward trace conditioning where an olfactory cue was paired with a reward following a fixed interstimulus interval. Each session consisted of 200 trials, and reward was omitted on 10-15% of these trials. We first examined how the properties of dopaminergic signals and anticipatory behavior on omission trials evolved across the first four days of training (2.5 s interstimulus interval). As mice learned the task, they showed a higher incidence of anticipatory licking during or shortly after the interstimulus interval. In parallel, the first lick time became more consistent across trials, while the mean first lick time remained constant. This implies that learning impacted both the probability and temporal precision of reward-conditioned motor responses. Alongside these behavioral changes, the dopaminergic reward omission dips increased in magnitude, their trough timing became more

consistent from trial to trial, and their mean trough time remained constant. Crucially, the timing of reward omission dips was a significantly better predictor of motor timing than the timing of cue-evoked dopaminergic peaks. To further characterize the temporal properties of dopaminergic reward omission dips, we trained a separate group of mice to associate two distinct cues with different interstimulus intervals (1.5 and 3.5 s). After training, both the mean and variance of the first lick time scaled with the time to reward in a cue-dependent manner. We found corresponding temporal scaling properties in dopaminergic reward omission dips, with both the mean and variance of the dip time scaling with the interstimulus interval. Taken together, these results show that the temporal properties of dopaminergic reward omission dips evolve with learning and scale with the interstimulus interval, suggesting that dips may share a common timing mechanism with reward-conditioned motor responses.

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Poster

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Topic: F.03. Basal Ganglia

Title: To move or not to move - the differential contribution of dopamine substantia nigra neurons to voluntary movement

Authors: *D. SCHENKEL, P. VOGEL, N. HAMMER, J. ROEPER;
Inst. of Neurophysiol., Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: Dopamine substantia nigra (DA SN) neurons are important for voluntary movement control and their degeneration in Parkinson Disease leads to motor impairments. We performed chronic multi-electrode recordings in awake freely moving male C57Bl/6N mice, aged 8 - 16 weeks, while simultaneously tracking their movements in an open field. We identified putative DA SN neurons by their response (>50% reduction of mean firing rate) to the systemically injected D2-receptor agonist quinpirole. In accordance to Da Silva et al. (2018), our data set of n=59 (N=16) putative DA SN neurons confirmed the non-uniformity of electrical activity of DA SN neurons associated with self-paced movement initiation and termination: only 30% of DA SN neurons (n=17/59) significantly increased their firing rates (baseline to max: +5.3 ± 4.8Hz, mean ± SD) in a 500ms time window before accelerometer-defined initiation of self-paced movements. A similar fraction (ca. 30%; n=18/59) of different DA SN neurons transiently decreased their firing rates (baseline to min: -3.6 ± 1.2Hz, mean ± SD) shortly after initiation of self-paced movements in a 500ms time window. A topographical analysis of anatomical positions of recorded DA SN showed that those neurons with transient rate reductions before movement initiation were about twice as prominent in the medial SN (n=11/22) compared to the central SN (n=7/30). Moreover, inhibitory responses were not found in the lateral SN (n=0/7). In

contrast, the proportion of DA SN neurons with transient rate increases prior to movement initiation were about three-fold more prominent in central SN (n=13/30) compared to medial SN (n=3/22) and lateral SN (n=1/7). As topographical positions of DA SN neurons have been shown to be associated with axonal projections (Farassat et al. 2019), we are currently recording DA SN neurons with identified axonal projections. Here, we apply a recently established protocol (Hammer et al. 2023) to use AA9-based retrograde axonal tracing for selective expression of the inhibitory DREADD hM4D in DA SN neurons. We identify axonal projections, e.g to the dorsolateral striatum, by inhibitory rate changes in response to the systemic application of the selective DREADD agonist deschloroclozapine (DCZ). Moreover, we have extended our accelerometer-based movement analysis to DeepLabCut-based video analysis, where similar pre-locomotion onset excitation and post-locomotion onset inhibition patterns were observed. We aim to present the motion and locomotion-associated firing patterns of projections identified DA SN neurons.

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Poster

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Title: Characterization of striatal cholinergic and dopaminergic signaling during the acquisition and maintenance of skilled motor behaviors

Authors: *A. T. HODGE[1], C. BURGESS[2], D. K. LEVENTHAL[1];
[1]Neurol., [2]Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Cortico-striatal plasticity is essential to learn coordinated dexterous movements and is regulated by striatal dopamine (DA) and acetylcholine (Ach). Their release is highly correlated and may be mutually regulatory, but the degree to which this relationship is necessary for normal motor learning and dexterous motor control is unclear. We have shown that DA dynamics evolve with skilled reaching training to reflect specific subactions and reach success. To determine the relationship of DA dynamics, Ach dynamics, and dexterous motor control, we used 2-color fiber photometry to simultaneously track DA and Ach dynamics in the dorsolateral or dorsomedial striatum of mice as they learned to perform a dexterous reach-to-grasp task. The correlation between striatal DA and Ach release is unaffected by training experience, striatal subregion, or individual trial outcome. Reach-related DA dynamics are similar to those that we have previously reported. Both DA and Ach signals are sensitive to task outcome in a subregion-

specific manner, with dynamic peaks varying in amplitude depending on whether a given trial was successful or *how* a trial failed. However, DA and Ach signals are primarily aligned to different subactions within the reach-to-grasp movement. The degree of outcome sensitivity within striatal subregions also differs between DA and Ach signaling. This indicates that while tightly correlated, striatal DA and Ach subserve distinct functions during the complex and coordinated reach-to-grasp behavior. These results provide a more complete model of how cortico-striatal plasticity is regulated during dexterous motor control, as well as insights into the mechanisms behind loss of dexterous motor control in disease states.

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Poster

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Title: The superior colliculus strongly excites cholinergic and glutamatergic neurons in the pedunculopontine nucleus

Authors: *B. J. BERNSTEIN[1], P. A. FORCELLI[2], R. C. EVANS[1];
[1]Neurosci., Georgetown Univ. Med. Ctr., Washington, DC; [2]Dept of Pharmacol. & Physiol., Georgetown Univ., Washington, DC

Abstract: Sensory-motor integration in the brainstem is crucial for daily functioning and ultimately survival. Two structures involved in this process are the pedunculopontine nucleus (PPN) and the superior colliculus (SC). The PPN is a heterogeneous structure that is critical for sleep, arousal, and motor function and is implicated in both Parkinson's disease (PD) and epilepsy. Stimulation of the PPN is therapeutic in animal models of both disorders with a topography that is specific to cell type and location. The SC is important for integrating multisensory inputs to trigger motor responses, but the effect of SC projections to subregions and different cell types of the PPN is unknown. To address this gap in knowledge, we injected channelrhodopsin (ChR2) into the SC of ChAT-Cre/Ai9, Vglut2-Cre/Ai9, and Vgat-Cre/Ai9 (tdTomato) mice to determine functional connectivity between SC synaptic inputs to PPN subpopulations using optogenetics and whole-cell patch clamp recordings in *ex vivo* brain slices. We find that almost all cholinergic and glutamatergic PPN neurons recorded received excitatory synaptic input from the SC compared to around 75% of GABAergic PPN neurons. Since these cell types also show diverse motor effects across the rostral-caudal axis of the PPN, we separated this data into rostral and caudal subgroups. Comparing across cell types, we find that the SC

sends stronger projections to the caudal PPN cholinergic neurons compared to caudal glutamatergic and GABAergic neurons, as measured by the amplitude of excitatory postsynaptic currents (EPSCs). We also measured inhibitory connectivity and find that inhibitory SC inputs have a higher probability of connectivity and larger amplitude currents in the caudal cholinergic PPN compared to the rostral subregion. Based on these results, we are using rabies viral tracing to dissect the anatomical organization of connectivity from the SC to PPN subpopulations. Additionally, we are evaluating the behavioral outcomes of the SC projections to the PPN subpopulations using *in vivo* fiber photometry. Given the important role the PPN plays in regulating arousal states and motor function, uncovering how the PPN responds to different inputs from the SC is important in understanding the modulation of movement in response to sensory stimuli.

Disclosures: B.J. Bernstein: None. **P.A. Forcelli:** None. **R.C. Evans:** None.

Poster

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Topic: F.03. Basal Ganglia

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Title: Comprehensive mapping of SST^+, TH^+, PV^+, and $ChAT^+$interneurons across the mouse dorsal striatum

Authors: *J. M. MUHSINOV[1], E. ILIAKIS[2], W. TU[2], A. RAMIREZ[4], M. V. FUCCILLO[3]; [1]Col. of Arts and Sci., [3]Neurosci., [2]Univ. of Pennsylvania, Philadelphia, PA; [4]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: The dorsal striatum orchestrates motor control, action selection, and habit learning through a balance of excitatory inputs from thalamus and cortex and inhibitory control from interneurons. Recent developments highlight distributed behavioral functions along the anteroposterior and mediolateral striatal axes. Although interneurons critically shape striatal output, a comprehensive cell type specific atlas of their spatial distribution and density within the entire dorsal striatum is lacking. To address this gap, we quantitatively mapped four genetically defined interneuron classes: somatostatin-positive (SST+), tyrosine hydroxylase-positive (TH+), parvalbumin-positive (PV+), and choline acetyltransferase-positive (ChAT+) neurons across the adult mouse dorsal striatum. We have used validated Cre-driver mouse line mice crossed to the Ai14-tdTomato reporter to robustly express tdTomato in interneurons throughout the dorsal striatum. Automated detection of interneurons was mapped onto the Allen Mouse Brain Atlas (CCFv3) to quantitatively describe the localization and density of four major interneuron subtypes. Our results provide a comprehensive map of the distribution of these interneuron

subtypes along the anteroposterior, mediolateral, and dorsoventral axes of the dorsal striatum. We replicate known distribution patterns of striatal interneurons, including higher abundance of PV+ interneurons laterally, and reveal previously unknown density gradients along the anteroposterior axis. By providing the first comprehensive, genetically defined atlas of major interneuron classes in the mouse dorsal striatum, our study has laid the groundwork for targeted investigations into how these cell types contribute to striatal network function in health and disease.

Disclosures: J.M. Muhsinov: None. **E. Iliakis:** None. **W. Tu:** None. **A. Ramirez:** None. **M.V. Fuccillo:** None.

Poster

PSTR453: Basal Ganglia: Physiology and Plasticity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.16/V4

Topic: F.03. Basal Ganglia

Support: HHMI Gilliam Fellowship GT17029
BRAIN Initiative K99/R00 R00NS112417

Title: Cholinergic neurons in the pedunculopontine nucleus receive local glutamatergic input

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Abstract: The pedunculopontine nucleus (PPN) influences motor control and serves as a therapeutic target for deep brain stimulation (DBS) in Parkinson's disease, but is not consistently effective. The PPN contains cholinergic, glutamatergic, and GABAergic subtypes and is divided into a rostral and caudal region. The heterogeneity of the PPN may underlie the highly variable DBS outcomes. Indeed, the rostral and caudal cholinergic PPN have different connectivity with the basal ganglia and may operate as separate populations. However, little is known about the local circuitry between PPN subpopulations. To understand the degree of local excitatory synaptic input provided to the cholinergic PPN, we injected a CamKIIa-promoted channelrhodopsin (ChR2) into the PPN of ChAT-cre/Ai9 mice and recorded from PPN cholinergic neurons using whole-cell patch clamp electrophysiology and optogenetics to activate CamKIIa-positive PPN cell bodies and axons. We find strong local connectivity from glutamatergic to cholinergic neurons within the PPN. The strength and characteristics of this synaptic connection did not differ between the rostral and caudal regions. Interestingly, in these voltage-clamp experiments, we saw that both rostral and caudal cholinergic PPN cells exhibit a decrease in baseline current upon application of GABA blockers, suggesting that these neurons may be under the influence of a tonic GABA current. To further investigate this, we conducted a separate set of voltage-clamp whole-cell patch clamp electrophysiology experiments in ChAT-

cre/Ai9 mice and recorded the holding current required to keep the cells at -50 mV during sequential local y-tube application of Gabazine and CGP, GABA-A and GABA-B receptor blockers, respectively. Our early experiments show that the tonic GABA current appears stronger in the caudal cholinergic neurons. We also plan to investigate if the cholinergic PPN receives local inhibitory input and evaluate if the tonic GABA current is partially regulated by local GABAergic input onto the cholinergic PPN neurons. Uncovering the local connectivity between PPN subpopulations in a healthy condition will help us better understand how the PPN functions locally to regulate motor function.

Disclosures: L.A. Russ: None. **R.C. Evans:** None.

Poster

PSTR453: Basal Ganglia: Physiology and Plasticity

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.17/V5

Topic: F.03. Basal Ganglia

Support: German Research Foundation – Project-ID 424778381 – TRR 295
Parkinson Foundation Postdoctoral Award

Title: Behavioral dynamics of cortico-subthalamic neuronal patterns during dyskinesia in Parkinson's disease

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Abstract: People with Parkinson's disease suffer from levodopa-induced dyskinesia, adversely to chronic dopaminergic medication. These involuntary movements affect quality of life and are linked to lowered motor inhibition in the cortico-basal-ganglia motor network during hyperdopaminergic states. Several cortical and subcortical spectral biomarkers are associated with dyskinesia, but the oscillatory patterns associated with the behavioral complexity of involuntary movement and voluntary movement suppression that defines dyskinesia, is not studied so far. To elucidate these spatio-temporal dynamics and its behavioral relevance, we studied cortico-subthalamic oscillations in 21 Parkinson's patients during a dyskinesia-provoking experiment. We differentiated between non-dyskinetic and dyskinetic periods, and split data based on a kinematic movement registration, leading to respectively resting states and voluntary movement, and active movement suppression and dyskinetic movement. Elevated theta-activity and attenuated beta-activity was found in the subthalamic nucleus during voluntary movement suppression within dyskinetic periods, while cortico-subthalamic gamma-activity was only elevated during dyskinetic movement presence. Subthalamic spectral changes significantly

predicted dyskinesia presence, and the amount of registered movement significantly affected the predictive value of dyskinesia predictions. We propose a dyskinetic macrostate to consist of distinct behavioral microstates of dyskinetic movements versus movement suppression, both associated with distinct oscillations in the cortico-subthalamic motor network.

Disclosures: J. Habets: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Parkinson Foundation. **R. Lofredi:** None. **W. Neumann:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); DRG, ERC. **A.A. Kuehn:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); DRG. F. Consulting Fees (e.g., advisory boards); Medtronic.

Poster

PSTR454: Cortical Planning and Execution: Human Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.01/V6

Topic: F.04. Voluntary Movements

Title: Closed-loop neurofeedback training of event-related desynchronization of sensorimotor rhythm speeds up movement initiation in human whole-body movement: A double-blind sham-controlled study

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Abstract: Humans are capable of generating coordinated muscle activity during whole-body voluntary movements, such as dancing, walking, and running. Recent meta-analysis showed that neurofeedback training (NFT) for motor cortical activities enhances ability for rapid motor responses to sensory cues. However, it remains unclear whether such NFT is effective for improving whole-body motor responses. This study aimed to develop a neurofeedback protocol usable in real-world physical environments and to evaluate its potential to improve motor performance. Forty-three healthy adults (30 males and 13 females) were randomly assigned to an experimental group (n = 23) or a control group (n = 20). Participants performed a reaction task from a crouching start position, simulating an athletic posture. Reaction time (RT) was measured using electromyography (RT-EMG) during voluntary movement initiation in response to auditory cues. The experiment spanned three consecutive days: baseline RT was recorded on Day 1, and NFT effects were assessed pre- and post-intervention on Day 3. Electroencephalogram was used for real-time acquisition of sensorimotor rhythm (SMR) from the left motor cortex (C3) using a mobile system (eego^{TM}sports), and NFT using sonification of SMR magnitude was implemented to provide feedback of the magnitude of event-related desynchronization (SMR-ERD), that reflects motor cortical excitability. The experimental group received real-time feedback from their own EEG, while the control group received prerecorded feedback from others. The sonified SMR-ERD was presented throughout training in both groups.

For the RT calculation, we employed Grubbs' test to exclude outliers from RT-EMG data using MATLAB 2023b. A two-way repeated-measures ANOVA revealed a significant interaction between Group and Time ($p < 0.05$, $\eta^2 = 0.119$). Post hoc Tukey tests showed a significant reduction in RT from pre- to post-NFT in the experimental group ($p < 0.05$, $d = 0.501$), with no significant change in the control group. These results indicate that NFT for volitional regulation of SMR-ERD contributes to reduction of RT during whole-body movement.

Disclosures: H. Tanaka: None. **S. Iwama:** None. **J. Ushiba:** A. Employment/Salary (full or part-time): A representative director of LIFESCAPES Inc., receiving a salary and holding shares in the company, in which this research did not receive any equipment, financial support, or human resources..

Poster

PSTR454: Cortical Planning and Execution: Human Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.02/V7

Topic: F.04. Voluntary Movements

Title: Subjectively spontaneous decisions are more difficult to predict based on brain activity

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Abstract: Spontaneous decisions feel immediate and free, however neuroimaging studies suggest they may be initiated in the brain well before our awareness of them. To test how early such decisions can be decoded from brain data, we invited two groups of 21 participants each to make simple motor decisions while recording electroencephalography (EEG) data. One group was asked to decide between pressing a button with their right or left hand. The other group was asked to decide between pressing or not pressing a button with their right hand (after a set delay). On some trials we asked participants to make these decisions spontaneously, and on other trials we asked them to premeditate and decide well in advance. In offline analyses, we trained multiple powerful machine learning algorithms to predict the upcoming decisions. We found that despite being able to decode upcoming premeditated decisions well in advance, decisions that were made spontaneously could only be decoded within a short window immediately preceding the action. This result better aligns with the experience of spontaneously deciding. These distinct temporal profiles of spontaneous versus premeditated decisions have implications for models of volition and motor preparation.

Disclosures: L. Jeay-Bizot: None. **A. Whitmarsh:** None. **U. Maoz:** None. **A. Schurger:** None.

Poster

PSTR454: Cortical Planning and Execution: Human Neurophysiology

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Program #/Poster #: PSTR454.03/V8

Topic: F.04. Voluntary Movements

Support: dtec.bw/MEXT (European Union - NextGenerationEU)
University of the Bundeswehr Munich

Title: The influence of pulse shape and current direction of TMS on test-retest reliability, and variability of measurement outcomes.

Authors: *D. AGBOADA[1], R. RETHWILM[2], W. SEIBERL[2], W. MACK[1];
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Abstract: Background: Pulse parameters of transcranial magnetic stimulation (TMS) critically affect the stimulation outcomes. There is, however, a lack of understanding on how these parameters influence test-retest reliability and variability of single-pulse TMS protocols. Objectives: This study aims to investigate the effects of four combinations of pulse shapes and current directions (TMS-waveform conditions) on outcome measurements, test-retest reliability, and variability. Methods: Using robot-assisted neuronavigation, nineteen participants were stimulated with four TMS-waveform conditions in three repeated sessions within the same day. Sessions 1 and 2, and Sessions 1 and 3 were separated by 30 min, and approximately 7 h, respectively. The four TMS-waveform conditions were: biphasic and monophasic pulses delivered in either posterior-anterior (PA) or anterior-posterior (AP) current directions. TMS protocols investigated were resting/active motor thresholds, stimulus intensity for inducing 1 mV peak-to-peak motor-evoked potential (MEP) amplitude, corticospinal excitability measurements (MEP amplitudes and latencies) with three inter-stimulus intervals (ISIs) of 5, 10, and 15 s; input-output (I/O) curve, and cortical silent period. Results: TMS-waveform influenced all spTMS protocol outcome measures except for the I/O. TMS pulses in the PA current direction generally induced less variable MEP amplitudes and latencies. Moderate to excellent test-retest reliability was also found for all protocols except the I/O, however TMS-waveform only influenced the reliability of the AMT and MEP latency protocols. Monophasic pulses in the PA direction were more reliable compared to pulses in AP for MEP latency, while biphasic pulses in the AP direction showed significantly lower reliability compared to other TMS-waveform conditions for the AMT. Conclusion: This systematic evaluation does shed more light on protocols and TMS pulse parameters that induce reliable and less variable measurements.

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Poster

PSTR454: Cortical Planning and Execution: Human Neurophysiology

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Program #/Poster #: PSTR454.04/V9

Topic: F.04. Voluntary Movements

Support: 1R01NS134772-01, NINDS, NIH
OHSU Parkinson's Center Pilot Grant
Medical Research Foundation of Oregon New Investigator Grant

Title: Electrophysiology of motor imagery in parkinson's disease

Authors: *S. AYOUBIPOUR[1], A. KAREKAL[1], H.-Y. HAWONG[2], C. MUÑIZ SANCHEZ[1], N. C. SWANN[1];
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Abstract: Motor imagery (MI) shares neural processes with movement execution (ME), and it has been suggested that it may hold therapeutic potential as an intervention to improve motor function in Parkinson's disease (PD). Electroencephalography (EEG) studies during ME show beta (13-30 Hz) power decreases during movement. Similar modulations, though reduced in amplitude, are observed in MI. Alternations in beta dynamics have been observed in PD during movement, and one study observed alternations in electrophysiological complexity during MI and ME. While not implicated in MI specifically, theta activity (4-8 Hz) is involved in cognition and altered in PD. However, electrophysiological studies exploring differences between MI and ME in PD remain scarce, particularly in the context of dopaminergic medication. To address this gap, we recorded 64-channel EEG from 20 PD patients (6 females; mean age = 68.6 ± 7.9 years) ON and OFF medication, and 23 age-matched healthy controls (HC; 15 females; mean age = 70.5 ± 6.6 years), during ME and kinesthetic MI tasks. Average beta and theta power from sensorimotor (C3, C4) and mid-frontal (Fz) electrodes were extracted with a Morlet wavelet. Cluster-based permutation tests were conducted for power across time for MI and ME tasks, between PD ON and OFF medications (paired) and HC and PD (unpaired). Theta power decreased during MI for all groups, but this decrease was more pronounced during certain time intervals for HC compared to PD ON over ipsilateral sensorimotor cortex ($p<0.05$). Theta power also decreased during ME in contralateral sensorimotor cortex, and this decrease was more pronounced in PD ON compared to HC shortly after movement initiation ($p<0.05$). Beta power decreased during ME for all groups. This decrease was significantly larger in later phases of continuous movement for HC compared to PD OFF in midfrontal and ipsilateral sensorimotor cortex ($p<0.05$). Overall, average theta and beta power decreased during ME and MI for all groups. For ME, beta dynamics differed between groups over midfrontal and ipsilateral, but not contralateral sensorimotor cortex. Interestingly, theta activity was modulated between groups over contralateral sensorimotor cortex. In MI, on the other hand, theta power differed between groups over ipsilateral sensorimotor cortex. This work suggests that both theta and beta are modulated by MI and ME, and these dynamics differ as a function of PD and PD medication. Future research may consider neurofeedback combined with MI to better understand MI-related neural processes.

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Poster

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Topic: F.04. Voluntary Movements

Support: NIH Grant 1R21EY032180-01A1

Title: Mapping the human action observation network using stereo-EEG recordings and neural manifold analyses

Authors: *L. POLLINA[1,2], M. ARMENDARIZ[2], S. SHOKUR[1,3,4], G. KREIMAN[2], S. MICERA[1,4], A. CASILE[5];
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Abstract: In primates, a network of areas in parietal and frontal cortices is active both during action execution and observation (Action Observation Network, AON). This system is thought to support key cognitive functions such as motor learning, action understanding, and social interaction. Key questions regarding the AON are the temporal dynamics of neuronal activations within and between nodes and their similarities and differences during action observation and execution. Non-invasive techniques, normally used in humans, cannot conclusively resolve these issues because of their intrinsic spatial and temporal trade-off. Here, we leveraged intracranial stereo-EEG recordings and modern neuronal manifold analysis to overcome this limitation. In our experiments, 12 individuals with drug-resistant epilepsy performed or observed reach-to-grasp actions toward different objects with either a precision or power grip, while we recorded their neural activity with electrodes implanted for clinical purposes. Despite inter-subject variability in electrode placement, this approach enabled a broad sampling of cortical areas. We first used power spectral density analysis to identify electrodes showing modulations in their activity during action execution and/or observation in several frequency bands. Consistent with previous results, this analysis revealed a distributed fronto-parietal network encompassing the superior frontal, precentral, postcentral, superior parietal, supramarginal gyri, and the insular cortex. Interestingly, sensorimotor cortices in the precentral and postcentral gyri showed modulation across multiple frequency bands while other regions within the network displayed frequency-specific responses. Novel to this study, we investigated the functioning of this network of areas by means of a neural manifold approach. To this end, within each responsive brain region, we applied Principal Component Analysis across channels and frequency bands to uncover low-dimensional neural representations. Notably, we found that these manifolds captured both shared- and condition-specific activity patterns for execution and observation. We quantified manifold alignment between conditions and assessed if these neural representations encoded task-relevant information by decoding grasp type from projected neural activity. Our findings provide new insights into the spatial and spectral organization of the human action-

observation network, and they further support the usefulness of neural manifold analysis in characterizing cognitive and motor representations across the brain.

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Poster

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Program #/Poster #: PSTR454.06/V11

Topic: F.04. Voluntary Movements

Support: NIHR Imperial BRC PhD Fellowship

Title: Rapid, simultaneous cortical mapping of multiple upper limb muscles: Enhancing protocols for clinical application

Authors: *R. BOYLES, N. KIATWONGWANICH, M. VICENTE, S. ZIBORDI, P. H. STRUTTON;
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Abstract: Introduction: Neuronavigated transcranial magnetic stimulation (TMS) enables rapid mapping of corticospinal connectivity and drive which can be used to determine motor cortex organisation and function in both healthy and neurologically impaired populations. Mapping studies typically analyse responses from a single muscle, but the ability to produce cortical maps for several muscles simultaneously may be useful after neurological events such as spinal cord injury or stroke, since independent physical function requires coordinated control of multiple muscle groups. Previous studies mapping multiple upper limb muscles have used time-intensive grid-based mapping or produced inconsistent results for proximal muscles. The present study used a modified mapping protocol to facilitate mapping of proximal as well as distal muscles, and incorporated advances in offline automatic MEP latency analysis to enable thorough characterisation of MEP latencies throughout the motor representation of a given muscle.
Methods: Nineteen healthy participants (11 female) were recruited. Neuronavigated TMS was performed and surface EMG recorded from 8 upper limb muscles. Cortical maps were produced by stimulating 80 times in random walk fashion at 1.2, 1.4, 1.8 and 2.0 times resting motor threshold (RMT) for the first dorsal interosseus (FDI) muscle over a 6 x 6 cm grid centred over the FDI hotspot. An ‘active’ map was recorded at 1.2 times RMT whilst the participant contracted their upper limb muscles. Cortical maps based on MEP amplitude were produced using a method previously described. We used a modified version of an existing latency analysis software to extract MEP latencies and create latency maps.
Results: Simultaneous mapping produced somatotopic centres of gravity (CoG) for all muscles tested. Map area and volume increased with increasing stimulus intensity and in active vs resting conditions. Distal muscle maps were larger than proximal muscle maps. Map area and volume

for proximal muscles were modulated more by background activity, but for distal muscles more by stimulation intensity. As expected, MEP latencies were shorter in active conditions and for proximal muscles; however, they did not vary linearly with distance from a muscle's CoG. Conclusion: Neuronavigated cortical mapping facilitates rapid, comprehensive assessment of corticomotor drive for multiple upper limb muscles in healthy individuals. Muscle activation resulted in more reliable responses from proximal muscles than at rest. A version of this protocol may be useful for characterising the extent of corticospinal sparing after neurological injury, for example in spinal cord injury or stroke.

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Poster

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Program #/Poster #: PSTR454.07/W1

Topic: F.04. Voluntary Movements

Support: John Templeton Foundation #61283
Fetzer Memorial Trust #4189

Title: Motor-cortical neuronal activity during movement preparation—hard-wired or under volitional control? An intracranial study in humans.

Authors: C. VERBAARSCHOT[1,4], A. DE MIGUEL GOMEZ[5], A. SCHURGER[6], J. L. COLLINGER[2], R. A. GAUNT[3], ***U. MAOZ**[5,7,8];
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Abstract: After more than a century and a half of research, much about the functional role of motor cortex in motor preparation remains unknown. To better understand motor cortex function, we worked with three human participants implanted with intracranial electrodes in motor and somatosensory cortex. Our machine-learning classifier found spiking patterns that were highly predictive of upcoming movement in real time (>80% accuracy). We then investigated three research questions. (1) To what extent is the neuronal activity leading up to voluntary action hard-wired versus under volitional control? (2) Are humans aware of their decision to move by the time that the preparatory motor-cortical activity is apparent? (3) How similar are the neural signatures of the same movement in the motor cortex across different tasks?
Participants played a strategic game, where their objective was to flip as much slime as possible from a slow-filling bucket on a virtual "robot" opponent before it flipped the bucket on them. The robot was activated by a real-time classifier that tracked the participant's intention to move. Hence, to win, participants needed to alter their preparatory neuronal activity. However, in

multiple sessions over days and weeks, participants lost to the robot on more than 80% of the trials. They also reported being aware of their decision to move when the robot flipped the bucket on them (~90% of the time). Moreover, the classifier predicted movement similarly well in a different setting, when participants scrolled through visual content in a self-paced manner. Our study thus provides evidence for limited volitional control of motor-preparatory neuronal activity in motor cortex rather than full conscious control.

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Poster

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Program #/Poster #: PSTR454.08/W2

Topic: F.04. Voluntary Movements

Support: JPMJPR21S4
23H04329

Title: Anticipatory breath holding as a proactive adjustment for voluntary movements

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Abstract: Breathing is essential for our life through gas exchange and is also closely linked to the regulation of cognitive functions and motor control. Many studies have reported that respiration modulates the oscillation of neuronal activity, particularly in the cerebral cortex, and influences behavior. For example, response to the auditory stimulus is faster during inhalation than exhalation phase (Gallego et al., 1991). While controlling respiratory phases has the potential to enhance performance, no studies have suggested its practical application in behavior. Therefore, in this study, we analyzed respiratory phases during the anticipatory period to assess whether respiration is proactively modulated before motor execution.We used two saccade paradigms: a pro-saccade task, in which participants made a reflexive saccade toward the visual target, and an anti-saccade task, in which they suppressed a saccade to the visual target (pro-saccade) and voluntarily made saccades away from it. Each trial began when the participant pressed a button, after which a white fixation point appeared at the center of the screen (Start-cue). Then, it changed color to indicate the task rule (Instruction-cue). Following a fixation period of 2,000-4,000 ms, a white cue (Saccade-cue) appeared on the left or right side on the screen, and participants made a saccade according to the task rule. These tasks were conducted under two conditions to examine whether the motivation affects respiratory control: a “feedback condition” in which participants received feedback based on their reaction time at the end of trial and enhance the motivation to the task, and a “no-feedback condition” in which no such

feedback was provided.Among 30 subjects, 28 have held their breath during the anticipatory period (from 1,800 ms after Instruction-cue to Saccade-cue) compared with the baseline period (−1,500 to −500 ms from Start-cue). Additionally, in trials involving anticipatory breath holding, the probability of Saccade-cue being presented during the exhalation phase increased. There is no significant difference in respiratory changes between task difficulty (pro- vs. anti-saccade) and motivational condition (feedback vs. no-feedback). However, in the anti-saccade task, greater respiratory change correlated negatively with reaction time, indicating that stronger modulation led to faster responses. Taken together, although the anticipatory breath-holding was found regardless of the task condition, it affects only the performance of voluntary movement. Respiration may proactively regulate the voluntary movement by adjusting the timing of physiologically stable phase, such as exhalation.

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Poster

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Topic: F.04. Voluntary Movements

Support: Research Council of Finland grant #350528

Title: Menstrual phase-dependent effects of estradiol and progesterone on maximum force, cortical inhibition and facilitation

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Abstract: Estradiol can bind to estrogen receptors of neurons to blunt γ-aminobutyric acid (GABA) and enhance glutamatergic functioning, whereas progesterone may interfere with estrogen receptor availability. Therefore, hormonal fluctuations during the menstrual cycle may alter motor pathway functioning, which could affect motor output. This study examined motor pathway excitability across varying concentrations of estradiol and progesterone corresponding to different phases of the menstrual cycle. Seventeen females (aged 20-30 years) participated in randomized test sessions during the early and late follicular and mid-luteal phases, representing low estradiol/low progesterone, high estradiol/low progesterone, and high estradiol/high progesterone conditions (hormone levels not yet confirmed). Fifteen completed all three sessions; two completed two. The late follicular phase was confirmed by ovulation test-identified estradiol concentration with mid-luteal phase 7-9 days after the luteinizing hormone surge. Each session began between 7-8 AM after an overnight fast and included basal blood sampling, body composition assessment, and electrophysiological testing. Maximal isometric elbow flexion was

performed to measure maximum voluntary contraction (MVC) force and 0-50 ms rate of force development (RFD). Transcranial magnetic stimulation (TMS) elicited motor-evoked potentials (MEPs) via single-pulse (120% of active motor threshold (aMT)) and double-pulse protocols assessing short-interval intracortical inhibition (SICI: 80/120% aMT, 3 ms), long-interval intracortical inhibition (LICI: 120/120% aMT, 50 ms), and intracortical facilitation (ICF: 80/120% aMT, 15 ms). Data were analyzed using repeated measures Generalized Estimating Equations. MVC was greater in the early compared to the late follicular phase (294 N vs. 284 N, P = 0.006) and this was accompanied by greater LICI inhibition (62% vs. 49%, P = 0.033), but the aMT difference did not reach statistical significance (49.6% vs. 46.0% maximum stimulator output, P = 0.053). The mid-luteal phase produced the lowest ICF compared to both early (-18% vs. 6%, P = 0.04) and late follicular (22%, P = 0.045). No other differences were observed between menstrual cycle phases. Cortical excitability and glutamatergic facilitation appear to increase, while GABA-B-mediated inhibition decreases at the late follicular phase. In contrast, mid-luteal phase progesterone appears to negatively affect only glutamatergic facilitation. Despite these neural modulations, motor output does not seem to be influenced. Notably, MVC was highest when both hormone concentrations were at their lowest.

Disclosures: S. Walker: None. **V. Romppanen:** None. **R. Mikkonen:** None. **J. Ihalainen:** None. **D.J. Kidgell:** None.

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.01/W4

Topic: F.05. Brain-Machine Interface

Title: Intuitive avatar control through brain-computer interface induces sense of embodiment in virtual reality

Authors: *T. SERI[1], S. IWAMA[2], J. USHIBA[2];
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Abstract: The sense of embodiment-the feeling that one's body is one's own-is a foundational aspect of self-consciousness. It has been traditionally attributed to multisensory integration of visual and somatosensory feedback, however, emerging frameworks suggest that volitional control over bodily action may also play a causal role in shaping embodiment. Here, we tested the hypothesis that controllability, defined as the successful execution of intended actions, modulates embodiment in the absence of somatosensory input. We developed a brain-computer interface (BCI) system that enables users to control avatar gait in virtual reality, decoding intention based on electroencephalogram (EEG) and eye-gaze. We assessed embodiment both psychologically and physiologically, using questionnaires and auditory event-related potentials (ERPs) elicited by tones presented as the avatar passed through gates. Across three experiments, participants performed motor imagery of gait to initiate and keep movement (N = 32), terminated

imagery to voluntarily stop moving (N = 28), and moved their eye-gaze toward the intended direction to select optimal route (N = 8). Four experimental conditions were tested: observing others' control, using a gaming controller, BCI control based on EEG recorded in real-time, and BCI control based on pre-recorded EEG from another individual. In experiment 1, ERP amplitude was significantly higher when the avatar was controlled by BCI or a gaming controller, compared to just observing others' control [$F(3, 84) = 28.54$; $p < 0.001$]. Questionnaire ratings mirrored this pattern [$F(3) = 78.90$; $p < 0.001$]. In experiment 2, ERP amplitude significantly increased when successfully stopped in front of the gate and restarted movement, compared to simply passing through the gate. [$F(1, 25) = 24.06$; $p < 0.001$]. In experiment 3, ERP amplitude was significantly higher when successfully passed through the intersection in the intended direction, compared to unintended pass [$F(3, 18) = 6.69$; $p = 0.003$]. As a result, ERP amplitude was modulated by controllability, with larger responses when intended actions were successfully executed. Surprisingly, there was no significant difference in questionnaire ratings or ERP amplitude between two BCI conditions. This suggests that alignment between intention and action, rather than closed-loop feedback, may enhance embodiment. Overall, the results indicate that embodiment arises not only from bottom-up multisensory integration, but also from top-down causal inference about controllability. This study provides a novel framework for developing BCI-controlled devices to restore and enhance embodiment.

Disclosures: T. Seri: None. **S. Iwama:** None. **J. Ushiba:** A. Employment/Salary (full or part-time): A representative director of LIFESCAPES Inc., receiving a salary and holding shares in the company, in which this research did not receive any equipment, financial support, or human resources.

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.02/W5

Topic: F.05. Brain-Machine Interface

Title: Transcranial static magnetic stimulation over somatosensory cortex selectively decreases thalamo-cortical input

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Abstract: Transcranial static magnetic field stimulation (tSMS) is a novel, non-invasive brain stimulation technique that reduces cortical excitability simply by placing a neodymium (NdFeB) magnet over the scalp. It has gained attention as a safe and easy-to-administer method for modulating brain activity without electrical current. Previous studies have reported that tSMS over the primary somatosensory cortex (S1) attenuates the amplitude of the N20 component of

somatosensory evoked potentials (SEPs), which reflects the activity of area 3b in the S1. The purpose of this study was to examine the effect of tSMS over the S1 on high-frequency oscillations (HFOs) that is superimposed over the N20. Ten healthy young adults participated in this study. Either tSMS or sham stimulation was placed over the left S1, corresponding to the C3 position of the international 10-20 EEG system, for 20 minutes. SEPs in response to right median nerve stimulation were recorded from the left somatosensory cortex at three time points: before, immediately after, and 20 minutes after the stimulation. SEP waveforms were filtered with a 300 Hz low-pass filter to isolate the N20 component, and with a 400-800 Hz band-pass filter to extract HFOs. The HFOs were further divided into two components: early HFOs (from the N20 onset to the N20 peak), thought to reflect thalamo-cortical input, and late HFOs (from the N20 peak to the P25 peak), attributed to the activity of GABAergic interneurons within the S1. The results showed that tSMS over the left S1 significantly reduced the amplitude of early HFOs 20 minutes after stimulation while no significant changes were observed in the sham condition. Late HFOs remained unaffected in both conditions. These findings suggest that tSMS over the somatosensory cortex selectively suppresses thalamo-cortical input to area 3b, without influencing the activity of local GABAergic interneurons. This study provides novel insight into the physiological mechanisms underlying the modulatory effects of static magnetic fields on sensory cortical processing.

Disclosures: Y. Tanaka: None.

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

Location: SDCC Halls B-H

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Program #/Poster #: PSTR455.03/W6

Topic: F.05. Brain-Machine Interface

Title: Brain-state dependent cues for motor imagery initiation can improve performance in brain-machine interface training

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Abstract: Recent studies suggest that resting-state brain activity prior to task execution may influence subsequent cognitive and motor performance. Likewise, the resting-state sensorimotor activity during brain-machine interface (BMI) rehabilitation, in which participants volitionally regulate excitability of the motor cortex, may influence subsequent BMI performance. However, it remains unclear whether controlling task onset based on resting-state motor cortex activity can improve BMI performance. To address this issue, this study tested whether initiating BMI tasks when a high-amplitude sensorimotor rhythm (SMR), that reflects idling state of the motor cortex, was detected could improve BMI operation performance. We first conducted retrospective analysis using a large-scale historical EEG dataset collected from 30 healthy right-handed

participants performing right-hand extension MI tasks. EEG amplitudes from the C3 electrode were analyzed, and the proportion of high-amplitude sensorimotor rhythms (8-13 Hz) during resting state was quantified. Results indicated a negative correlation between high resting-state amplitude and subsequent MI EEG amplitude, suggesting stronger ERD in trials initiated from higher resting activity. Building on this, we designed a controlled experiment with 28 healthy right-handed volunteers, dividing them into a triggered group (Trig) and a non-triggered group (Non-Trig). In the Trig group, MI tasks were initiated only when a predefined high-amplitude resting EEG threshold was detected. ERD magnitude was used as the primary performance metric. Results showed that the Trig group exhibited significantly stronger ERD during BMI training (GLMM, $F(1, 24.27) = 15.8$, $p < 0.001$, $\eta_p = 0.39$), supporting the hypothesis that initiating training from an optimal brain state enhances task performance. However, no significant difference in learning effect (pre- vs. post-training ERD) was observed between the groups, likely due to the short duration (single-day, 60 trials) of the intervention. These findings suggest that real-time monitoring of resting-state EEG to trigger MI tasks could optimize BMI training sessions, potentially contributing to more effective neurorehabilitation strategies. Future work should investigate the long-term effects of this triggered-BMI paradigm, particularly in clinical populations such as stroke patients.

Disclosures: Y. Katayama: None. **S. Iwama:** None. **J. Ushiba:** A. Employment/Salary (full or part-time): A representative director of LIFESCAPES Inc., receiving a salary and holding shares in the company, in which this research did not receive any equipment, financial support, or human resources..

Poster

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Program #/Poster #: PSTR455.04/W7

Topic: F.05. Brain-Machine Interface

Support: Support from Max Planck Society

Title: Functional plasticity changes after Brain-Computer Interface in chronic stroke: insights from fMRI during motor attempts

Authors: *A. FLORES SANDOVAL[1,3], K. A. GRIGORYAN[1], K. MUELLER[2,4], B. SEHM[1], A. VILLRINGER[1,5,6];
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Abstract: EEG-based brain-computer interface (BCI) training has been shown to facilitate motor recovery in chronic stroke patients, even beyond the limited improvements of traditional therapies. This study aimed to investigate the neural mechanisms underlying BCI-driven rehabilitation in chronic stroke. We hypothesized that a 6-day BCI intervention would promote functional plasticity, reflected as changes in BOLD activity. Twenty chronic stroke patients (5 females; mean age: 60 ± 8.03 years) underwent six consecutive days of BCI training. Fugl-Meyer Assessment for Upper Extremity motor tests were performed before and after the intervention. fMRI scans were acquired twice before (one week apart) and twice after the intervention. During BCI training, participants performed motor imagery of wrist dorsiflexion following auditory and visual cues, and functional electrical stimulation was delivered as feedback. fMRI was recorded during motor attempts paced by a visual metronome. Pre-processing was conducted using the CONN toolbox (v22.a). SPM12 (v7771) was used to calculate first-level contrasts of movement versus no movement. These contrasts were then analysed at the group level in a flexible factorial design to identify changes after BCI training. The changes were localized using the JuBrain Anatomy Toolbox (v3.0). Behaviorally, FMA-UE scores improved significantly after the intervention. Also, after the intervention, a decrease in BOLD responses was observed in the ipsilesional motor cortices (macroanatomy: PreCG and JLC; cytoarchitecture: 6mc, 6dl, and 64a), as well as in the contralesional areas associated with sensorimotor transformations (macroanatomy: PosCG and SPL; cytoarchitecture: areas 2 and 1, as well as IPS). These findings are consistent with neural efficiency gains post-training—a phenomenon observed in motor learning and rehabilitation studies. As prior work indicates that contralesional activity supports motor function in severe hemiparesis, both ipsilesional and contralesional enhanced processing may reflect adaptive plasticity in the present sample (FMA-UE baseline = 25.9). In conclusion, our results suggest that even short-term BCI training may promote the functional rearrangement of sensorimotor areas in chronic stroke patients, potentially reflecting adaptive neuroplastic changes.

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Poster

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Program #/Poster #: PSTR455.05/W8

Topic: F.05. Brain-Machine Interface

Title: Design of a non-invasive BCI system using EEG for cost-effective motor assistive technology

Authors: *G. ISMAIL, C. ROBINETT, A. GUERRERO, S. SATALOF, P. WU, J. EWING, Y.-C. YU, L. A. GABEL;
Lafayette Col., Easton, PA

Abstract: Brain-Computer Interfaces (BCIs) offer promising solutions for individuals with motor impairments by enabling direct communication between neural activity and external devices, such as wheelchairs or service robots. We are designing a modular, real-time brain-computer interface (BCI) system in C++ that integrates OpenBCI hardware and the Lab Streaming Layer (LSL) for synchronized EEG acquisition and low-latency processing. Unlike traditional BCI platforms that rely on lab-grade amplifiers or proprietary software, our architecture leverages commercial off-the-shelf (COTS) components to create a low-cost, deployable solution. The robot will be controlled using relaxation, eye blinking, jaw clenching, and left-right motor imagery. To capture these signals, an EEG cap is used to record occipital alpha power density, frontal muscular artifacts, and sensorimotor mu rhythms. We are using software-based mitigation strategies, alongside high and low-pass filters, to isolate EEG signals from ambient electrical noise. Particular focus is given to interference from household sources not typically present in clinical environments. We are using real-time visual feedback to enhance training procedures in order to improve successful control of the external device. Finally, we are testing whether the participant can use these commands to navigate a robot through a maze, which serves as a model for an assistive device. This research has the potential to contribute to the advancement of non-invasive neurotechnology for assistive device control, as well as to provide a more affordable, accessible, and user-friendly option.

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Poster

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Topic: F.05. Brain-Machine Interface

Support: Nakatani Foundation, a Grant-in-Aid for Scientific Research (B) (#21H03340)
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JKA through its promotion funds from KEIRIN RACE
Tateisi Science and Technology Foundation

Title: Eeg decoding of motor intentions using gel-free microneedle electrodes for brain-machine interfaces

Authors: *T. YAMAGUCHI[1], H. YOKOYAMA[2];
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Abstract: Brain-Machine Interfaces (BMI) offer promising solutions for motor rehabilitation, with electroencephalography (EEG) being the most widely used modality. To routinely

incorporate BMI into rehabilitation practices, it is essential to have EEG electrodes that are both easy to use and capable of recording high-quality signals. Traditional wet electrodes are cumbersome due to the necessity of conductive gel, whereas dry electrodes typically suffer from reduced signal quality. To address these limitations, we fabricated microneedle electrodes (MNEs) designed to penetrate the stratum corneum using fine needles, and we evaluated their performance in decoding motor intention from EEG signals. Our MNEs consisted of 7x7 arrays of microneedles (length: 1500 μm) made from polyimide and coated with Ag/AgCl via electrostatic spray coating. Three healthy young males, confirmed to have sufficient motor imagery (MI) capability using the Vividness of Movement Imagery Questionnaire-2 (VMIQ-2), participated in a stepping MI task. Participants imagined lifting their leg while watching a corresponding video to enhance imagery vividness. Each trial consisted of 3 seconds of MI followed by 6 seconds of rest, repeated 100 times per electrode type. EEG signals were recorded from 10 channels primarily located over the motor cortex at a sampling rate of 1000 Hz. Power spectral density (PSD) in the theta, alpha, beta, and gamma frequency bands, along with slow cortical waves (<4 Hz) in the time domain, were computed from the EEG signals. A shallow neural network was trained using these PSD and cortical wave as inputs for binary classification (Rest vs. Stepping). Classification accuracy was evaluated in the MNEs and conventional wet electrodes. MNEs achieved an average accuracy of 75.0% (±3.2), slightly surpassing the wet electrodes' 72.3% (±7.2). Additionally, the total setup and removal time averaged 6 minutes 48 seconds for MNEs compared to 12 minutes 23 seconds for wet electrodes, highlighting significant operational efficiency improvements. These results indicate that MNEs achieve comparable or superior accuracy in decoding motor intentions while offering a gel-free, user-friendly alternative, underscoring their strong potential for BMIs in routine clinical rehabilitation applications.

Disclosures: T. Yamaguchi: None. **H. Yokoyama:** None.

Poster

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Program #/Poster #: PSTR455.07/W10

Topic: F.05. Brain-Machine Interface

Support: DTRA Contract HQ003419D0006

Title: Evaluating EEG-Based BCI for Screen Interaction in Mobility- and Voice-Constrained Settings

Authors: *L. C. DIAZ, M. E. WIMBISH, J. L. RIVERA, E. J. BUBAR, F. V. TENORE, C. A. SCHOLL, G. W. MILSAP;
Johns Hopkins Univ. Applied Physics Lab., Laurel, MD

Abstract: Noninvasive, electroencephalogram (EEG) -based brain computer interfaces (BCIs) have become more robust in recent years as both hardware and software components have matured. Despite this promising development, the utility of EEG-based BCI outside of laboratory settings has remained largely limited to assistive, novelty, and gaming interfaces, as traditional human interface devices (HIDs) including mouse and voice control consistently outperform EEG-based BCIs. One underexplored domain for EEG-based BCI is to interact with screens while wearing restrictive protective gear, such as a hazmat suit, which can impair motor and voice channels used for traditional HIDs. We designed a closed-loop EEG-based BCI system capable of controlling Bluetooth-enabled devices based on the decoding of steady state visually evoked potentials (SSVEP). Participants were directed to select one of two locations on a screen with both traditional HIDs and SSVEP-based BCI. Traditional HIDs tested were: stylus on a tablet, hand tracking in Augmented Reality (AR), and controllers in AR, as assessed with a center-out task. Traditional and BCI-based screen selections were assessed while still and while walking, and with/without cumbersome hazmat-style personal protective equipment (PPE) on the body. We then compared the accuracy of the center-out task with the SSVEP-based selection within a 2 second reaction time window and found that the SSVEP-based noninvasive BCI showed favorable performance relative to movement and the presence of cumbersome equipment, whereas the native (non-BCI) control was degraded by both conditions, albeit differentially by control type. These results demonstrate potential utility for EEG-based BCI for able-bodied individuals in scenarios where protective gear may impede traditional HID control for interactions with screens.

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Poster

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Program #/Poster #: PSTR455.08/W11

Topic: F.05. Brain-Machine Interface

Support: NSF Grant 1849213

Title: Eeg biomarkers of graded motor effort for rehabilitative brain-computer interface applications

Authors: *S. GARCIA PAVA, S. SUNDERAM;
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Abstract: Rehabilitative brain-computer interfaces (rehab-BCIs) translate neural activity into control signals for motor recovery, enabling user engagement even in the absence of movement. Unlike traditional rehabilitation approaches requiring residual motor function, rehab-BCIs allow individuals with severe impairments to actively participate in therapy. However, most systems

rely on binary movement classification, limiting their ability to reflect the graded nature of motor effort, essential for fine motor rehabilitation and real-time feedback.
We previously demonstrated that event-related desynchronization in the mu-beta band of the EEG reflects graded motor effort during hand grip and finger extension tasks. Even in the absence of overt movement due to spasticity, stroke participants exhibited distinct ERD patterns that enabled above-chance classification of intended effort levels. Building on this, we evaluated two candidate biomarkers for decoding of proportional effort: (1) the ERD spatial vector norm (vERD), and (2) a projection of ERD features, cERD, derived using canonical correlation analysis (CCA) to identify EEG components most correlated with graded effort. With IRB approval, neurotypical participants without a known hand impairment completed six runs per hand, performing visually cued finger extension at four effort levels: no-go, low, medium, and high. Each trial included a 1-4 s preparatory fixation, a 2 s planning cue (target display), a 5 s movement execution phase, and a 2 s rest.
The vERD analysis revealed significant differentiation across effort levels in 14/16 participants (left hand) and 12/16 (right) (Kruskal-Wallis, $p < 0.05$). However, post hoc tests indicated these effects were largely driven by contrasts between movement and no-movement. Notably, monotonic trends in vERD across effort levels were observed in 9 of 16 participants for the right hand ($p<0.05$). This suggests that the right hand showed a consistent and above-chance mapping between EEG features and graded motor intent. In contrast, only 6 participants showed such trends for the left hand, which did not reach significance. While cERD features moderately correlated with effort targets, they did not consistently follow monotonic trends.
We are actively exploring alternative preprocessing and feature extraction methods, including combining multiple EEG-based metrics and CCA-based spatial filters to optimize motor effort decoding. These efforts parallel the ongoing refinement of our rehab-BCI system, which currently supports proportional feedback, to advance fine motor recovery.

Disclosures: S. Garcia Pava: None. **S. Sunderam:** None.

Poster

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Program #/Poster #: PSTR455.09/W12

Topic: F.05. Brain-Machine Interface

Title: A Multi-Branch Convolutional Neural Network for Motor Imagery EEG Classification from Heterogeneous Cortical Spectrograms

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Abstract: Non-invasive EEG-based Brain-Computer Interfaces (BCIs) using Motor Imagery (MI, mental movement rehearsal) aim to restore motor function in neuromuscular disorders. MI-

EEG classification is challenged by low signal-to-noise ratios and variability. Convolutional Neural Networks (CNNs) excel with image data. We leverage this by converting EEG to spectrograms (time-frequency images) as CNN inputs, investigating efficiency/speed gains for MI-EEG BCI classification. This study develops a multi-branch CNN for three MI states (execution, imagination, relaxation) using EEG spectrograms, utilizing heterogeneous information from motor (MC) and somatosensory (SSC) cortices. Using "PhysioNet EEG Motor Movement/Imagery Dataset," EEG was preprocessed into MC (e.g.,C3,C4) and SSC (e.g.,P3,P4,Pz) derived spectrograms, forming two input streams. Baseline ResNet18 yielded ≤55% accuracy and rapid overfitting. Our proposed multi-branch model fuses the features from each individual pathway before entering in a common CNN block, it radiply outperforms ResNet18, in <10 epochs. This tailored deep learning approach handles heterogeneous EEG data. Successful public dataset validation will enable transfer learning to a custom FISCOG (IBCCF/UFRJ) EEG spectrogram dataset. This aims to enhance local data performance, advancing practical, personalized BCI applications for neurorehabilitation.

Disclosures: D. Marques: None. **P. Chagas:** None. **J.G. Soares:** None.

Poster

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Topic: F.05. Brain-Machine Interface

Support: European Commission, Horizon MSCA Program (grant n° 101151118)

Title: Imagined movement increases the segregation of brain-heart networks

Authors: *D. CANDIA-RIVERA, F. DE VICO FALLANI, M.-C. CORSI;
Paris Brain Institute: Inst. du Cerveau, Paris, France

Abstract: Motor imagery (MI), the mental simulation of movement without execution, plays a key role in neurorehabilitation. Understanding its neurophysiological mechanisms is essential for refining brain-computer interfaces (BCIs) and optimizing sensorimotor rehabilitation. While MI engages motor-related brain regions, its precise mechanisms remain unclear, particularly in relation to cardiac dynamics. Evidence suggests heart-rate variability features have potential to enhance tasks' classifications, yet the brain-heart relationship is not well understood. In this study, we examined MI learning using a BCI task involving right-hand grasping imagery. We found that MI is characterized by cardiac sympathetic uncoupling with directed connectivity within the motor cortex. Additionally, cerebellar-supplementary motor area uncoupling, in relation to cardiac parasympathetic activity, predicted BCI learning across sessions. These results suggest that co-varying patterns of heart rhythmicity and brain connectivity within the motor network actively shape MI, highlighting interoceptive mechanisms as crucial influencers of sensorimotor function and associated neuroplasticity of BCI learning.

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Poster

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Program #/Poster #: PSTR455.11/W14

Topic: F.05. Brain-Machine Interface

Title: Reliable and Efficient TMS-EEG Using Ultra-Flat Active Electrodes

Authors: *C. GUGER, L. SCHREINER, S. SIEGHARTSLEITNER, K. MAYR, J. GRUENWALD;
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Abstract: Transcranial magnetic stimulation combined with EEG (TMS-EEG) enables the direct assessment of cortical excitability and connectivity via TMS-evoked potentials (TEPs). Although passive electrodes remain the gold standard, they require extensive preparation to achieve low impedances. Active electrodes address this issue by tolerating higher impedances and reducing preparation time, but their increased physical height leads to greater coil-to-scalp distances, higher stimulation intensities, and reduced spatial precision - factors that have limited their widespread adoption in TMS-EEG applications. We present a novel TMS-EEG system featuring ultra-thin (3 mm) active electrodes and integrated, fully automated decay artifact removal. In a study with ten healthy adults receiving TMS over the left primary motor cortex, EEG was recorded simultaneously from active and passive electrodes. To assess signal consistency, we computed concordance correlation coefficients (CCC) between spatially matched electrode pairs. As shown in Figure 1, active and passive electrodes yielded highly similar TEPs, with median CCC values of 0.97 for early components (15-80 ms) and 0.96 for late components (80-350 ms). Within-type comparisons of adjacent electrodes revealed similarly high CCCs, ranging from 0.91 to 0.97, indicating strong internal consistency. Moreover, CCC values decreased systematically with spatial distance, consistent with physiological expectations and supporting the integrity of the recorded signals. These results confirm that signal morphology and amplitude are preserved in our active electrode setup. The low-profile design, combined with standardized, artifact-resistant preprocessing, enables fast, reproducible, and high-quality TMS-EEG acquisition.

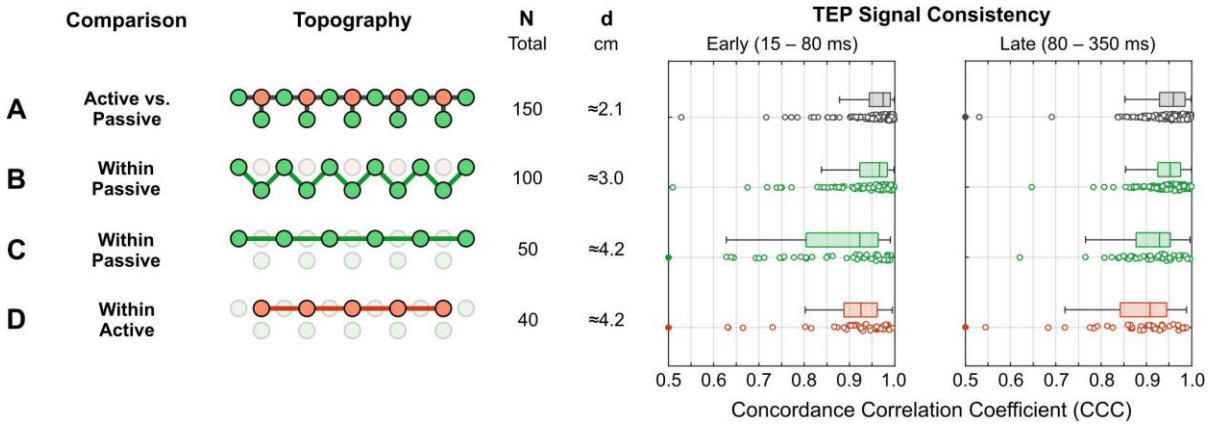


Figure 1: Signal consistency (CCC) across electrode pairs: (A) active vs. passive, (B) passive-diagonal, (C) passive-horizontal, (D) active-horizontal. Colors: red = active, green = passive. N: number of pairs; d: pairwise distance.

Disclosures: C. Guger: A. Employment/Salary (full or part-time): g.tec medical engineering GmbH. **L. Schreiner:** A. Employment/Salary (full or part-time): g. **S. Sieghartsleitner:** A. Employment/Salary (full or part-time): g.tec medical engineering GmbH. **K. Mayr:** A. Employment/Salary (full or part-time): g.tec medical engineering GmbH. **J. Gruenwald:** A. Employment/Salary (full or part-time): g.tec medical engineering GmbH.

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.12/W15

Topic: F.05. Brain-Machine Interface

Support: NIH R01 MH069456
NSF GRFP 2139841

Title: Neural dimensionality expands over the course of brain-computer interface learning

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[1]Dept. of Psychology, Yale Univ., New Haven, CT; [2]Wu Tsai Institute, Yale Univ., New Haven, CT

Abstract: Learning to perform a new behavior is constrained by the emergent, low-dimensional geometry of the neural population activity supporting that behavior. This latent geometry (or neural manifold) arises from the co-modulatory activity patterns of neural units driving a behavior, and in turn, the behaviorally relevant activity can be considered as trajectories along this neural manifold (Cunningham & Yu, 2014). Recent work demonstrates that the dimensionality of a neural manifold (i.e., intrinsic dimensionality) relates to variability in

performance on various cognitive tasks. For example, higher dimensional neural representations have been linked to faster object value learning (Tang et al., 2019) and to better episodic memory encoding (Sheng et al., 2022). However, how intrinsic dimensionality changes over the course of learning within individuals is unknown. This is especially important to consider in the context of brain-computer interfaces (BCIs), where neural manifolds serve as an important constraint on learning (Sadtler et al., 2014; Oby et al., 2019). Here, we leveraged a noninvasive BCI based on real-time fMRI neurofeedback to test how neural manifolds constrain human learning and, in turn, how the manifolds change with learning. In our closed-loop system, participants (N=20) learned to regulate patterns of brain activity across task-related regions of interest to navigate a virtual avatar in an arena. Across three neurofeedback sessions, individuals had to learn to generate activity patterns that either conformed to or conflicted with the brain's existing neural manifold geometry. Participants successfully learned to control the BCI when they needed to generate activity patterns that were "on-manifold" (i.e., manifold conforming) but not "outside-manifold" (i.e., manifold conflicting). Further, the intrinsic dimensionality of brain activity in the targeted regions increased from the start to the end of training during the on-manifold sessions but did not change during the outside-manifold session. Individual differences in this expansion of intrinsic dimensionality predicted the degree of behavioral BCI learning in the on-manifold conditions across participants. We are investigating the specificity of these dimensionality changes to regions targeted with neurofeedback versus distributed across the brain, as well as considering other topological features of brain activity related to BCI learning in humans.

Disclosures: E.L. Busch: None. **S. Krishnaswamy:** None. **N.B. Turk-Browne:** None.

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.13/X1

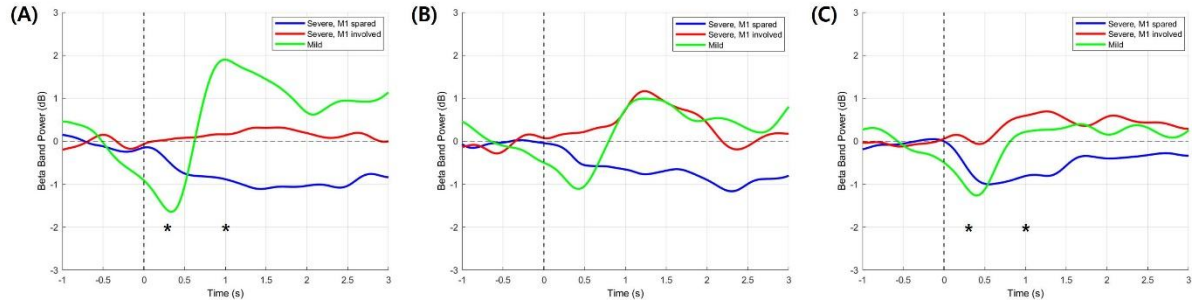
Topic: F.05. Brain-Machine Interface

Support: This study was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Science & ICT(RS-2024-00397674).

Title: Effect of Lesion Location and Motor Impairment Severity on ERD and ERS During Attempted Movement of the Paretic Hand in Patients with Subacute Stroke

Authors: H. KIM[1,2], G.-Y. CHOI[3], H. JU[2], J. MOON[2], W. CHANG[2], S. CHOI[2], J. KU[4], H.-J. HWANG[5], N.-J. PAIK[1,2], *W.-S. KIM[2];
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Abstract: Sensorimotor rhythm (SMR)-based brain-computer interface (BCI) systems rely on movement-related beta desynchronization (MRBD) and post-movement beta rebound (PMBR), but not all stroke patients exhibit reliable SMR responses. This study investigated how lesion location and motor impairment severity affect beta-band ERSP during attempted movement of the paretic hand in subacute stroke, aiming to identify neurophysiological markers relevant for BCI applicability. Sixteen patients with subacute stroke performed a 3-second fist-clenching task with their paretic hand. Based on FMA scores (<20 = severe, >50 = mild) and primary motor cortex (M1) lesion status, patients were grouped as: Group 1 (severe, M1 spared, n=6), Group 2 (severe, M1 involved, n=6), and Group 3 (mild, n=4). EEG was recorded using a 32-channel LiveAmp (Brain Products, 500 Hz) and preprocessed with CAR, 0.5-50 Hz filtering, and ICA. Beta-band (13-30 Hz) ERSPs were computed at C3, C4, and Cz using EEGLAB's newtimef. MRBD (0-0.5s) and PMBR (0.5-1.5s) were analyzed relative to baseline (-1 to 0s). Group differences were tested using Kruskal-Wallis and Bonferroni-corrected Mann-Whitney U tests. Significant group differences in MRBD and PMBR were observed at ipsilesional and Cz electrodes (MRBD p=0.01, PMBR p=0.05 at ipsilesional; MRBD p=0.02 at Cz). Group 2 (severe with M1 lesion) showed significantly lower MRBD than Group 3 (mild) (p=0.0095), and higher PMBR than Group 1 (severe, M1 spared) (p=0.0087) at ipsilesional sites. Similar differences were found at Cz (MRBD: Group 2 vs. 3, p=0.0095; PMBR: Group 1 vs. 2, p=0.0152). No significant differences were found in the contralesional hemisphere. These results, reflected in beta power time courses, show that patients with mild impairment exhibited robust MRBD and PMBR, while those with severe impairment and M1 involvement showed attenuated MRBD and exaggerated PMBR. This suggests that both impairment severity and lesion location influence SMR expression and should be considered when designing BCI-based rehabilitation strategies for stroke recovery.



Disclosures: H. Kim: None. **G. Choi:** None. **H. Ju:** None. **J. Moon:** None. **W. Chang:** None. **S. Choi:** None. **J. Ku:** None. **H. Hwang:** None. **N. Paik:** None. **W. Kim:** None.

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

Location: SDCC Halls B-H

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Program #/Poster #: PSTR455.14/X2

Topic: F.05. Brain-Machine Interface

Support: NIH NINDS K01NS127936
NIH NICHD K12HD073945
Washington University in St. Louis Department of Biomedical Engineering
Washington University in St. Louis Department of Neurosurgery
McDonnell Center for Systems Neuroscience at Washington University in St. Louis

Title: Transient effects in corticospinal and reticulospinal tract excitability induced by motor skill and isometric resistance training.

Authors: *R. HAWTHORN, N. PHELPS, R. KEESEY, C. ATKINSON, I. SEÁÑEZ; Biomed. Engin., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Rehabilitation for neuromotor disorders, such as spinal cord injuries (SCI), relies on personalized physical therapy to improve function. While therapy is tailored to injury level and patient needs, the neural mechanisms driving recovery—particularly in the lower limbs—remain unclear. Therefore, identifying training strategies that promote neuroplasticity is essential to optimize rehabilitation. This study examined changes in cortico-reticulo-spinal excitability after a single session of cue-paced motor skill training (MST) versus isometric resistance training (IRT). We hypothesized that MST enhances corticospinal excitability, while IRT increases reticulospinal excitability. In a cross-over design, unimpaired participants (N=23) completed both training paradigms on separate days. During MST, participants used a body-machine interface with inertial sensors on the right foot to control a computer cursor via ankle movements in a center-out-reaching task. During IRT, participants performed slow-ramped plantar flexion and dorsiflexion at 30% of maximum torque for 30 minutes. We assessed corticospinal excitability using motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation. Spinal excitability was evaluated via H-reflex/M-wave ratios and F-waves. Reticulospinal excitability was assessed via the StartReact response, a reduction in reaction time to a startling auditory cue. MST significantly increased MEP amplitude, and IRT showed a smaller but still significant increase. Measures of spinal excitability showed minimal change, and reticulospinal excitability appeared unaltered by either short-term intervention. These results highlight training-specific neural adaptations, with MST preferentially enhancing corticospinal excitability. The lack of change in reticulospinal excitability may reflect the limited ability of brief training protocols to recruit these pathways in unimpaired individuals. However, reticulospinal neurons are known to contribute to recovery following corticospinal tract injury and may play a more prominent role in motor function after SCI due to their wide distribution and partial sparing. Having validated our training and evaluation paradigms, we are now translating this work to individuals with SCI. Our ongoing study enrolls participants with chronic SCI to assess short-term changes in corticospinal, reticulospinal, and spinal excitability following activity-based training, spinal cord stimulation (SCS), and their combination. These efforts aim to elucidate the mechanisms by which SCS enables movement and inform targeted rehabilitation strategies for SCI.

Disclosures: R. Hawthorn: None. **N. Phelps:** None. **R. Keesey:** None. **C. Atkinson:** None. **I. Seáñez:** None.

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.15/X3

Topic: F.05. Brain-Machine Interface

Support: NIH ICHD Award Number K12HD073945
NIH NINDS Award Number K01NS127936
McDonnell Center for Systems Neuroscience at Washington University in St. Louis
German Federal Ministry of Education and Research (BMBF) project nr. 01ZZ2016
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Title: Fundamental limitations of kilohertz-frequency carriers in afferent fiber recruitment with transcutaneous spinal cord stimulation

Authors: *R. E. KEESEY[1], U. HOFSTOETTER[2], Z. HU[3], L. LOMBARDI[4], R. HAWTHORN[4], N. BRYSON[5], A. ALASHQAR[7], A. ROWALD[8], K. MINASSIAN[2], I. SEÁÑEZ[6];
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Abstract: The use of kilohertz-frequency (KHF) waveforms has rapidly gained momentum in transcutaneous spinal cord stimulation (tSCS) to restore motor function after paralysis. However, the mechanisms by which these fast-alternating currents depolarize proprioceptive afferent and motor efferent fibers remain unknown. Our study fills this research gap by providing a hypothesis- and evidence-based investigation using peripheral nerve stimulation, lumbar tSCS, and cervical tSCS in 28 unimpaired participants, as well as computational modeling. Peripheral nerve stimulation experiments and computational modeling showed that KHF waveforms negatively impact the processes required to electrically induce action potentials, thereby increasing response thresholds and notably biasing the recruitment towards motor efferent fibers. While these results translate to tSCS, we also demonstrate that lumbar tSCS still results in the preferential recruitment of proprioceptive afferent fibers, while cervical tSCS favors recruitment of motor efferent fibers, regardless of the waveform used. Given the assumed importance of proprioceptive afferent stimulation in motor recovery, our work suggests that the use of KHF waveforms should be reconsidered to maximize neurorehabilitation outcomes, particularly for cervical tSCS. We posit that careful analysis of the mechanisms that mediate responses elicited by novel approaches in tSCS is crucial to understanding their potential to restore motor function after paralysis.

Disclosures: **R.E. Keesey:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Listed as an inventor in patents or provisional patents related to spinal cord stimulation.. **U. Hofstoetter:** None. **Z. Hu:** None. **L. Lombardi:** None. **R. Hawthorn:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Listed as an inventor in patents or provisional patents related to spinal cord stimulation. **N. Bryson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Listed as an inventor in patents or provisional patents related to spinal cord stimulation.. **A. Alashqar:** None. **A. Rowald:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Listed as an inventor in patents or provisional patents related to spinal cord stimulation. **K. Minassian:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Listed as an inventor in patents or provisional patents related to spinal cord stimulation. **I. Seáñez:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Listed as an inventor in patents or provisional patents related to spinal cord stimulation..

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.16/X4

Topic: F.05. Brain-Machine Interface

Support: NIH NICHD K12HD073945
NIH NINDS K01NS127936
McDonnell Center for Systems Neuroscience at Washington University in St. Louis
Washington University in St. Louis Department of Biomedical Engineering
Washington University in St. Louis Department of Neurosurgery

Title: Towards the clinical translation of a non-invasive brain spine interface utilizing biofeedback-enabled neural adaptation

Authors: ***C. J. ATKINSON**[1,2], L. LOMBARDI[1,2], R. KEESEY[1,2], R. HAWTHORN[1,2], P. BRUNNER[1,2,3], I. SEÁÑEZ[1,2,3];
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Abstract: Transcutaneous spinal cord stimulation (tSCS) in combination with physical therapy has been shown to improve motor function in people with chronic spinal cord injury (SCI). However, stimulation is delivered continuously, regardless of movement intention. Recent

studies have shown that an implantable brain-spine interface that times SCS delivery with movement intention can further augment rehabilitation-induced recovery. In this work, we report our first steps in developing a non-invasive brain-spine interface (BSI) using electroencephalography (EEG) and tSCS. Seventeen unimpaired participants completed a cued knee extension task while synchronized EEG, electromyography (EMG), and inertial measurement unit (IMU) data were recorded. We trained a linear discriminant analysis (LDA) decoder to classify movement onset, and decoder performance was evaluated using the area under the receiver operating characteristic curve (AUC). Real-time decoder-modulated tSCS was integrated to assess the decoder's performance under closed-loop conditions. Our results show that the initiation of knee extension was associated with event-related desynchronization in the central-medial cortical regions at frequency bands between 4-44 Hz. The neural decoder achieved an average AUC of 0.83 ± 0.06 s.d. ($n = 7$) during a cued movement task offline. With the addition of real-time decoder-modulated tSCS, the neural decoder performed with an average AUC of 0.81 ± 0.05 s.d. ($n = 9$) on cued movement. While our findings demonstrate that the decoder can accurately predict the onset of lower limb movement better than chance, simplification of this system will likely be required to apply it as a clinical rehabilitation strategy. Furthermore, understanding similarities in neural activation patterns across participants and the extent of adaptation of neural strategies when individuals are provided with biofeedback could enable the clinical translation of this BSI as a rehabilitation strategy for people with SCI. In addition, we compare the performance of a generalized decoder trained on all participants' data to personalized decoders. Participants are given real-time biofeedback about the decoder's predictions and instructed to attempt to learn how to control the predictions over the course of a single session. Session- and subject-wise calibration methods are explored to enable mutual adaptation between the individual and the decoder.

Disclosures: C.J. Atkinson: None. **L. Lombardi:** None. **R. Keesey:** None. **R. Hawthorn:** None. **P. Brunner:** None. **I. Seáñez:** None.

Poster

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Topic: F.05. Brain-Machine Interface

Support: NIH NINDS K01NS127936
Washington University in St. Louis Department of Biomedical Engineering
Washington University in St. Louis Department of Neurosurgery
McDonnell Center for Systems Neuroscience at Washington University in St. Louis

Title: Cervical transcutaneous spinal cord stimulation with iliac crests electrodes evokes leg muscle responses by recruitment of efferent fibers

Authors: *N. PHELPS[1], R. KEESEY[1], R. HAWTHORN[1], I. SEÁÑEZ[2];
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Abstract: Transcutaneous spinal cord stimulation (tSCS) has shown to improve motor function in individuals with spinal cord injury (SCI). A common configuration involves placing cathode electrodes over the posterior cervical spine (C3/C4 and C6/C7) and anodes bilaterally over the anterior iliac crests. While this cervical-iliac tSCS setup is primarily studied for upper extremity rehabilitation, many participants have anecdotally reported sensations or responses in the legs. However, it remains unknown whether leg recruitment is occurring, and if so, the mechanisms by which they are recruited. Activation of afferent pathways is crucial for integrating stimulation with volitional movement and promoting motor rehabilitation. In this study, we investigated pathways involved in leg muscle recruitment during cervical-iliac tSCS. We compared cervical-iliac tSCS responses in unimpaired participants (n=12) with two other cathode-anode configurations: T11/T12-abdomen and cervical-clavicles. We hypothesized that cervical tSCS with the return anodes over the iliac crest activates leg muscles, via efferent rather than afferent fiber activation at the return site. In this case, we expected that 1) the cervical-clavicles configuration would not elicit leg muscle responses, 2) leg response latencies with the cervical-iliac configuration would be shorter than those of T11/T12-abdomen, and 3) there would be little-to-no suppression due to post-activation depression from double-pulse stimulation. We recorded electromyography at 4370 Hz from upper and lower limb muscles to assess response magnitude, latency, and paired-pulse suppression for each configuration. Preliminary results show that while cervical-iliac tSCS elicited leg muscle responses, cervical-clavicles did not. Additionally, response latencies in the leg muscles were shorter with cervical-iliac than T11/T12-abdomen, indicating recruitment is occurring further along the monosynaptic reflex pathway, in the anterior roots. We also observed strong suppression with T11/T12-abdomen—consistent with presynaptic afferent-mediated recruitment—but minimal with cervical-iliac. These findings support the hypothesis that cervical-iliac tSCS engages leg muscles via efferent fiber recruitment. Although cervical tSCS recruits leg muscles, these responses may be suboptimal in recruiting proprioceptive afferent fibers in the lumbosacral spinal cord. Understanding these recruitment mechanisms will help refine electrode configurations and stimulation protocols to selectively target intended neural circuits and reveal additional effects of cervical tSCS-assisted neurorehabilitation.

Disclosures: N. Phelps: None. **R. Keesey:** None. **R. Hawthorn:** None. **I. Seáñez:** None.

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.18/X6

Topic: F.05. Brain-Machine Interface

Title: A Flexible High-Density EMG Cuff for Wearable Neuromuscular Monitoring: Design and Validation

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Abstract: High-density electromyography (HD-EMG) offers a non-invasive measure of motor signaling in the neuromuscular system by capturing motor unit (MU) activity during voluntary muscle contractions. Traditional HD-EMG systems often suffer from rigid structures, reliance on skin abrasion or gels, and complex setups that limit their practicality for wearable applications. This study presents the design, fabrication, and validation of a novel flexible HD-EMG cuff designed for wearable use, integrating a custom-designed polyimide-based printed circuit board with dual onboard Intan RHD2164 bioamplifier chips and 128 gold-plated dry electrodes, each 3.18 mm in diameter, arranged in a dual 8×8 grid style with 5 mm inter-electrode spacing (center-to-center). The design accommodates limb diameter as small as 5 cm, and expands to a maximum width of 23 cm, ensuring a comfortable fit for a wide range of limb sizes. Benchtop testing with an agarose-based skin phantom demonstrated low impedance values across frequencies from 10 Hz to 5 kHz, with an average of 6.3 ± 5.4 kΩ (mean ± SD) at 1 kHz, supporting reliable charge transduction and consistent signal fidelity. Signal recordings with the cuff placed on the forearm were acquired using either an Open Ephys acquisition board (Open Ephys, Lisbon) or an RHD Recording Controller (Intan, Los Angeles) at a sample rate of 4 kHz, capturing EMG signals during isometric wrist flexion tasks. Motor unit decomposition using convolution kernel compensation revealed that the HD-EMG cuff reliably extracted motor unit action potentials, achieving yields of up to 15 MUs in a single trial. The cuff's performance was also benchmarked against a textile-based hydrogel system (SAGA 64+, TMSi, The Netherlands) with the same tasks. Although dry electrodes exhibited slightly higher baseline RMS noise (22.48 ± 3.35 μV) compared to wet electrodes (19.60 ± 4.65 μV), the device maintained high signal quality and demonstrated feasibility for real-world MU analysis. Notably, the cuff successfully distinguished unique muscle activation patterns in an individual with spinal cord injury that was attempting to form specific hand and finger gestures, underscoring its potential for clinical neuromuscular assessments. This modular, scalable, and low-cost design facilitates access and customizability for HD-EMG studies. Its flexible architecture also provides opportunities for integration with assistive technologies, including exoskeletons, neuroprosthetics, and advanced human-machine interfaces, paving the way for innovative research and clinical applications.

Disclosures: J. Shulgach: None. **P. Yadav:** None. **L. Borda:** None. **A. Ersoz:** None. **M. Murphy:** None. **D.J. Weber:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroOne, NeuronOff, Bionic Power, Inc., Reach Neuro, Inc..

Poster

PSTR455: BMI: Non-Invasive Neurophysiology

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Program #/Poster #: PSTR455.19/X7

Topic: F.05. Brain-Machine Interface

Support: NIH 1P41EB018783
Stratton VA Medical Center, Albany, NY
New York State Spinal Cord Injury Research Board (SCIRB) C32236GG & C33279GG

Title: Brain-computer interface (BCI) training and heksor-mediated skill acquisition: two case studies

Authors: *T. M. VAUGHAN[1], J. R. WOLPAW[2], J. S. CARP[3], H. BAHARI[4], J. C. ANDERSEN[5], C. TUCK[6];
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Abstract: New recognition that the central nervous system (CNS) remains plastic through life, and new understanding of how muscle-based skills are learned and maintained can provide insight into how a BCI might prove clinically useful. A natural (i.e., muscle-based) skill is produced by a network of neurons and synapses that may extend from cortex to spinal cord. This network has been given the name heksor, from the ancient Greek word hexis. A heksor changes through life; it modifies itself as needed to maintain the key features of its skill, the attributes that make the skill satisfactory. Heksors overlap; they share neurons and synapses. Through their concurrent changes, heksors keep neuronal and synaptic properties in a negotiated equilibrium that enables each to produce its skill satisfactorily. A BCI-based skill is produced by a synthetic heksor, a network of neurons, synapses, and software that produces a BCI-based skill and changes as needed to maintain the skill's key features. A synthetic heksor could modify natural heksors by joining in the interactions that produce the negotiated equilibrium (see Wolpaw & Kamesar, DOI: 10.1113/JP283291 & Wolpaw, J Neural Eng, in press). In this study, we describe motor-skill acquisition by two nonverbal children without prior useful motor control (P1, age 16, with cerebral palsy and blindness; P2, age 5, with GM3 synthase deficiency, impaired vision and audition of cortical origin) who participated in at least 11 sessions of the Glenrose BCI Program. In a BCI Session, each dons a 14-channel EPOC X^{TM} cap covering prefrontal, premotor, and sensory-visual areas. To calibrate the BCI, each is asked to either relax or imagine moving [pushing (P1), or hand tapping (P2)] 7-10 times for each condition. P1 used an Assistive Technology Hub to play music and P2 used a Think2Switch to activate and maintain a switch-adaptive bubble maker. Each child achieved realization of cause and effect during their first BCI session (S1). With further sessions, they initiated and sustained a motor action on verbal command for the first time: clapping (P1) and tapping (P2) by S15 and S10, respectively. Engagement level was assessed by the Pediatric Rehabilitation Intervention Measure of Engagement - Service Provider version (PRIME-SP). Their striking improvement led to their readmission to regular hospital therapy. Thus, in addition to their BCI sessions, they now use

their new motor skill functionally. These encouraging results suggest that a synthetic heksor can improve natural heksors impaired by CNS injury or disease.

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Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

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Program #/Poster #: PSTR456.01/X8

Topic: F.05. Brain-Machine Interface

Support: NIH Grant 5F32MH132145
NIH Grant R01NS110564

Title: Intracortical microstimulation induces rapid microglia process convergence

Authors: *N. P. WILLIAMS[1], A. M. KELLY[1], X. S. ZHENG[1], A. VAZQUEZ[2], T. CUI[3]; [1]Bioengineering, [2]Radiology, [3]Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Intracortical microstimulation (ICMS) has demonstrated the potential to restore vision and hearing by stimulating relevant cortical regions in both animals and humans, offering significant clinical promise for sensory restoration. While the neuronal response to ICMS has been extensively studied at the cellular level through electrophysiology and two-photon (2P) imaging, the response of non-neuronal cells, particularly microglia, as well as the effects of ICMS on blood-brain barrier (BBB) integrity remain poorly understood. In this study, we applied ICMS under 2P imaging in dual-reporter mice, with green fluorescent protein labeling microglia and a red fluorescent Ca^{2+} indicator labeling neurons. We also monitored vascular dye leakage to assess BBB integrity throughout the experiment. Using clinically relevant waveform parameters, we tested a range of current amplitudes. Surprisingly, we found that microglia responded rapidly, within 15 minutes of stimulation, by converging their processes (MPC) on areas of high neural activity. The prevalence of MPC increased with higher current amplitudes, but intriguingly, it did not correlate with the strength of the local electric field. Additionally, vascular dye penetration into brain tissue was higher in stimulated animals than in implanted but non-stimulated controls, and increased with current amplitude. This study reveals a rapid microglia and BBB response to ICMS that has not been reported previously, underscoring the need for further research to fully characterize the biological response to ICMS and establish improved safety standards.

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Poster

PSTR456: BMI: Direct Neurophysiology

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Program #/Poster #: PSTR456.02/X9

Topic: F.05. Brain-Machine Interface

Support: NIH R01NS136622
NIH T32GM075770

Title: Microelectrode arrays with integrated enzyme-based biosensors for neurotransmitter detection in the dorsal root ganglion

Authors: *C. H. THOMPSON[1], P. GHELICH[5,2], J. E. LOEZA ALCOCER[3], T. CUI[4];
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Abstract: Chronic pain is a condition that affects nearly twenty percent of the world population and is described as pain that regularly restricts routine life and/or work activities and generally decreases an individual's quality of life. Chronic pain is also associated with an increased risk of opioid misuse, depression, and anxiety. In contrast to acute pain, which plays a protective and adaptive role and typically resolves after healing, chronic pain endures beyond the normal healing process and is maladaptive as it serves no known biological purpose. Ascending somatosensory input from the skin and visceral organs is detected by sensory neurons whose somata reside in the dorsal root ganglion (DRG). As the DRG is a locus of somatosensory input from the peripheral nervous system, it is of particular interest in the development of chronic pain at a mechanistic level. While there are no traditional synapses between neurons in the DRG, SGCs express glutamate and gamma-aminobutyric acid (GABA) transporters and have been shown to receive and secrete these neurotransmitters within the local extracellular space as a method of neuromodulation. Upon injury or inflammation, SGCs can enter an activated phenotype that alters healthy SGC function and directly contributes to neuronal sensitization and the development of chronic pain. However, the dynamics of glutamate and GABA within the DRG remain to be fully understood in the context of chronic pain. Additionally, there are very few studies that provide neurotransmitter detection within intact DRGs. Thus, we hypothesize that there are measurable neurotransmitters released in the DRG and that the concentrations of these neurotransmitters may be different between naïve and chronic pain model animals. Here, we present a flexible microelectrode array (MEA) integrated with enzyme-based biosensors to enable real-time amperometric detection of neurotransmitters glutamate and GABA within biological tissues. By utilizing our enzyme biosensors, we have successfully observed neurotransmitter release in intact electrically stimulated DRGs from naïve and spared-nerve animals which may indicate differences in neurotransmitter release and concentration in chronic pain models. We believe that these differences in neurotransmitter release may indicate one way that the interplay between activated SGCs and sensitized neurons in the DRG contribute to the development of chronic pain. This technology and the results of this study may enable more targeted and precise monitoring and treatment of chronic pain at the neurotransmitter level and expand our understanding of the mechanisms of the DRG in the development of chronic pain.

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Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.03/X10

Topic: F.05. Brain-Machine Interface

Support: NIH Grant 1U01NS126052-01
NSF Grant NGE-244108

Title: Amplitude Resolution of Ultra-Microelectrodes for Intracortical Microstimulation

Authors: *E. SU[1,2], A. COLLINS[1], E. OLIVO[2], S. MOOLA[1], S. COREY[3], K. J. OTTO[2]; [2]Weldon Sch. of Biomed. Engin., [1]Purdue Univ., West Lafayette, IN; [3]Case Dept. of Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: Intracortical microstimulation involves directly activating neural tissue to modulate or produce experiences, which can restore sensory function when implanted in the appropriate cortices. However, current microelectrode technology used to interface with the brain has 2 major issues. First, their lifespan is limited by the foreign body response (FBR) which encapsulates the device in glial scarring. This reduces the quality of recorded signals and increases the amount of current required to elicit a percept. Second, non-specific activation arises from a high neuron to electrode ratio, reducing the fidelity of artificial sensation. Ultramicroelectrodes may solve both of these issues. It has been established that electrodes with subcellular dimensions can reduce the severity of the FBR [1]. This work aims to understand if ultra-microelectrodes (UMEs) can additionally produce more targeted stimulation with better amplitude resolution, compared to traditional microelectrodes. Ultra-microelectrode devices were custom designed in partnership with NeuroNexus Inc., with 32 planar electrodes of 5 to 50 μm diameters. To improve charge-storage capacity, electrodes were coated with a sputtered iridium oxide film (SIROF). The electrodes were implanted to a depth of 1450 μm in the somatosensory cortex of rats. Stimuli were delivered to electrode sites at 200 Hz using 650 ms pulse trains with 0.2 ms phase duration and 0.04 ms interpulse intervals. The total charge injected per electrode site was kept below the maximum charge density for each electrode site to avoid tissue or electrode damage. Just-noticeable difference testing was determined through a modified conditioned avoidance behavioral paradigm [2]. Chronic behavioral responses to neural stimulation were observed, with consistent difference thresholds achieved for each electrode size. Reducing electrode diameter affected the ability of each subject to discriminate amplitude. These insights highlight the feasibility of ultra-microelectrodes to improve both chronic lifespans and stimulation specificity of intracortical microstimulation. This research paves the way for further innovations in brain-machine interface technology to enhance sensory feedback for persons with paralysis. [1] Luan, L., et al (2017). Ultraflexible nanoelectronic probes form

reliable, glial scar-free neural integration. *Science Advances.* 3:e1601966. doi:10.1126/sciadv.1601966 [2] Kunigk, N. G., et al (2022). Reducing behavioral detection thresholds per electrode via synchronous, spatially-dependent intracortical microstimulation. *Frontiers in Neuroscience.* 16:876142. doi: 10.3389/fnins.2022.876142

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Poster

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Program #/Poster #: PSTR456.04/X11

Topic: F.05. Brain-Machine Interface

Support: R01 MH110514/MH/NIMH
NSF BRAIN EAGER SMA 1451221

Title: Robotic Exploratory Control Via Subcortical Oscillations

Authors: *I. L. JACKSON[1], R. KOHLI[1], L. K. QUINN[1], Y. LOU[1], L. BRESTON[2], J. WILES[3], A. A. CHIBA[1,2], E. J. LEONARDIS[4];
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Abstract: Navigation through real-world environments remains a difficult task for intelligent robots, due to a constantly changing landscape of potential hazards and new information. To address this, roboticists and neuroscientists have turned to the brains and behaviors of rodents — some of nature's most successful explorers — to inspire feasible solutions. Most approaches model patterns of activation in the hippocampus and associated circuitry, leveraging rodents' exceptional memory of spatiotemporal sequences for navigation. None, however, have utilized the coupled activity of multiple subcortical regions that balance navigation with regulatory behaviors (e.g., grooming, immobility), a key optimization strategy that animals use in real-world scenarios. Indeed, neural oscillations in the amygdala, olfactory bulb, and hippocampus are instrumental during free-roaming and navigation tasks involving potential stressors. The oscillatory activity of subcortical regions involved in both regulation and exploration reflects the active switching between these behaviors observed in naturally behaving rats. The current exploratory study investigates the effectiveness of co-opting neural oscillations in these brain regions as control signals for robotic navigation. This leverages the natural hierarchy of rodent subcortical activity as a decision-making architecture for robotics. Building such hierarchical control systems with self-regulatory mechanisms is crucial for developing intelligent robotics that perform natural tasks as biological agents do.
We utilize PiRat, a rat-sized robot previously established as a social robotics tool for rats. In this work, the robot is equipped with an ontology of external and internal states, and simple two-

dimensional movement. We begin our investigation with an offline training procedure using data from previous recordings, during which rats with electrode implants in the CA2 region of the hippocampus, medial amygdala, and main olfactory bulb were allowed to roam freely with a conspecific. During offline training, we explored a suite of modeling approaches trained to generate actions based on previous states. We then ran the models on the remaining test data, and the actions generated by the models at each timestep were combined into continuous trajectories. These were compared to the actual rat positions at each corresponding timestep, serving as a metric for how rodent-like the robot's free roaming behavior was. Thus far, the defined state and action spaces demonstrate that rodent-like exploratory and regulatory behaviors may be generated via streams of local field potential data from CA2, MOB, and MeA.

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Poster

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Program #/Poster #: PSTR456.05/X12

Topic: F.05. Brain-Machine Interface

Support: Wyss funding 532933

Title: Kirigami-based soft electrode arrays for long-term recording of motor intention in Non-Human Primates

Authors: *L. KOLLY[1], H. LONDOÑO RAMÍREZ[1], V. DRUET[1], C.-F. V. LATCHOUMANE[2], S. SUN[3], G. SCHIAVONE[1], J. BLOCH[4], G. COURTINE[5], S. P. LACOUR[6];
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Abstract: Soft neural interfaces address the biomechanical mismatch between neural tissue and inorganic electrode materials, which can trigger a foreign body reaction and ultimately lead to interface failure. Most soft neurotechnologies experience a progressive loss of insulation between channels, caused by the diffusion of ionic species through the polymer encapsulations. This degradation compromises the reliability of soft neural interfaces, and remains a major barrier to their deployment in neuroprosthetic medicine. To address this challenge, we developed a microfabrication process enabling thin-film platinum (Pt) conductive tracks with kirigami micropatterns to be encapsulated in a thermoplastic polymer with a ceramic lining, providing an integrated long-term barrier. We use these sealed conductors as stretchable interconnects embedded in silicone membranes to form easy-to-handle, conformable electrode arrays. At the

electrode sites, a soft Platinum-PDMS composite ensures impedance compatible with low-noise neural recordings. Electromechanical characterization reveals the encapsulated kirigami interconnects deform reversibly up to 15% uniaxial strain. Cyclic stretching for one million cycles at 10% strain resulted in a 5% increase in track resistance, indicating minimal fatigue. *In vitro* accelerated aging of interdigitated electrodes (IDE) soaked in PBS at 67 °C for 27 days showed leakage currents under 10 nA at 1 V bias, indicating high hermeticity, equivalent to >100 MΩ after 208 days at 37 °C for Arrhenius processes. We deployed the technology in vivo as a recording cortical interface in a motor neuroprosthetic system targeting a non-human primate model of subcortical stroke. Bilateral 30-channel Electrocorticography (ECoG) devices were designed for subdural recording of motor and somatosensory activity in both hemispheres. Impedance modulus at 1 kHz increased from 20 - 100 kΩ intraoperatively to 30 kΩ - 4 MΩ 1 month after implantation, then stabilized. Recording quality was sufficient to determine motor intention throughout a 3-month experiment. Our preliminary results suggest kirigami-sealed conductor as a solution for long-term soft ECoG recordings in neuroprosthetic systems. These advancements aim to develop stable, durable soft neural interfaces suitable for chronic applications.

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Poster

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Topic: F.05. Brain-Machine Interface

Support: NINDS Grant F31NS129099
NINDS Grant F32NS093709
NINDS Grant R01NS107271

Title: Disentangling indirect versus direct effects of somatosensory cortex microstimulation on motor cortex neurons

Authors: B. RUSZALA[1], K. A. MAZUREK[2], *M. H. SCHIEBER[3];
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Abstract: The development of intracortical microstimulation in the primary somatosensory cortex (S1-ICMS) to provide on-line feedback for bidirectional brain-machine interfaces will require understanding the modulation produced by S1-ICMS in the activity of the motor cortex neurons used to decode motor intent. We therefore investigated the effects of S1-ICMS on neurons in both the primary motor cortex (M1) and the ventral premotor cortex (PMv) during a

reach-grasp-manipulate task in which some trials were instructed with visual cues and other trials with S1-ICMS. We observed both indirect modulation that could occur during and/or after ICMS trains, as well direct modulation time-locked to the individual S1-ICMS pulses within trains, with all possible combinations of the two types of modulation found among the majority of M1 and PMv neurons. When S1-ICMS produced both indirect and direct modulation in the same neuron, the effects could be both excitatory, both inhibitory, or one excitatory and the other inhibitory. Indirect effects were more prevalent and larger than direct effects. With a simulation of direct effects, we were able to isolate the concurrent indirect effects, revealing that isolated direct effects typically failed to account for the isolated indirect effects. Furthermore, indirect effects could be present 1 second or more after ICMS trains had terminated, when no direct effects could have occurred. Although the performance of movement decoders trained on visually-instructed trials was poor when applied to ICMS-instructed trials, decoders trained on ICMS-instructed trials performed well on ICMS-instructed trials, indicating that S1-ICMS altered the discharge of M1 and PMv neurons but did not degrade the decodable information available. When decoding movement intent from neural activity in M1 and/or PMv, accounting for the indirect and direct modulation produced by S1-ICMS may improve the ability of bidirectional brain-machine interfaces to incorporate artificial somatosensory feedback and restore functional movement.

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Poster

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Program #/Poster #: PSTR456.07/X14

Topic: F.05. Brain-Machine Interface

Support: NIH Grant 1U01NS126052-01

Title: Analysis of Electrode Charge Density Using Ultramicroelectrodes for Synchronous Intracortical Microstimulation

Authors: *E. OLIVO[1], Y. WU[2], M. KHAJEHZADEH[3], S. F. COGAN[4], M. E. ORAZEM[5], K. J. OTTO[1];
[1]Weldon Sch. of Biomed. Engin., Purdue Univ., West Lafayette, IN; [2]Material Sci. Engin., Univ. of Texas at Dallas, Dallas, TX; [4]Bioengineering, [3]The Univ. of Texas at Dallas, Dallas, TX; [5]Chem. Engin., Univ. of Florida, Gainesville, FL

Abstract: Intracortical microstimulation (ICMS) is a promising technique for treating neurological disorders and restoring sensory function in paralysis by targeting the primary somatosensory cortex (S1). However, chronic foreign body responses (FBR) often encapsulate implants, increasing stimulation thresholds and reducing device longevity. To address this, ultramicroelectrode arrays (UMEAs) have been developed to reduce encapsulation and improve

long-term performance. Smaller electrode-site areas, however, increase current density, risking damage to tissue or the device.This study evaluates ultramicroelectrode arrays designed to provide effective ICMS while mitigating the FBR. The goal is to develop multichannel UMEAs suitable for chronic neuromodulation. Devices were custom-fabricated with 19 electrodes in diameters of 5, 10, 15, and 20 μm (19.63-314.15 μm^2). Electrodes were coated with sputtered iridium oxide film (SIROF) to enhance charge capacity and implanted 1,700 μm deep in S1. ICMS was delivered at 320 Hz using 650 ms pulse trains (0.2 ms/phase, 0.04 ms interpulse). Charge limits scaled with electrode size: 0.8-16.4 nC/phase.A modified conditioned avoidance behavioral paradigm was used to determine detection thresholds in rats. Water-deprived rats were monitored for licking patterns during safe trials (controls) and warning trials (ICMS stimulus). Detection thresholds were determined with an adaptive algorithm that decreased stimulus amplitude if the animal successfully detected the stimulus ("hit") and increased if stimulus detection was unsuccessful ("miss"), converging after three reversals to determine the detection threshold.Behavioral responses confirmed reliable thresholds across electrode combinations. All animals were tested with different site sizes and groupings, from four 20 μm sites (1,256.6 μm^2) to a single 5 μm site (19.63 μm^2). As in prior work, total charge per threshold decreased with fewer stimulated electrodes. In one subject, for thresholds obtained using four 20 μm diameter sites the average charge per phase per electrode was 0.36 nC/phase, while the average total charge applied for the same electrode configuration was 1.46 nC/phase. For thresholds with one 5 μm diameter site, the average charge per phase per electrode and average total charge needed for a detection threshold was 0.76 nC/phase. These insights highlight the feasibility of achieving chronic ICMS using multi-channel ultramicroelectrode arrays. These devices have the potential to open new therapeutic avenues for enhancing sensory feedback and maintaining reliable chronic treatments for neurological conditions.

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Poster

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Program #/Poster #: PSTR456.08/X15

Topic: F.05. Brain-Machine Interface

Support: NIH UO1 1U01NS126052-01

Title: In Vivo Impedance Characterization of Ultramicroelectrode Arrays for Longitudinal Chronic Neural Interface Performance

Authors: *Q. DONG[1], D. GUAN[1], S. BOROOMAND[1], B. W. BINEY[2], J. F. HETKE[3], S. F. COGAN[4], M. E. ORAZEM[2], K. J. OTTO[1];

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Abstract: Chronic neural interfaces require stable electrochemical performance to ensure reliable recording and stimulation over time. Ultramicroelectrode arrays (UMEAs) offer a promising solution due to their small footprint and high spatial resolution. However, the long-term impedance behavior of such electrodes *in vivo* remains poorly understood, particularly under the influence of chronic stimulation. In this study, we investigated the temporal evolution of *in vivo* impedance in SIROF-coated UMEAs implanted in the rat somatosensory cortex. Our second-generation (G2) electrode arrays from NeuroNexus Technologies, Inc. (Ann Arbor, MI) are constructed on a silicon substrate with gold contacts coated in Sputtered Iridium Oxide Film (SIROF). Electrode arrays consisted of four shanks, each 3 mm in length and 15 μm in thickness, fabricated with sputtered iridium oxide (SIROF)-coated gold sites. Each shank contained six working electrode sites and two additional functional sites (reference site, terminal, or loop), yielding a total of 32 electrical connections across the array. Of these, 24 were designated as working electrodes for recording and stimulation. Two shanks featured circular electrode sites with diameters of 5 μm and the remaining two with 10 μm diameter sites. Within each size group, one shank was designated for stimulation while the other served as a non-stimulated control. Electrochemical impedance spectroscopy (EIS) was performed weekly, and data were fit to an equivalent circuit model to extract physiologically relevant parameters, including SIROF film resistance and capacitance (R_i, C_i), double-layer capacitance (Q_f), Ohmic resistance (R_e), and stray capacitance (Q_w). EIS was performed using an Autolab PGSTAT12 with a two-electrode setup, across a frequency range of 10 Hz-100 kHz *in vivo*. We implanted G2 devices into the rat somatosensory cortex. Our results indicate that double-layer and wire-related parameters remained consistent across groups, suggesting that the observed changes in impedance arose primarily from biological interactions at the tissue interface rather than from electrode material instability. These findings demonstrate the stability of ultramicroelectrode arrays with variable electrode size and stimulation history. Our results support the use of ultramicroelectrodes for long-term applications and provide guidance for the optimization of electrode design and stimulation protocols in future neural interfaces.

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Poster

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Program #/Poster #: PSTR456.09/X16

Topic: F.05. Brain-Machine Interface

Support: Tohoku University Advanced Graduate School Research Initiative for International Scholarly Excellence Program

Title: In vivo evaluation of a Wrap Around Electrode for directional neural signal recording in the cervical spinal cord

Authors: ***K. TSUJI**[1], A. NINOMIYA[2], N. IWANUMA[3], S. OBA[3], K. KITTA[1], H. KINO[4], T. ENDO[5], N. KATAYAMA[6], K. NIIZUMA[2,7,8], T. FUKUSHIMA[1,3], T. TANAKA[1,3];
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Abstract: Cervical spinal cord injury causes severe and often irreversible neurological impairments such as quadriplegia, significantly diminishing patients' quality of life (QOL). Despite decades of intensive research, a fundamental treatment has yet to be established. To address this issue, we are currently developing the "Wrap Around Neural-Pass," a fully implantable neuromodulation device on the cervical spinal cord. This device enables localized and precise modulation of spinal neural circuits. In this study, we conducted an in vivo functional evaluation of its core component, the flexible neural probe, known as the "Wrap Around Electrode." The Wrap Around Electrode was fabricated using photolithography-based microfabrication techniques, employing SU-8 as the flexible substrate and gold (Au) as the electrode material. The array comprises 31 rows circumferentially and 3 columns longitudinally, totaling 93 recording channels. This configuration enables high-resolution mapping of neural activity across both circumferential and rostrocaudal axes. It allows the identification of neural activity presence and intensity along the circumference, as well as the direction of conduction (ascending or descending), facilitating discrimination of region-specific activity in spinal tracts such as the dorsal column and corticospinal tract.
The electrodes exhibited an impedance of approximately 1 MΩ at 1 kHz, demonstrating its suitability for stable and high-fidelity neural recording. Experiments were conducted using 8-week-old female Sprague-Dawley rats. Biphasic pulse stimulation was applied to the sciatic nerve at 10-second intervals using a stimulator and isolator to evoke ascending sensory neural activity. Evoked potentials were recorded epidurally using the Wrap Around Electrode, followed by signal averaging with synchronization. Clear evoked peaks were observed compared to the no-stimulation condition. In addition, variations in peak latency across electrodes were also observed. The results suggested the successful recording of multiple types of neural activity propagating through distinct spinal pathways. These findings support the Wrap Around Electrode's ability to resolve spatially and temporally diverse neural responses and to discriminate region-specific activity within the cervical spinal cord. This study represents a critical step toward realizing the Wrap Around Neural-Pass. It provides a foundation for next-generation neuromodulation technologies designed to restore neural function after cervical spinal cord injury.

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Poster

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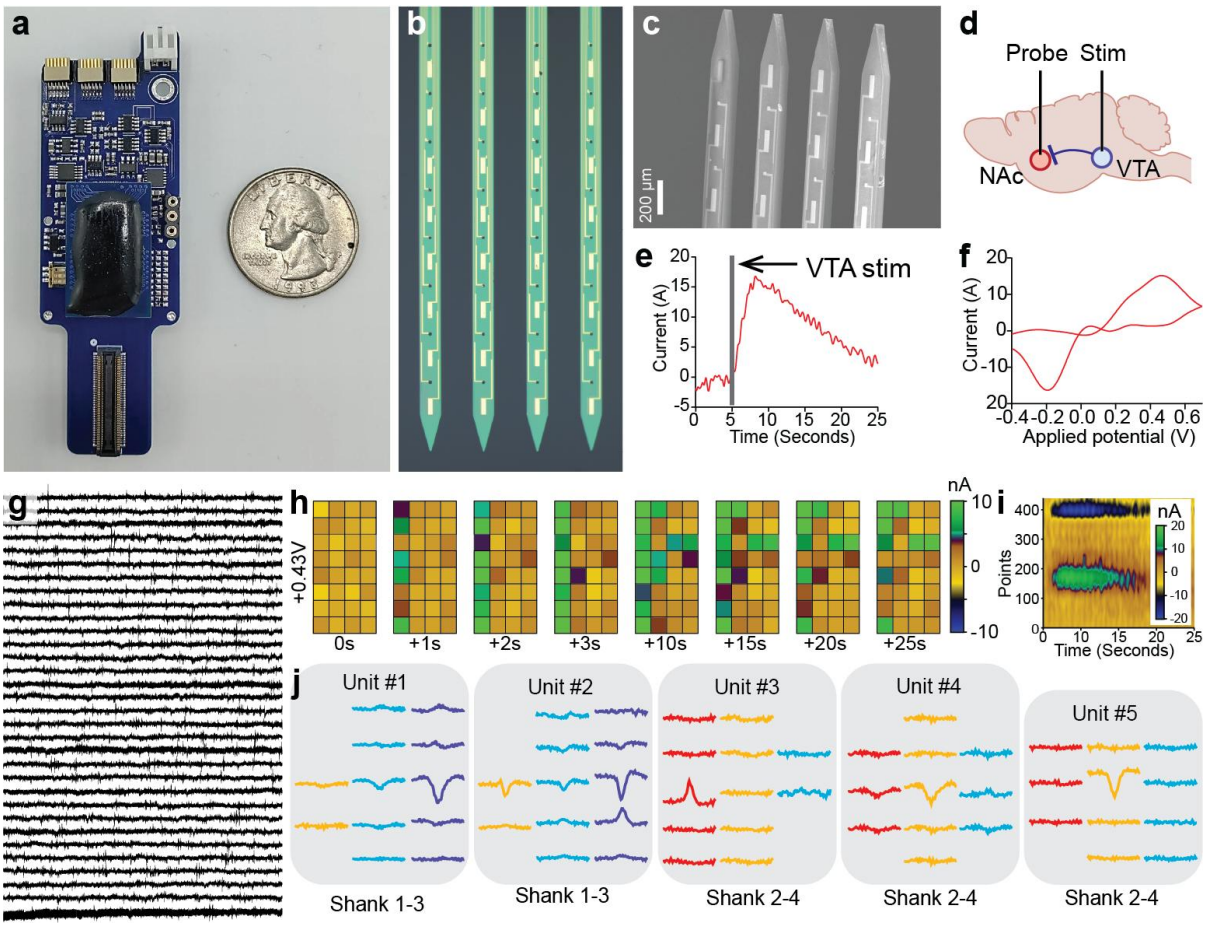
Topic: F.05. Brain-Machine Interface

Support: NSF Grant 2411567
NSF Grant 2143140
AFOSR Grant FA9550-21-1-0117

Title: High-density dual-mode probe technology for simultaneous recordings of dopamine and neural spike activities

Authors: *K. A. WHITE, M. DARROUDI, M. A. CROCKER, V. S. BAPANAPALLI, C. S. LIPSCOMB, B. S. JOHN, L. S. BARAKAT, B. N. KIM;
Bioengineering, The Univ. of Texas at Dallas, Richardson, TX

Abstract: Dopamine (DA) is a critical neurotransmitter in reward-driven behaviors, motor control, and cognitive functions. To better understand the intricate role of DA in various behaviors, new neurotechnology is needed for high spatiotemporal mapping of sub-regional heterogeneous DA distribution in the brain. Current methods for capturing neurochemical activity is insufficient as they lack either the spatial resolution for high-density mapping (carbon fiber electrodes) or the temporal resolution (functional Magnetic Resonance Imaging).
To address this emerging need in neurotechnology, we have developed a high-density dual-mode system that can simultaneously map DA and neural spike activity. The presented system combines 32 neurochemical and 32 neural spike channels on a single headstage (Fig. a). Our current probe design features four shanks, each shank with eight electrodes for both modalities, a pitch of 300 µm along each shank for both neurochemical and neural spike electrodes, and a 336 µm pitch between shanks (Fig. b-c). For the data collected using our system, we placed the probe in the nucleus accumbens and stimulated the brain at the ventral tegmental area, a known dopaminergic pathway (Fig. d-f). We successfully demonstrated simultaneous recordings of heterogeneous distribution of DA using fast-scan cyclic voltammetry, with the oxidation signal occurring at +0.43 V (Fig. h-i), and neural spike activity, with neural units identified by Kilosort4 (Figs. g and j).
Using the presented high-density dual-mode probe technology, we can study the spatiotemporal and heterogeneous distribution of DA, as well as the simultaneous neural spike activity, from dopaminergic pathways. This new technology offers the potential to yield new insights into our understanding of dopaminergic dysregulation due to psychiatric disorders like depression and addiction, as well as neurological disorders such as Parkinson’s and Alzheimer’s disease which leads to motor and cognitive impairments.



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Poster

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Program #/Poster #: PSTR456.11/Y2

Topic: F.05. Brain-Machine Interface

Support: NIH: R01:EB027584
ANR-18-NEUC-0002-02

Title: Enhancing Selectivity of Neuromodulation with Intrafascicular Stimulation of the Vagus Nerve

Authors: *A. ORTEGA SANABRIA[1], A. HOLMES[1], L. REGNACQ[2], J. ASBEE[1], D. IRBY[3], J. LOWERY[3], L. M. MCPHERSON[4], R. JUNG[1], J. J. ABBAS[1];

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Abstract: Vagus nerve stimulation (VNS) is an FDA approved therapeutic approach to treating epilepsy, depression and, more recently, stroke. However, the effectiveness of this bioelectronic medicine approach is limited by its side effects such as cough and dyspnea, which contributes to poor patient adherence to the treatment protocols. VNS side effects are predominantly caused by the activation of motor fibers that activate the muscles within the neck. Enhanced selectivity for VNS is necessary to achieve the desired therapeutic outcome while avoiding unwanted activation of these motor fibers. We have previously demonstrated that subfascicular selectivity can be achieved using longitudinal intrafascicular electrodes (LIFEs) for neurostimulation. In this study, in a porcine model, we explored the use of LIFEs for enhancing selectivity on VNS. Autonomic responses to the stimulation were collected by recording heart rate (HR) using an electrocardiogram (ECG), blood pressure (BP) with a transducer in the femoral artery and respiratory rate (RR) using a breathing belt. M-waves on muscle activation of the cricothyroid (CT) were recorded using a 32-channel High-Density epymisial electromyogram (HD-eEMG) grid. Acute experiments were conducted in anesthetized domestic pigs (2 male and 2 female). A three-contact cuff electrode was implanted for baseline recording and then 4 to 6 LIFEs were implanted in the left vagus nerve. Monopolar biphasic symmetrical square pulses were delivered at pulse width (PW) between 300-400 μs at four different pulse amplitudes (PAs) (below and above threshold) at 30 Hz for 30 seconds using a custom neurostimulator, with 2 minutes rest in between PAs. The threshold of nerve fiber activation was determined as the PA that stopped breathing. Root mean square of the M-wave responses on neurostimulation was used to assess spatiotemporal spread of muscle activity across the HD-eEMG grid using heatmaps. HR, BP and RR were calculated to assess the autonomic effects of VNS. Preliminary results showed that multiple LIFEs can be implanted in the pig vagus nerve, and fascicles can be activated selectively. The location of the LIFEs changes the magnitude of the effect on the RR and graded activation of the nerve fibers can be accomplished. These findings could provide insights into alternative approaches for stimulating more complex nerves and demonstrate how advanced stimulation strategies can ensure selective recruitment of end-organ functions thereby minimizing off-target effects.

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Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.12/Y3

Topic: F.05. Brain-Machine Interface

Title: The Microcircuitry within the hollow tip of the NeuroNexus Neurotrophic Electrode

Authors: *P. R. KENNEDY;
Neural Speech Inc, Duluth, GA

Abstract: The Neurotrophic Electrode (NE) has provided stable signals for years in rats, monkeys and humans including one human participant who exhibited stable signals a decade after implantation. The mechanisms underlying this stability are examined here by exploring the microcircuitry of the neuropil that grows into the tip of the electrode. Implantation of rat cortex with a new version of the NE provides the opportunity to study this microcircuitry. This updated 16 recording channel NE was microfabricated by NeuroNexus Inc. and is called the NeuroNexus Neurotrophic Electrode (NXNE). It has the same tip dimensions as the original NE. This poster describes the NXNE electrode and its microcircuitry, including its manufacture, assembly and recording characteristics, as well as the histology of the ingrown neuropil. The recording data includes numbers of axonal spikes verified by inter-spike interval histograms, auto correlograms and peri-event time histograms to blink responses and vibrissa deflections. Cross correlations combined with the histological data provide an understanding of the microcircuitry of the neuropil inside the tip of the electrode. The profile of the NE and NXNE contrasts sharply with all metal tipped electrodes that have significant challenges to signal stability and longevity. These promising findings suggest that the NXNE is an attractive electrode of choice for lifetime recording.

Disclosures: P.R. Kennedy: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neural Speech Inc. 100%, CEO.

Poster

PSTR456: BMI: Direct Neurophysiology

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.13/Y4

Topic: F.05. Brain-Machine Interface

Support: NIH Grant UH3NS120191

Title: Tendon vibration to enhance motor-related activity on the Stentrode

Authors: *A. K. FELDMAN[1], K. KACKER[2], N. VERMA[3], A. MERKLEY[4], N. CHETTY[3], J. BENNETT[6], P. YOO[7], N. Y. HAREL[8], D. LACOMIS[9], N. OPIE[6], J. L. COLLINGER[10], T. J. OXLEY[6], D. J. WEBER[5];
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Abstract: Brain-computer interfaces (BCIs) provide a novel modality by which users may interact with their surroundings. While there is a large focus on making these devices less invasive, there is growing curiosity surrounding how intuitive the devices are to operate. To this end, the role of somatosensory feedback in motor control, especially when supplemented alongside BCI usage, is of particular interest.
The Stentrode provides a platform by which we can probe this question. Seated in the Superior Sagittal Sinus, the Stentrode is delivered endovascularly via catheter and can record bilaterally from the motor (M1) and somatosensory (S1) cortices - crucial for measuring sensory input and motor output. Here, we present data from one participant from an Early Feasibility clinical trial in the United States (ClinicalTrials.gov, NCT05035823). We assess the effects of providing somatosensory feedback on both the strength of and quantifiable information within vascular electrocorticographic (vECoG) signals measured during a motor task. Though the participant in this analysis has severe paralysis from Amyotrophic Lateral Sclerosis, at the time of data collection they were partially ambulatory and reported no sensory deficits in the lower extremities. Thus, we constrained our collection to dominant ankle movement.
Three sensory feedback conditions were tested: no task-related feedback (motor imagery), typical task related feedback (motor attempt) and enhanced task-related feedback (motor attempt with vibration). In the first condition, the participant was asked to imagine slowly pulling their toes towards them with low force and holding for several seconds. During the second condition, the participant actually performed this movement, again at a low force level. The third condition again required the participant to perform the low force movement with the addition of vibration along the Achilles tendon. This tendon vibration aims to entrain muscle spindles in the ankle extensor muscles during a dynamic task, evoking the sensation of a longer, faster and higher force movement than the participant is actually performing. By assessing power differences between rest and the movement hold, we found that tendon vibration enhances motor related Beta (13-30 Hz) desynchronization during a low force movement to be similar or greater than that observed during a maximal force movement. Additionally, we investigate the flow of information from S1 to M1 along the Stentrode during motor imagery, motor attempt and motor attempt with vibration using directed information theoretic measures.

Disclosures: A.K. Feldman: None. **K. Kacker:** None. **N. Verma:** None. **A. Merkley:** None. **N. Chetty:** None. **J. Bennett:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options from Synchron. **P. Yoo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options from Synchron, Patent holder with Synchron. **N.Y. Harel:** None. **D. Lacomis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UptoDate. **N. Opie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options from Synchron, Patent holder with Synchron, Cofounder of Synchron. **J.L. Collinger:** None. **T.J. Oxley:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options from Synchron, Patent holder with Synchron, Cofounder of Synchron. **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, Stock options from NeuronOff, Cofounder of Reach Neuro, Inc, Cofounder of Bionic Power, Inc, Shareholder in Bionic Power, Inc.

Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.14/Y5

Topic: F.05. Brain-Machine Interface

Title: Thermally drawn multifunctional all-hydrogel fibers for anti-fibrotic and multimodal neural interfaces

Authors: *C. SUNG[1], K. NAM[2];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]KAIST, Daejeon, Korea, Republic of

Abstract: Hydrogels have emerged as promising candidates for the development of anti-fibrotic interfaces, owing to their mechanical and chemical resemblance to native biological tissues. Nevertheless, their implementation in multimodal interfaces remains limited, largely due to the technical challenges associated with micro-structuring multiple functional hydrogels within confined spatial resolutions. In this research, we present a thermal drawing process that enables the integration of several thermoplastically deformable, functional hydrogels into a single, compact multimodal fiber. By systematically optimizing critical processing parameters, we successfully fabricated compact, multifunctional neural interfaces composed entirely of hydrogel fibers. These fibers offer a novel approach for anti-fibrotic neural interfacing by concurrently reducing gliosis through their high mechanical compliance and facilitating immediate anti-inflammatory drug delivery via the hydrogel itself upon implantation. Moreover, these multifunctional fibers allow for the seamless incorporation of diverse hydrogel-based components, including a step-index hydrogel optical fiber, an electrically conductive hydrogel electrode, and a hydrogel-based microfluidic channel. The integrated design enables a range of multimodal functionalities, which we demonstrate through applications such as neural signal monitoring (e.g., single-unit recordings) and neural modulation (including optically evoked potentials and chemically induced neural circuit activation).

Disclosures: C. Sung: None. **K. Nam:** None.

Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.15/Y6

Topic: F.05. Brain-Machine Interface

Title: Improved Electrode Material for Deep Brain Stimulation

Authors: *A. PETROSSIANS;
EPIC Med. Inc., Pasadena, CA

Abstract: *Abstract*— In the United States, over 100,000 deep brain stimulation (DBS) devices have been implanted to date for treatment of basic tremor, Parkinson's disease and dystonia, and clinical trials are underway to evaluate indications for chronic pain, severe depression, migraines and dimentia. DBS devices belong to a class of devices called implantable electrical stimulators, and close to 1 million of these devices are implanted annually. These devices use electrodes in contact with tissue to deliver electrical pulses to targeted cells, to elicit specific therapeutic responses. Devices must be replaced as batteries wear down, thus improvements in device efficiency will extend device lifetime and reduce the number of replacement surgeries. While effective in many cases, DBS shows limited effectiveness in others and also has side effects. Preclinical studies predict that DBS arrays comprised of many densely packed, small electrodes can precisely target brain stem region to improve therapy. In general, the neuromodulation industry has been evolving towards smaller, less invasive electrodes. Thus, there are strong clinical, engineering and power motivations for moving towards smaller electrodes. However, current electrode materials do not support small sizes without severely restricting the stimulus output. Hence, an improved electrode material will benefit present and future DBS systems.

Disclosures: A. Petrossians: None.

Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

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Program #/Poster #: PSTR456.16/Y7

Topic: F.05. Brain-Machine Interface

Support: NIH R01DC020707
NIH F99AG088438
NSF 2416385

Title: Recording local field potentials from DBS implants with sensing capability during behavioral experiments: common artefacts and signal processing solutions

Authors: *H. WANG[1], J. A. HERRON[2], G. CLER[1], A. KO[2], L. MAX[1];
[1]Dept. of Speech and Hearing Sci., [2]Dept. of Neurolog. Surgery, Univ. of Washington, Seattle, WA

Abstract: The neural circuits associated with subcortical structures, such as the basal ganglia and the cerebellum, are critical to human behaviors. However, direct neurophysiological evidence from these structures in humans has been limited due to methodological constraints. Medtronic Percept(TM) PC neurostimulator is the first commercially available deep brain stimulation (DBS) device capable of sensing local field potentials (LFPs) by means of the electrodes implanted in target structures such as the subthalamic nucleus (STN) or the internal

globus pallidus (GPi) in patients with Parkinson's disease (PD), or the ventral intermediate nucleus of the thalamus (Vim) in patients with essential tremor (ET). Thus, it offers exciting research opportunities by allowing investigators to record neural activity from subcortical structures outside of the operating room. Here, we report cases in which STN, GPi, or Vim LFPs were recorded from patients performing various behavioral tasks, and we focus on several common signal artefacts and possible techniques to remove them.
All data were recorded from patients implanted with the Percept(TM) PC neurostimulator in STN, GPi, or Vim who performed a series of speech production tasks twice, once with DBS ON and once with DBS OFF. During the tasks, LFPs were sampled at 250 Hz and transmitted wirelessly to a tablet. We also applied surface electrodes to patients' head and neck area and concurrently digitized the signal from these surface electrodes and the acoustic speech signal into a single A/D system. The DBS status (ON/OFF) was quickly switched at the beginning and end of each task to intentionally induce simultaneous artefacts in the LFP and surface electrode signals as this allows us to temporally align the LFP and speech acoustic data offline.
LFPs have been recorded from 6 PD patients with STN-DBS, 2 PD patients with GPi-DBS, and 1 ET patient with Vim-DBS. Bilateral sensing was possible for 6 patients, whereas sensing was limited to one hemisphere for 3 patients. The ON/OFF switching induced a sequence of artefacts in the LFPs and surface electrode signals that was unique to each patient. With DBS ON, we identified several forms of contamination of the LFP signal, including artefacts at the stimulation frequency and its harmonics, artefacts due to aliasing, and regular and irregular cardiac artefacts. Stimulation-induced high gamma entrainment was also observed in some PD patients. Thus, to analyze the LFPs recorded from DBS implants for behavioral neuroscience studies, it is imperative to closely inspect the signals from individual patients and combine multiple signal processing techniques to minimize artefacts.

Disclosures: H. Wang: None. **J.A. Herron:** None. **G. Cler:** None. **A. Ko:** None. **L. Max:** None.

Poster

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Program #/Poster #: PSTR456.17/Y8

Topic: F.05. Brain-Machine Interface

Title: Axon Probes: a flexible high-density neural probe with 512 recording sites and 512 µLEDs with integrated signal processing for chronic electrophysiology

Authors: *M. ROTHMAN, E. RAY, S. SANCTIS, H. JANG, A. DASGUPTA, N. SLAGER, V. THERAYIL SASIKUMAR, E. B. KNUDSEN, K. ZAPPITELLI, J. REEDER, Y. KONG, M. J. HODAK;
Sci. Corp., Alameda, CA

Abstract: Flexible neural probes are preferred for chronic neural recordings due to their mechanical compatibility with brain tissue, but manufacturing active probes on a flex substrate is difficult due routing constraints and system integration challenges. Here we present Axon Probes, a novel class of flexible neural interface with integrated ASICs that addresses the channel count limitations on existing chronically implanted thin film devices. This 4-layer metal and polyimide probe is fabricated with a 5 μm minimum feature size, incorporating up to 512 20×20 μm low-impedance titanium nitride (TiN) electrodes and up to 512 20x50 μm gallium nitride (GaN) μLEDs with 140 μm inter-site spacing. The layout of Axon Probes is configurable, allowing the active area to be customized into arbitrary geometries to support a range of user applications. The probe integrates the Nixel512 ASIC for on-probe amplification, filtering, and digitization, for 256 fully differential channels, significantly reducing noise and crosstalk compared to off-probe processing. The Nixel512 ASIC supports local-differential referencing for enhanced common-mode rejection as well as single-ended global referencing, and records at 12-bit resolution, with an adjustable sampling rate up to 32kHz. The system achieves a noise floor of 5.8 μV RMS, enabling high-fidelity detection of both action potentials and local field potentials. Integration of Pixel16k, a custom passive μLED driver ASIC, allows for simultaneous optogenetic stimulation and neural recording, enabling high-precision closed-loop neuroscience experiments. Validation studies in a rabbit model demonstrated successful chronic LFP recording with minimal tissue reaction over extended periods.

Disclosures: **M. Rothman:** A. Employment/Salary (full or part-time): Science Corporation. **E. Ray:** A. Employment/Salary (full or part-time): Science Corporation. **S. Sanctis:** A. Employment/Salary (full or part-time): Science Corporation. **H. Jang:** A. Employment/Salary (full or part-time): Science Corporation. **A. Dasgupta:** A. Employment/Salary (full or part-time): Science Corporation. **N. Slager:** A. Employment/Salary (full or part-time): Science Corporation. **V. Therayil Sasikumar:** A. Employment/Salary (full or part-time): Science Corporation. **E.B. Knudsen:** A. Employment/Salary (full or part-time): Science Corporation. **K. Zappitelli:** A. Employment/Salary (full or part-time): Science Corporation. **J. Reeder:** A. Employment/Salary (full or part-time): Science Corporation. **Y. Kong:** A. Employment/Salary (full or part-time): Science Corporation. **M.J. Hodak:** A. Employment/Salary (full or part-time): Science Corporation.

Poster

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Program #/Poster #: PSTR456.18/Y9

Topic: F.05. Brain-Machine Interface

Support: NSF Grant 2411567
NSF Grant 2143140
AFOSR Grant FA9550-21-1-0117

Title: A Fully Wireless High Spatiotemporal Resolution FSCV-based Neurochemical Sensing System for Untethered Animal Studies

Authors: *M. CROCKER[1], K. WHITE[1], B. KIM[2];
[2]Bioengineering, [1]Univ. of Texas at Dallas, Richardson, TX

Abstract: Dopamine (DA) is heterogeneously distributed spatially and temporally throughout the brain. DA regulation significantly contributes to human motor control, motivation, reward, and behavior selection. Major healthcare challenges ranging from addiction and mental illness to neurodegenerative disorders are directly modulated by these regulatory processes. There is a need for a system capable of direct measurement of neurochemical signaling, with high spatial and temporal resolution, to elucidate the role of neurochemical transmission. This work focuses on neurochemical sensing across dense electrode arrays for the investigation of extracellular neurotransmitter regulation and dysfunction, specifically targeting heterogeneous dopamine regulation and the neural circuitry of the brain. These regulation processes directly affect behavior, as a result, it is desirable for this work to minimize all possible behavioral influences on animal models. Thus, it is beneficial to provide the capability for this work to operate tether-free.
A miniaturized wireless neurochemical sensing technology is presented in this work. The system features an array of 32 neurochemical amplifiers capable of simultaneous measurement of neurochemical concentrations across a connected array of 32 microelectrodes using fast-scan cyclic voltammetry (FSCV). A high-density neurochemical amplifier array CMOS chip has been designed, fabricated, and validated. The system uses a field-programmable gate array (FPGA) for system control, enabling the FSCV process, allowing specified-at-runtime waveforms and timing through digital-to-analog converters (DACs), data acquisition through analog-to-digital converters (ADCs), as well as data processing and packaging. A wireless module handles the transmission process and can support up to 45 megabits/second of data throughput. This work is designed for head-mounting on rats, as such, the system minimizes size and weight.

Disclosures: M. Crocker: None. **K. White:** None. **B. Kim:** None.

Poster

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Program #/Poster #: PSTR456.19/Y10

Topic: F.05. Brain-Machine Interface

Title: Advanced Regenerative Peripheral-Nerve Interfaces

Authors: *J. W. JUDY[1], B. SMADI[1], K. A. FLUKER JR.[1], L. JIRACEK[1], M. A. SCHIEFER[2];
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Abstract: We report on the design, fabrication, and in vitro characterization of advanced regenerative peripheral-nerve interfaces that integrate three-dimensional microelectrode arrays into various biologic nerve conduits and scaffolds. Unlike our prior work on Tissue-Engineered Electronic Nerve-Interface (TEENI), which relied on templated hydrogels or empty conduits, our new advanced regenerative peripheral-nerve interfaces use a stingray-shaped thread-set design that is embedded directly into the biologic nerve conduits based on small intestine submucosa (SIS) and nerve scaffolds based on decellularized nerve allografts. These approaches use a native scaffold to improve the number and density of microchannels that regenerate adjacent to microelectrode arrays while simultaneously maintaining their positioning accuracy and mechanical stability. The nerve interfaces we describe are best suited for amputees and could be implanted as part of a targeted muscle reinnervation (TMR) surgical procedure.

Disclosures: J.W. Judy: None. **B. Smadi:** None. **K.A. Fluker Jr.:** None. **L. Jiracek:** None. **M.A. Schiefer:** None.

Poster

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Program #/Poster #: PSTR456.20/Y11

Topic: F.05. Brain-Machine Interface

Title: Brain Controlled Epidural Spinal Cord Stimulation Modulates Descending Motor Control After Spinal Cord Injury

Authors: *Z. BOOGAART[1], R. FADLI[1], A. SASAKI[2], A. YUASA[4], N. MUSIKIC[1], H. SAITO[5], R. DE FREITAS[6], N. MACELLARI[7], J. D. GUEST[3], E. PIRONDINI[8], M. CAPOGROSSO[9], M. MILOSEVIC[10];
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Abstract: Epidural spinal cord stimulation (ESCS) is widely used in neurosurgery for chronic pain management. In recent years, research has explored its potential to modulate spinal circuits and improve motor function in individuals with stroke, spinal cord injury (SCI), and movement disorders. However, few studies have examined ESCS paired with a brain-computer interface (BCI) for upper-limb motor recovery. We present the month-long findings and follow-up for chronic, cervical SCI participants who underwent BCI-ESCS therapy after unilateral cervical ESCS placement. To assess whether ESCS could enhance arm function in a combined BCI-ESCS paradigm, percutaneous leads were placed in the right epidural space caudal to the injury,

targeting upper-limb sensorimotor circuits through the dorsal rootlets from approximately C5 to T1. Over one month, the participants showed improved grasping and reaching abilities paired with improvements in electrophysiological outcomes indicative of neuroplastic changes. Upper-limb function was assessed using the Toronto Rehabilitation Institute Hand Function Test (TRI-HFT) and Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) at baseline, post-therapy, and one month after explant. The TRI-HFT object manipulation task improved by an average 12.5 points in the targeted right hand across subjects. The GRASSP quantitative prehension score increased by an average 3.5 points in the targeted right hand across subjects. Additionally, the participants showed significant improvements in MEP amplitude from baseline to immediately following one month of BCI-ESCS therapy, signifying long-term potentiation and synaptic plasticity across the levels of injury. This data supports using ESCS to modulate descending control for upper-limb function and enhance activities of daily living after chronic cervical SCI. The findings establish a precedent for incorporating ESCS into future upper-limb rehabilitation studies.

Disclosures: Z. Boogaart: None. **R. Fadli:** None. **A. Sasaki:** None. **A. Yuasa:** None. **N. Musikic:** None. **H. Saito:** None. **R. de Freitas:** None. **N. Macellari:** None. **J.D. Guest:** None. **E. Pirondini:** None. **M. Capogrosso:** None. **M. Milosevic:** None.

Poster

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Location: SDCC Halls B-H

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Program #/Poster #: PSTR456.21/Y12

Topic: F.05. Brain-Machine Interface

Title: Assistive and short-term effects of brain-controlled epidural spinal cord stimulation on upper limb motor function in chronic cervical spinal cord injury

Authors: *A. SASAKI[1], R. FADLI[2], A. YUASA[3], Z. BOOGAART[2], H. SAITO[4], N. MUSIKIC[2], R. DE FREITAS[5], N. MACELLARI[6], E. PIRONDINI[7], J. D. GUEST[9], M. CAPOGROSSO[8], M. MILOSEVIC[10];
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Abstract: Spinal cord injury (SCI) disrupts corticospinal pathways and impairs voluntary movement, often resulting in chronic paralysis. For individuals with cervical SCI, upper-limb motor deficits severely limit independence and quality of life. Although epidural spinal cord stimulation (ESCS) can facilitate residual motor output by modulating spinal excitability, its capacity to promote rapid corticospinal plasticity remains uncertain, particularly for upper-limb function. Moreover, integrating ESCS with a brain-computer interface (BCI) that decodes motor

intent in real time may enhance its effects by aligning stimulation with volitional cortical activity.Here, we investigated the immediate (assistive) and short-term effects of a BCI-controlled cervical ESCS (BCI-ESCS) system in individuals with chronic cervical SCI. Participants performed a series of upper-limb motor tasks, including grasping, reaching, and object manipulation, under three experimental conditions: no stimulation, tonic ESCS (continuous stimulation), and BCI-ESCS (triggered by electrocortical detection of motor intent). During stimulation, both ESCS paradigms improved motor performance compared to no stimulation, but BCI-ESCS elicited substantially greater grip force, indicating a stronger assistive effect. Improvements in functional tasks such as reaching and object manipulation under both stimulation conditions further support the role of cervical ESCS in facilitating upper-limb output, even in the absence of overt descending control.To examine short-term effects, we compared neurophysiological and motor performance before and after a single 28-minute session. Following BCI-ESCS, but not tonic ESCS, motor-evoked potentials (MEPs) recorded from the extensor and flexor carpi radialis muscles significantly increased, indicating enhanced corticospinal excitability. These changes emerged rapidly, suggesting that intent-driven stimulation can engage activity-dependent plasticity mechanisms even in chronic SCI. This rapid modulation of corticospinal excitability may underlie more substantial gains when BCI-ESCS is applied over repeated therapeutic sessions. Although behavioral improvements (e.g., Box and Block Test) were modest, the electrophysiological findings indicate meaningful neurophysiological remodeling.Together, these findings demonstrate that BCI-ESCS not only immediately amplifies volitional motor output but also induces short-term corticospinal facilitation in chronic SCI. This intent-driven approach may serve as a powerful platform for neuromodulation-based therapy aimed at restoring upper-limb function.

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Poster

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Topic: F.05. Brain-Machine Interface

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Intramural grant 132584

Title: Development and Multimodal Validation of a Sub-10-µm-Diameter Electrode Intracortical Array in a Large Animal Model for Brain-Computer Interfaces

Authors: *J. L. W. LAM[1], J. G. LETNER[3], M. COPENHAVER[3], N. SLOSAR[4], M. ISBRECHT[4], L. A. WALKER[5], M.-C. CHENG[4], A. WARD[2], K. PALOKAJ[4], J. SIMONS[4], A.

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[1]Neurosurg., [2]Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [3]Biomed. Engin., [5]Cell and Developmental Biol., [4]Univ. of Michigan, Ann Arbor, MI; [6]Biomed. Engin., Univ. of Michigan, ANN ARBOR, MI; [7]Cell and Developmental Biol., Michigan Neurosci. Institute, Univ. of Michigan, Ann Arbor, MI

Abstract: The Utah Electrode Array (UEA) currently is the gold standard recording hardware for intracortical speech and motor brain-computer interfaces (BCIs). However, its clinical viability is limited by glial scarring, immune response, neuronal loss, and an average lifespan of 1.7 years (Sponheim, 2021). Carbon-fiber electrode arrays (CFEAs) are 5-10 times thinner, biocompatible, and electrophysiologically stable over time (Patel, 2016). However, implantating arrays of sub-10-µm-electrodes in animals larger than rodents is challenged by inherent buckling and breakage of such scale electrodes against the thicker leptomeninges of larger animals. CFEAs (10 x 10, 9.4-µm diameter, 1-mm length, blowtorch sharpened, Parylene C coated, 400-µm pitch) were inserted into cortex of N = 4 sheep in vivo with intact leptomeninges at 0.1 mm/s. 15/16 CFAs fully inserted with a maximum force of 36.0 ± 21.7 mN, 1.76±0.58 mm of brain dimpling, and negligible bleeding. At the same velocity, the UEA failed to insert below the 98 mN (10 g) load cell capacity. Pneumatically inserted UEAs caused immediate visible bleeding. Preliminary analysis of relative red intensity of white light epi-illuminated 300-µm histological slices in N = 1 sheep revealed minimal hemorrhage in CFA-implanted brain (0.505 ± 0.70% intensity) compared to UEA-implanted brain (15.6 ± 5.7%, $p < 0.0001$). Beyond microelectrode arrays, there is great interest in wireless, individualized electrodes, often termed "neural dust" (Seo 2016), but accurately implanting these submillimetric devices is an ongoing challenge. We tested the feasibility of implanting carbon fiber "motes", consisting of a carbon fiber (8.4-µm diameter, 1-mm length, sharpened) in a nonfunctioning 240 x 240 x 300 µm silicon chip, mounted in dissolvable polyethylene glycol on an insertion rod. A 4 x 4 array of motes was chronically implanted in N = 1 sheep. All 16 motes in the array successfully inserted with no complications. Ongoing work includes immunohistochemistry to determine acute effects on neuronal density and the chronic histological response after 6 months of implantation.

Disclosures: J.L.W. Lam: A. Employment/Salary (full or part-time): University of Michigan. **J.G. Letner:** None. **M. Copenhaver:** None. **N. Slosar:** None. **M. Isbrecht:** None. **L.A. Walker:** None. **M. Cheng:** None. **A. Ward:** None. **K. Palokaj:** None. **J. Simons:** None. **A. Hite:** None. **D. Cai:** None. **C.A. Chestek:** A. Employment/Salary (full or part-time): University of Michigan.

Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.23/Y14

Topic: F.05. Brain-Machine Interface

Support: ERC Consolidator Grant in Living Bionics (771985-1)

Title: An organotypic model to study biohybrid interfaces ex vivo

Authors: ***M. BOULINGRE**[1], R. PORTILLO LARA[2], R. GREEN[2];
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Abstract: Biohybrid approaches have been explored to promote the biological integration of neural implants into the nervous system. One salient example is the use of tissue engineered coatings to bridge the communication gap between physiological tissues and implantable neural interfaces. However, conventional in vitro models poorly replicate these complex phenomena, and *in vivo* studies are limited by low throughput, high cost and ethical concerns. This study reports the development of an organotypic model to study cell level responses within biohybrid interfaces *ex vivo*.Heterocellular constructs were generated by encapsulating primary neural progenitor cells (NPCs) isolated from E14 Sprague-Dawley (SD) embryos, which were co-cultured with primary hippocampal astrocytes that were isolated from P4 SD pups. Biosynthetic poly-vinyl alcohol-gelatin (PVA-GEL) hydrogels were used to support the growth and differentiation of encapsulated cells *in vitro*. Organotypic hippocampal slices from P4 SD pups were then grown on top of the cell-laden hydrogels and maintained *in vitro* for up to 3 weeks. Morphological and phenotypic assessment of lineage differentiation was performed via immunofluorescent staining (IFS) and confocal microscopy.Fluorescence and bright-field micrographs showed that organotypic slices could effectively develop and integrate into the underlying neural construct, as demonstrated by the presence of β-tubulin III^+ neurons and a migratory edge comprised mainly of $GFAP^+$ astrocytes. IFS of pre- and post-synaptic markers (i.e., synaptophysin and PSD95, respectively) revealed the establishment of new synaptic connections between the construct and the target tissue.This organotypic approach provides multiple technical and scientific advantages to study biohybrid interfaces with higher physiological relevance than conventional cell-based models, as well as increased accessibility and convenience than animal models. Moreover, the ability to monitor the growth and the development of complex neural constructs in real time and with higher throughput holds great potential for applications in drug screening or disease modelling.

Disclosures: M. Boulingre: None. **R. Portillo Lara:** None. **R. Green:** None.

Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.24/Y15

Topic: F.05. Brain-Machine Interface

Support: HORIZON-EIC-2022-ACCELERATOR-01, Project No 190118958

Title: Recent Improvements of the Wireless Link of the CorTec Brain Interchange Implanted BCI

Authors: *M. SCHUETTLER[1], M. THEODOR[2], C. BENTLER[2], M. MOELLER[3], M. BURDUMY[2], C. GKOGKIDIS[2], F. KOHLER[2];
[1]Cortec GmbH, Freiburg Im Breisgau, Germany; [2]CorTec GmbH, Freiburg, Germany; [3]CorTec GmbH, Freiburg im Breisgau, Germany

Abstract: The CorTec Brain Interchange is an implanted sense/stim BCI that requires a wireless power and data link for operation. As the data link operates in the WiFi and Bluetooth frequency band (2.45GHz), interference is expected and will lead to drop of data packets.
Here, we investigate the influcence of the location of the antenna on the robustness of the wireless data link.
Material, Methods and Results:
Two scenarios are compared with respect to their wireless data link robustness: RF communication between the implant and the antenna located (A) in the communication unit, 30cm away from the implant and (B) in the headpiece, opposite to the implant. The data link performance is quantified as data packets lost in percent. Moving the antenna to the headpiece substantially reduced packet loss as shown in the table, in the scenarios investigated here.
Conclusion:
Change of antenna position from communication unit to headpiece improved the wireless link quality.

Disclosures: M. Schuettler: A. Employment/Salary (full or part-time): CorTec GmbH. **M. Theodor:** A. Employment/Salary (full or part-time): CorTec GmbH. **C. Bentler:** A. Employment/Salary (full or part-time): CorTec GmbH. **M. Moeller:** A. Employment/Salary (full or part-time): CorTec GmbH. **M. Burdumy:** A. Employment/Salary (full or part-time): CorTec GmbH. **C. Gkogkidis:** A. Employment/Salary (full or part-time): CorTec GmbH. **F. Kohler:** A. Employment/Salary (full or part-time): CorTec GmbH.

Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.25/Y16

Topic: F.05. Brain-Machine Interface

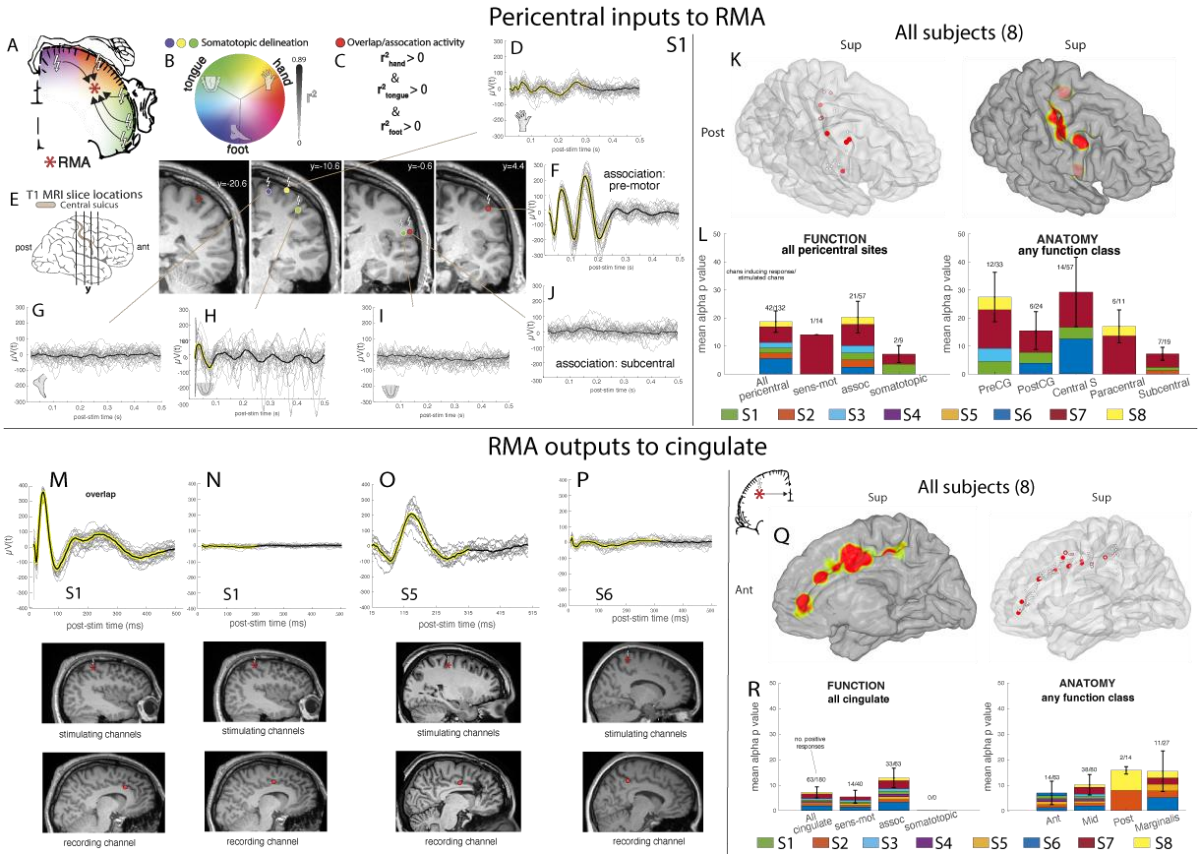
Support: NIH U01-NS128612
5F31NS135898-02

Title: Cortical connectivity of the Rolandic Motor Association Area

Authors: *M. JENSEN[1], M. MONTOYA[2], P. BRUNNER[4], D. HERMES[2], K. J. MILLER[3];
[2]Physiol. and Biomed. Engin., [3]Neurosurg., [1]Mayo Clin., Rochester, MN; [4]Dept. of Neurosurg., Washington Univ., St. Louis, MO

Abstract: Cortical connectivity of the Rolandic Motor Association AreaIntroduction:
Traditionally, the primary motor cortex was thought of as being organized somatotopically, in

which individual correspond control the movement of specific regions of the body. Recently, several works have come out describing challenging this model[1, 2], describing distinct regions where somatotopy is not present. This region has been named the Rolandic Motor Association area (RMA) and its exact role of these regions is dependent upon its connectivity with the rest of the brain. An exploration using into the effective connectivity of this region using single pulse electrical stimulation and the resulting Brain Stimulation Evoked Potentials (BSEPs) has yet to be performed. It is incumbent upon the field to pursue this as BSEPs provide additional temporal and morphological information regarding connectivity. **Methods:** Across eight subjects (5 female, ages 13-36), electrode pairs were stimulated up to 12 times each (average 10) with a single biphasic pulse of 6mA amplitude and 100 µs pulse width per phase every 3-7 s, using a g.EstimPro electrical stimulator (gTec, Schiedlberg, Austria) while BSEPs were recorded at all other sites. **Results:** Our results demonstrate that premotor regions appear to induce phase locked oscillations in the RMA implicating a functional role in movement while its strongest output is to the cingulate which may represent a connection to the limbic network. Interestingly, these interactions distinguish the RMA from many other subregions of the pericentral cortex.**Conclusion:** The RMA serves to communicates in a directionally specific manner to several regions of the cortex that unique from its counterparts in the precentral gyrus.
References1. Jensen, M.A., et al., *A motor association area in the depths of the central sulcus.* Nature neuroscience, 2023. **26**(7): p. 1165-1169.2. Gordon, E.M., et al., *A somato-cognitive action network alternates with effector regions in motor cortex.* Nature, 2023. **617**(7960): p. 351-359.



Disclosures: M. Jensen: None. **M. Montoya:** None. **P. Brunner:** None. **D. Hermes:** None. **K.J. Miller:** None.

Poster

PSTR456: BMI: Direct Neurophysiology

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Program #/Poster #: PSTR456.26/Z1

Topic: F.05. Brain-Machine Interface

Support: NINDS grant UH3NS095553
NSF GRFP

Title: Evaluating speech-motor outcomes in closed-loop deep brain stimulation for essential tremor

Authors: *A. BURGESS[1], A. GUNDUZ[1], K. FOOTE[2];
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Abstract: Deep Brain Stimulation (DBS) targeting the ventral intermediate nucleus (VIM) of the thalamus is an established therapy for patients with medication-refractory essential tremor (ET). However, speech-related side effects, such as dysarthria, frequently arise presumably from electrical current spreading into adjacent thalamic nuclei or cerebellothalamocortical tracts involved in speech coordination. Dysarthria is characterized by reduced intelligibility, articulation, precision, slurring, etc. with an upwards of twenty-nine percent of observed dysarthria following DBS surgery. After DBS surgery, it has been estimated that seventy-five percent of ET patients experience a disruption in quality of life as a result of speech difficulties. Closed-loop DBS (CL-DBS) is hypothesized to reduce speech effects by only delivering stimulation when tremor is detected; however, the evaluation of its performance on speech longitudinally is not widely known. The objective of this study is to investigate the tradeoffs of balancing tremor suppression and speech effects across open-loop (OL-DBS), CL-DBS, and DBS OFF conditions in five ET patients (4-unilateral, 1-bilateral) implanted with the Medtronic Summit RC+S device over 24 months. CL-DBS, stimulation was modulated in real-time based on neural biomarkers from local field potentials (LFPs) recorded from the thalamus. Speech was assessed using diadochokinesis (DDK) tasks that evaluates articulatory precision while tremor severity was independently rated by a blinded neurologist using the Fahn-Tolosa-Marin Tremor Rating Scale (TRS). The results indicated that CL-DBS achieved superior tremor suppression compared to OL-DBS and DBS-OFF longitudinally. However, OL-DBS and DBS OFF longitudinally preserved speech outcomes more effectively despite reduced tremor suppression compared to CL-DBS. While CL-DBS reduced incidence of speech effects in month-to-month analyzes, overall, it was not the preferred condition for ET patients experiencing speech effects. ET patients preferred OL-DBS and DBS-OFF qualitatively for speech despite the introduction of tremor, which suggests tradeoffs with optimizing DBS parameters. The significance of this work demonstrates the importance and feasibility of balancing closed-loop stimulation parameters to

optimize tremor suppression while minimizing adverse speech effects. This highlights the potential for CL-DBS to further enhance selectivity of closed-loop algorithms for speech preservation in ET.

Disclosures: A. Burgess: None. **A. Gunduz:** None. **K. Foote:** None.

Poster

PSTR456: BMI: Direct Neurophysiology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.27/Z2

Topic: F.05. Brain-Machine Interface

Title: GPCR-mediated optogenetic inhibition of Harmaline-induced tremor using eOPN3: in vivo kinetics and therapeutic potential

Authors: K. L. BAR-OR[1], E. SWISSA[1], Y. KFIR[1], I. SARAF-SINIK[2], O. YIZHAR[2], O. LEVI[1], ***Y. ELDAR**[1];
[1]Modulight Biotherapeutics, Boston, MA; [2]Weizmann Inst., Rehovot, Israel

Abstract: Essential tremor (ET) is a prevalent movement disorder characterized by debilitating rhythmic, involuntary oscillations. Despite its prevalence, current therapies often fail to provide sustained, targeted relief; thus, there is a critical need for novel, mechanism-based interventions. Here, we show that optogenetic inhibition of Purkinje cells axonal projections to the deep cerebellar nuclei (DCN), reduces tremor severity in a well-established harmaline-induced model of ET in mice. We use the engineered bistable type II opsin eOPN3, a GPCR opsin known for its superior light sensitivity and extended off-kinetics, making it suitable for translational applications. Targeted expression of eOPN3 in Purkinje cells was achieved through bilateral stereotactic injection of AAV5/2-CaMKII-eOPN3-mScarlet-WPRE-synp(A) in 2 months old C57BL/6 male mice, followed by implantation of an optical fiber above the deep cerebellar nuclei (DCN). Three months following viral injections, tremor was induced by IP injection of harmaline, and measured using an accelerometer-based system and high-speed videography. Illumination with green (535 nm) or red (625 nm) light resulted in an immediate and robust suppression of tremor. These effects were repeatable, within animals, and were not observed in control mice expressing only a fluorophore but not eOPN3. Notably, the tremor-suppressing effects persisted for ~2 minutes following light cessation, likely due to the off-kinetics of eOPN3 in the pre-synaptic terminal. While green light produced consistently strong effects, red light suppressed tremor albeit with faster offset kinetics and more variability. This study provides the first in vivo disease-relevant characterization of eOPN3 kinetics and establishes a compelling preclinical rationale for cerebellar-targeted, eOPN3 therapies for ET. Our findings also offer critical design parameters, including opsin dynamics, wavelength flexibility, and illumination duration, that will inform future development of optogenetic strategies for treating not only movement disorders but other neurological conditions.

Disclosures: **K.L. Bar-Or:** A. Employment/Salary (full or part-time): Modulight Bio. **E. Swissa:** A. Employment/Salary (full or part-time): Modulight Bio. **Y. Kfir:** A. Employment/Salary (full or part-time): Modulight Bio. **I. Saraf-Sinik:** None. **O. Yizhar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Modulight bio. **O. levi:** A. Employment/Salary (full or part-time): Modulight Bio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Modulight.bio. **Y. Eldar:** A. Employment/Salary (full or part-time): Modulight Bio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Modulight bio.

Poster

PSTR457: BMI: Decoding Methods

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.01/Z3

Topic: F.05. Brain-Machine Interface

Support: National Institutes of Health (NIH) R01MH123770
National Institutes of Health (NIH) R61MH135407
National Institutes of Health (NIH) RF1DA056402

Title: Nonlinear flexible dynamical modeling of human intracranial neural activity

Authors: ***K. VAZIRI**[1], L. L. OGANESIAN[1], H. JO[1], R. MARTIN DEL CAMPO VERA[1,2], C. Y. LIU[2], B. LEE[2], M. M. SHANECHI[1];
[2]Keck Sch. of Med., [1]USC, Los Angeles, CA

Abstract: Dynamical modeling of multiregional human intracranial neural activity has important translational implications, such as in the development of clinical brain-computer interfaces (BCIs) for treating neurological disorders. Many prior BCI works in modeling intracranial electroencephalography (iEEG) data have used linear state-space models given their nice properties, such as their capacity for flexible and real-time decoding. However, neural activity exhibits complex nonlinear dynamics that may not be adequately captured by linear models. Thus, it is beneficial to develop models of iEEG activity that capture nonlinearity while also enabling flexible inference. Recent work has introduced a deep learning approach termed DFINE that combines neural networks with stochastic state-space models to both capture nonlinearity and enable flexible inference (Abbaspourazad, H. et al. 2024). However, DFINE was developed for intracortical spiking and local field potential activity in non-human primates. Here, we extend DFINE for modeling of multiregional iEEG recordings from the human brain. We compare DFINE against a linear state-space model and a gated recurrent unit (GRU), and evaluate each model's ability to forecast future neural activity from the past. Across datasets from multiple human subjects, we demonstrate that the nonlinear models better forecast iEEG activity. Moreover, even though DFINE, unlike GRU, uses a linear state-space backbone to enable

flexible inference, it still performs comparably to GRU in neural forecasting. Taken together, DFINE can provide a useful tool for accurate modeling of human intracranial neural recordings with important implications in the development of next-generation BCIs and closed-loop neuromodulation systems.

Disclosures: K. Vaziri: None. **L.L. Oganesian:** None. **H. Jo:** None. **R. Martin Del Campo Vera:** None. **C.Y. Liu:** None. **B. Lee:** None. **M.M. Shanechi:** None.

Poster

PSTR457: BMI: Decoding Methods

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.02/Z4

Topic: F.05. Brain-Machine Interface

Support: NIH Grant DP2MH126378
NIH Grant RF1DA056402

Title: Probabilistic geometric principal component analysis (PGPCA) learns the distribution of neural population activity around nonlinear manifolds

Authors: *H.-L. HSIEH[1], M. M. SHANECHI[2];
[1]Electrical and computer engineering, USC, Los Angeles, CA; [2]Electrical and Computer Engin., Univ. of Southern California, Los Angeles, CA

Abstract: Numerous studies have demonstrated that neural population activity is distributed around a low-dimensional nonlinear manifold embedded within a high-dimensional Euclidean space. As such, accounting for this underlying manifold structure can significantly enhance the efficacy of dimensionality reduction techniques for neural data. However, a major challenge in doing so is that, due to its inherent noise and high dimensionality, neural population activity does not lie precisely on top of a low-dimensional manifold but is distributed around it. This probabilistic attribute must also be considered in neural dimensionality reduction. While probabilistic PCA (PPCA) and its extensions perform probabilistic dimensionality reduction, they are mainly based on linear models and can only describe the data in a Euclidean coordinate system around the mean of data rather than around a nonlinear manifold. To fill this gap, we develop Probabilistic Geometric Principal Component Analysis (PGPCA), a new dimensionality reduction algorithm that merges probabilistic modeling and geometry and can explicitly incorporate knowledge about a given nonlinear manifold that is first fitted from data. Additionally, we derive a manifold-based geometric coordinate system, different from the Euclidean system, to capture the deviation of the data from the manifold. Finally, we provide a data-driven learning algorithm for fitting the PGPCA models. Through analysis of neural recordings from the mice thalamo-cortical head direction circuit, we find that neural firing rates are distributed not precisely on, but around, a loop manifold. We then find that PGPCA significantly outperforms PPCA in modeling the data. Furthermore, PGPCA not only enables

dimensionality reduction aligned with the manifold structure but also provides a probabilistic framework for testing whether a geometric coordinate system offers a better fit than the Euclidean counterpart. Intriguingly, we find that the geometric coordinate system more accurately captures the deviation of the firing rates from the main loop manifold compared with the Euclidean one, suggesting that the noise not accounted for by the main loop manifold also originates from the same geometric structure rather than being in the Euclidean space. In summary, PGPCA enhances the efficacy of modeling high-dimensional, noisy datasets, particularly in neuroscience, by incorporating manifold geometry into probabilistic frameworks for dimensionality reduction.

Disclosures: H. Hsieh: None. **M.M. Shanechi:** None.

Poster

PSTR457: BMI: Decoding Methods

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.03/Z5

Topic: F.05. Brain-Machine Interface

Support: NIH R01MH123770
NIH R61MH135407
One Mind Foundation Rising Star Award
Foundation for OCD Research (FFOR)

Title: Cross-subject spatiotemporal modeling of multi-regional intracranial human brain activity

Authors: *S. HASHEMI[1], L. L. OGANESIAN[2], M. M. SHANECHI[2];
[1]Computer Sci., [2]Electrical and Computer Engin., USC, Los Angeles, CA

Abstract: Human intracranial electrophysiology (iEEG) enables simultaneous measurement of multiregional neural activity across multiple days, making it a useful tool for studying brain network activity. However, modeling and analyzing intracranial neural recordings is challenging due to the complex spatiotemporal interactions that they exhibit. Moreover, inter-individual variability in electrode placement and recording locations may further complicate cross-subject analyses. To address these challenges, we present a novel transformer model designed to encode temporal and spatial features to achieve cross-subject/session modeling of iEEG data. Further, we demonstrate that our model, when trained using a self-supervised masked reconstruction task, is capable of learning rich latent representations that can be used for downstream decoding. Taken together, our modeling framework can be a useful tool for studying complex spatiotemporal interactions in multiregional, intracranial neural recordings, with possible implications for the design of iEEG neural foundation models.

Disclosures: S. Hashemi: None. **L.L. Oganesian:** None. **M.M. Shanechi:** None.

Poster

PSTR457: BMI: Decoding Methods

Location: SDCC Halls B-H

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Program #/Poster #: PSTR457.04/Z6

Topic: F.05. Brain-Machine Interface

Support: NIH R61MH135407
NIH DP2MH126378
NIH RF1DA056402
NSF CRCNS IIS-2113271

Title: Multimodal neural fusion for studying brain-behavior relationships

Authors: *P. AZIZEDDIN, E. ERTURK, M. M. SHANECHI;
Electrical and Computer Engin., USC, Los Angeles, CA

Abstract: Understanding how neural activity gives rise to behavior can be advanced by integrating different measurement modalities that reflect distinct spatial and temporal aspects of brain function. Different neural recording modalities—such as spiking activity and local field potentials (LFPs)—offer complementary views of neural processes. Spiking activity reflects rapid, transient events at the scale of individual neurons and millisecond timescales while LFPs capture slower activity patterns that evolve over broader timescales and spatially integrate signals from larger neuronal populations. Moreover, behavioral signals reflect high-level outputs of the brain and often exhibit complex relationships with underlying neural activity. Prior studies have aimed to dissociate the dynamics that link neural activity to behavior. However, such models largely rely on unimodal neural activity, such as spikes alone or LFPs alone, which may limit the ability to fully capture brain-behavior relationships. Here, we present a unified deep learning framework designed to jointly model the dynamics of multiple distinct neural modalities alongside behavioral data and account for the distinct statistical properties of each modality. By modeling all these signals jointly, our approach captures cross-modal neural interactions while also dissociating their behaviorally relevant components.
We evaluate the framework using both simulation studies and publicly available spike-LFP datasets from the motor cortex during distinct arm movement tasks. Our findings indicate that combining multiple neural modalities improves the identification of behaviorally relevant neural dynamics, enhances behavioral decoding, and improves multimodal neural prediction. This work highlights the value of integrating multimodal neural data with behavioral data for advancing our understanding of brain function and opens new possibilities for interpreting population-level neural dynamics in behavioral contexts and enhancing performance and robustness in brain-computer interfaces.

Disclosures: P. Azizeddin: None. **E. Erturk:** None. **M.M. Shanechi:** None.

Poster

PSTR457: BMI: Decoding Methods

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Program #/Poster #: PSTR457.05/Z7

Topic: F.05. Brain-Machine Interface

Support: NIH R61MH135407
NIH DP2MH126378
NIH RF1DA056402
NSF CRCNS IIS-2113271

Title: Transferring representational knowledge from spikes to local field potentials

Authors: *E. ERTURK[1], S. HASHEMI[2], M. M. SHANECHI[3];
[2]Computer Sci., [1]USC, Los Angeles, CA; [3]Electrical and Computer Engin., Univ. of Southern California, Los Angeles, CA

Abstract: Local field potentials (LFP) and spiking signals are routinely recorded together and measure different spatiotemporal scales of neural activity. Recent neural modeling efforts have focused primarily on spiking activity due to its higher fidelity and the inherent challenges of modeling LFPs, such as difficulties in disentangling individual sources of variability in the aggregate activity measured by LFPs, which often result in lower predictive power. However, LFPs offer a complementary spatiotemporal measure of neural population activity for neuroscience studies as well as key advantages for real-time brain-computer interfaces (BCIs), such as improved long-term stability, robustness to electrode shifts and degradation, and lower power requirements. As such, developing powerful models of LFP activity will greatly benefit neuroscience and neurotechnology. To address the challenges of LFP modeling and improve their predictive performance, we propose an unsupervised framework that transfers representational knowledge from spikes to LFPs. Using motor cortical recordings from 6 monkeys across 3 distinct datasets, we show that representational knowledge transfer significantly improves downstream behavior decoding performance using LFP signals alone, and the improved performance can generalize to LFP signals of other recording sessions without additional knowledge transfer. Overall, our findings establish representational knowledge transfer from high-fidelity spike signals to LFP signals as a powerful strategy for building robust, high-performance, and scalable neural decoding models for neuroscience and neurotechnology applications such as BCIs.

Disclosures: E. Erturk: None. **S. Hashemi:** None. **M.M. Shanechi:** None.

Poster

PSTR457: BMI: Decoding Methods

Location: SDCC Halls B-H

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Program #/Poster #: PSTR457.06/Z8

Topic: F.05. Brain-Machine Interface

Support: NSF Grant DGE1842487
NIH R01MH123770
NIH R61MH135407

Title: Characterizing the Dynamics of the Human Brain Network Response to Deep Brain Stimulation

Authors: *D. JILANI, H. JO, R. MARTIN DEL CAMPO VERA, C. LIU, B. LEE, M. M. SHANECHI;
USC, Los Angeles, CA

Abstract: Our limited mechanistic understanding of deep brain stimulation (DBS) towards modulating networks of brain regions is a barrier towards the advancement of systems neuroscience research and the clinical treatment of dysfunctional brain networks, such as those associated with major depressive disorder and epilepsy. In this work, we apply data-driven system identification and machine learning techniques to learn a dynamic model that characterizes the intracranial EEG (iEEG) response to time-varying DBS stimulation. Through rigorous statistical analysis, we identify many channels and brain regions that are modulated by stimulation. Our findings reveal that iEEG responses are distributed across widespread cortical and subcortical regions. Further, we show that by deriving the frequency response, we can characterize how strong and fast the iEEG response is to the spectral contents of stimulation. Taken together, these results highlight the utility of dynamical modeling for uncovering the broad impact of DBS on brain network activity and informing the design of neuromodulation strategies.

Disclosures: D. Jilani: None. **H. Jo:** None. **R. Martin Del Campo Vera:** None. **C. Liu:** None. **B. Lee:** None. **M.M. Shanechi:** None.

Poster

PSTR457: BMI: Decoding Methods

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Program #/Poster #: PSTR457.07/Z9

Topic: F.05. Brain-Machine Interface

Support: NIH R01MH123770
NIH R61MH135407

Title: Resting-state coherence predicts the strength of distributed neural responses to electrical brain stimulation

Authors: *H. JO[1], D. JILANI[1], R. MARTIN DEL CAMPO VERA[2], C. LIU[1], B. LEE[1], M. M. SHANECHI[1];
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Abstract: Neurological and neuropsychiatric disorders affect millions of individuals globally. Electrical neurostimulation offers a promising therapeutic alternative, especially for the significant subset of patients who remain resistant to conventional pharmacological treatments, but its clinical impact is often constrained by an incomplete understanding of stimulation effects across distributed brain networks. Here, we study the stimulation-evoked changes in field potential power features using multi-site intracranial EEG (iEEG) recordings in the human brain. We demonstrate that power feature changes during ongoing stimulation can be explained by stimulation parameters. Interestingly, the explained variance was higher in channels exhibiting strong resting-state coherence with the stimulation site. Also, this explanation power is especially robust at higher stimulation amplitudes and is preserved in the imaginary part of coherence, suggesting that it reflects true neural connectivity rather than the artifacts from volume conduction. These findings suggest that resting-state coherence can serve as a biomarker for stimulation responsiveness, providing a potential pathway for stimulation site optimization in personalizing neurostimulation therapies.

Disclosures: H. Jo: None. **D. Jilani:** None. **C. Liu:** None. **B. Lee:** None. **M.M. Shanechi:** None.

Poster

PSTR457: BMI: Decoding Methods

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.08/Z10

Topic: F.05. Brain-Machine Interface

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Title: Spatiotemporal Modelling of Behaviorally Relevant Dynamics in Neural Imaging Data

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Abstract: High-dimensional imaging of neural activity, such as widefield calcium and functional ultrasound imaging, provides an unprecedented window into large-scale brain function and its relationship to behavior. However, these modalities exhibit high-dimensionality, complex spatiotemporal patterns, and significant neural variability not directly tied to specific behaviors.

These attributes present significant challenges for modeling these rich datasets. Traditional dynamical modeling methods often apply a preprocessing step on neural images first to make the subsequent analysis more efficient, but doing so can inadvertently discard important spatiotemporal information about neural dynamics and their behavioral correlates. To address these challenges, we introduce a novel deep learning framework designed to directly model raw neural imaging time-series, capture both local and global spatiotemporal dependencies, and disentangle behaviorally relevant and irrelevant neural dynamics. We termed this framework SBIND, for "Spatiotemporal modeling of Behavior in Imaging Neural Data". We applied this framework to diverse neural imaging datasets, including widefield calcium imaging as well as functional ultrasound imaging, which is an emerging modality whose dynamical modeling remains largely unexplored. We find that SBIND effectively captures complex, brain-wide activity patterns - including both global and local spatiotemporal dependencies - and successfully isolates behaviorally relevant neural dynamics. Notably, our approach leads to significantly improved predictions of both neural activity and behavior compared to existing methods, which utilize preprocessing. This framework provides a versatile means for investigating the neural mechanisms of behavior in neural imaging data and can pave the way for utilizing functional ultrasound as a modality in brain-computer interfaces (BCIs).

Disclosures: S. Hosseini: A. Employment/Salary (full or part-time): full-time PhD Student, University of Southern California. **M.M. Shanechi:** None.

Poster

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.09/Z11

Topic: F.05. Brain-Machine Interface

Support: Raynor Cerebellum Project

Title: Disentangling shared and private neural dynamics with SPIRE: A latent modeling framework for deep brain stimulation

Authors: *R. SOROUSHMOJDEHI[1], S. JAVADZADEH NO[1], M. ASADI[1], T. D. SANGER[2,1];
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Abstract: Deep brain stimulation (DBS) is a powerful intervention for movement disorders like dystonia, but the network-level mechanisms underlying its effects remain poorly understood. We present SPIRE (Shared-Private Inter-Regional Encoder), a deep latent variable model that disentangles shared (inter-regional) and private (region-specific) dynamics in intracranial LFP recordings from the globus pallidus internus (GPi), subthalamic nucleus (STN), and thalamic nuclei (VA/VO/VIM). SPIRE was trained on off-stimulation data and evaluated on both off- and on-stimulation recordings collected during clinical DBS at 85, 185, and 250 Hz.

We evaluated SPIRE on data from 10 pediatric dystonia patients (17 hemispheres for GPi, 13 for STN, and 13 with thalamic recordings). The model achieved robust disentanglement: reconstructions using both latent types yielded the lowest errors (GPi: median MSE = 0.0013; STN: 0.0008), and private latents alone outperformed shared latents (GPi: 0.0043 vs. 0.291; STN: 0.0014 vs. 0.448; $p < 0.001$). Cross-region shared latents (e.g., GPi-shared decoded by STN) performed comparably to same-region shared latents, indicating the model captures distributed motifs. Importantly, SPIRE generalized from two-region (GPi-STN) to three-region (GPi-STN-thalamus) architectures while preserving separation of shared and private dynamics. To assess DBS effects, we computed pairwise Euclidean distances between on- and off-stimulation latents. Stimulation caused significantly greater distributional shifts in private latents compared to shared latents across all conditions ($p < 0.001$). Random Forest classifiers trained on latent trajectories decoded DBS frequency with high accuracy using private latents (GPi: mean = 81.0%, STN: 71.0%), outperforming shared latents (GPi: 51.8%, STN: 48.5%; $p < 0.001$). These findings suggest that while DBS induces significant changes in both shared and private latent spaces, only private latents reliably encode stimulation frequency. This highlights that DBS effects are more distinctly represented in region-specific neural dynamics, while shared inter-regional activity exhibits comparatively less specificity to stimulation parameters. SPIRE offers a principled framework for modeling distributed brain dynamics and provides insight into how neuromodulation reorganizes neural signals across deep brain networks.

Disclosures: R. Soroushmojdehi: None. **S. Javadzadeh No:** None. **M. Asadi:** None. **T.D. Sanger:** None.

Poster

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Topic: F.05. Brain-Machine Interface

Support: Raynor Celebellum Project

Title: Decoding Deep Brain Dynamics of Voluntary Movement with Graph Neural Networks

Authors: *M. ASADI[1], S. JAVADZADEH NO[1], R. SOROUSHMOJDEHI[1], A. SEYYED MOUSAVI[1], T. D. SANGER[2,1];
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Abstract: Understanding how deep brain regions coordinate voluntary movement remains a fundamental and underexplored challenge in neuroscience. While recordings from implanted deep brain electrodes provide rare access to these circuits, characterizing their dynamic, network-level organization remains difficult due to the complexity of the signals.Here, we present a graph-based neural decoding framework that models interpretable, phase-specific interactions between deep brain regions during voluntary movement. Local field potentials (LFPs) were

recorded from 80 electrodes implanted across bilateral subregions of the globus pallidus internus (GPi), ventral intermediate nucleus (VIM), and ventral oralis/posterior subthalamic nucleus (Vo/STN) during a cued forward reaching task in pediatric patients with dystonia. Each trial was segmented into four behaviorally aligned phases—Hold, Reaction, Execution, and Return—based on synchronized movement and cue onset markers.We developed a neural decoding model that uses gated recurrent units (GRUs) to capture temporal dynamics within each deep brain region. An adaptive graph learner infers an 8×8 inter-regional connectivity matrix, followed by attention-based graph convolution to model spatial interactions. The system classifies behavioral phases with approximately 70% accuracy and produces trial-specific connectivity graphs. Preliminary results suggest the model captures phase-dependent shifts in subcortical communication patterns, with emerging motifs that may reflect dynamic changes in motor circuit coordination. This framework offers a compact, structured representation of evolving deep brain activity and marks a promising step toward interpretable neural decoding in real-world clinical neurophysiology.

Disclosures: M. Asadi: None. **S. Javadzadeh No:** None. **R. Soroushmojdehi:** None. **A. Seyyed Mousavi:** None. **T.D. Sanger:** None.

Poster

PSTR457: BMI: Decoding Methods

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.11/AA1

Topic: F.05. Brain-Machine Interface

Support: Raynor Cerebellum Project

Title: Cross-subject integration of multi-region neural signals via functional embedding

Authors: *S. JAVADZADEH NO[1], R. SOROUSHMOJDEHI[1], M. ASADI[1], A. SEYYED MOUSAVI[1], T. D. SANGER[2,1];
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Abstract: Aggregating neural recordings across subjects is critical for understanding functional organization of the brain, yet anatomical variability, especially in pediatric and clinical populations, poses major challenges. In intracranial recordings such as stereo-electroencephalography, electrode number and placement vary widely across subjects and sessions. Spatial normalization methods like MNI coordinates offer a shared anatomical reference, but often fail to capture true functional similarity, particularly when brain anatomy is atypical or localization is imprecise. Even at matched coordinates, underlying neural dynamics may differ substantially between individuals.
We propose that a data-driven, functionally grounded embedding of neural signals can enable reliable classification of brain regions and support scalable, cross-subject analysis, even in the presence of anatomical variability.

We developed a deep learning framework using a Siamese neural network trained with contrastive loss to embed time-series segments from multi-region intracranial recordings into a shared functional latent space. This space is trained to be neighborhood-sensitive, such that signals from functionally similar brain regions are mapped nearby, while distinct regions are embedded farther apart.
The learned latent representation enables robust classification of brain regions, such as globus pallidus internus, subthalamic nucleus, and thalamus, based solely on the signal properties of local field potentials, even in unseen subjects. The embedding generalizes across individuals with heterogeneous electrode configurations and captures region-specific neural signatures that transcend electrode labels. This embedding can also be used during the tokenization step of a transformer-based model to unify data across subjects and construct large-scale training datasets. By learning a space where functional proximity reflects physiological similarity, our approach facilitates cross-subject aggregation and the development of functional brain atlases that are robust to anatomical variability. This has significant implications for large-scale analysis of intracranial recordings in pediatric and clinical populations.

Disclosures: S. Javadzadeh No: None. **R. Soroushmojdehi:** None. **M. Asadi:** None. **A. Seyyed Mousavi:** None. **T.D. Sanger:** None.

Poster

PSTR457: BMI: Decoding Methods

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Program #/Poster #: PSTR457.12/AA2

Topic: F.05. Brain-Machine Interface

Support: K. Lisa Yang Center for Bionics

Title: Force Magnetomicrometry: A Wireless Platform for Real-Time In Vivo Muscle-Tendon Force Estimation

Authors: *G. HERRERA-ARCOS[1], C. SHALLAL[2];
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Abstract: Understanding neuromuscular activity is essential for studying motor control and developing advanced neural prostheses. Current methods for assessing muscle dynamics—including electromyography (EMG), ultrasound, fluoromicrometry, and sonomicrometry—each present trade-offs in invasiveness, resolution, and suitability for real-world movement. Recently, magnetomicrometry (MM), a technique using implanted magnetic beads and external magnetic field sensors, has emerged as a promising alternative. MM enables real-time, wireless tracking of tissue length changes with submillimeter accuracy and <1 ms latency, without the need for post-processing. However, direct measurement of muscle-tendon force in vivo remains a longstanding challenge. To address this, we introduce force magnetomicrometry, a novel platform for estimating muscle-tendon force based on MM.We implanted pairs of 3 mm magnetic beads in

the Achilles tendons of two Yucatan minipigs. The procedure was minimally invasive, bead positions remained stable over 8-9 months, and histological analysis confirmed healthy tendon tissue with no signs of adverse reaction. Gait symmetry analysis before and after implantation showed no evidence of discomfort or locomotor disruption. Magnetometer arrays placed externally on the hindlimb tracked bead positions wirelessly as pigs walked on a treadmill at speeds from 0.6 to 1.6 m/s, and on an instrumented walkway with force plates. Kinematic data were captured using marker-based motion tracking. Several recording sessions per animal yielded thousands of gait cycles. Tendon dynamics varied predictably with speed—tendon elongation and peak stretch occurred earlier at higher speeds—consistent with known biomechanical patterns. To calibrate length changes to force, we developed an isometric dynamometer and collected synchronized force and MM data. Force magnetomicrometry data was highly correlated with ground reaction forces.
Together, these results validate force magnetomicrometry as a robust, wireless platform for real-time muscle-tendon force sensing in vivo. This technology opens new avenues for studying motor control in naturalistic settings and developing closed-loop neuromuscular prostheses.

Disclosures: G. Herrera-Arcos: None. **C. Shallal:** None.

Poster

PSTR457: BMI: Decoding Methods

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Program #/Poster #: PSTR457.13/AA3

Topic: F.05. Brain-Machine Interface

Support: K. Lisa Yang Center for Bionics

Title: Implanted magnets enable wireless muscle state sensing for neuroprosthetic control applications

Authors: *C. SHALLAL, G. HERRERA-ARCOS, H. HERR;
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Abstract: Powered lower-limb prostheses replicate ankle mechanics to reduce walking effort but often rely on state-based control schemes, limiting adaptability. Neural interfaces could improve control, yet surface EMG (sEMG) suffers from signal artifacts and inconsistency, while implanted EMG (iEMG) is highly invasive and impractical. As a result, current commercial prostheses depend solely on intrinsic sensing. We developed *magnetomicrometry* (MM), a minimally invasive method using implanted magnetic beads and external magnetometers to track muscle length and velocity with submillimeter accuracy. This study evaluates MM's performance relative to sEMG and iEMG for real-time prosthesis control.
One agonist-antagonist myoneural interface was created by using the lateral gastrocnemius (GAS) and tibialis anterior (TA) muscles. Two magnetic beads were implanted in each muscle, and bead positions were tracked using calibrated magnetometer arrays on the limb surface. Both

sEMG and iEMG signals were acquired for comparison. A custom low-latency signal processing algorithm, based on an information filter, estimated 3D bead positions at 1 kHz. This system reliably tracked magnets up to 6 cm deep with sub-millisecond latency, enabling real-time control.
We have had 3 patients with chronic implantation of the magnetic beads for up to 1 year. We compared the estimated phantom ankle trajectories from both sEMG, iEMG and MM against the reference trajectory from the contralateral limb, measured using a goniometer. Across all degree-of-mirroring metrics, specifically cross-correlation and percent error with the reference trajectory, MM consistently outperformed both sEMG and iEMG, with significantly lower position and velocity errors regarding the joint kinematics.The enhanced magnet tracking system which incorporates the new magnetometer hardware and filtering algorithm enabled stable tracking performance even at bead depths up to 6 cm, maintaining accuracy across a range of muscle sensing setups. Latency measurements confirmed that the system operates at real-time speeds (<1 ms), supporting its use in dynamic motor control tasks.
MM enables robust, real-time tracking of muscle dynamics via implanted magnetic beads, surpassing EMG in signal stability and control fidelity. Its minimal invasiveness, depth tolerance, and low-latency processing make it a promising approach for next-generation neural control of lower-limb prostheses.

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Poster

PSTR457: BMI: Decoding Methods

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Program #/Poster #: PSTR457.14/AA4

Topic: F.05. Brain-Machine Interface

Support: John Templeton Foundation
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Title: Determining accurate and early neural predictors of voluntary action in human motor cortex via reward-driven decoders

Authors: *A. DE MIGUEL GOMEZ[1], C. VERBAARSCHOT[3], R. A. GAUNT[4], J. L. COLLINGER[5], A. SCHURGER[6], U. MAOZ[2];
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Abstract: Brain-computer interface (BCI) systems are typically synchronous, explicitly cueing participants to attempt, imagine, or observe specific movements. These cues provide time-locked labels that allow decoders to learn a mapping between patterns of neural activity and intended behavioral outputs. In contrast, for asynchronous BCIs—especially those designed for decoding

movement preparation ahead of voluntary actions—movement onset time is up to the participant, rather than cued. Hence, when predicting actions online, the onset of decisive motor-preparatory neural activity needs to be inferred directly from the data and detected in continuous time. Current approaches commonly train binary classifiers to distinguish preparatory neural activity within a fixed pre-action time window, from non-preparatory activity taken from an early baseline period. This approach assumes that the determining neural pattern commences at a fixed time lag prior to movement onset. But the time lag varies, making fixed-time-window methods suboptimal—a design bottleneck that increases susceptibility to false positives and challenges the effectiveness of continuous decoding.To address this limitation, we introduce a reinforcement-learning framework in which an agent autonomously identifies the earliest neural signature that reliably predicts voluntary actions through rewards and continuous exploration. We evaluated this approach using intracortical microelectrode arrays implanted in the motor and somatosensory cortices of 3 tetraplegic participants, recording neural spiking activity during a self-paced intertemporal-choice game where players time the flip of a self-filling slime bucket to soak an opponent before being slimed themselves. Classifiers trained on seemingly optimal fixed time windows achieve at most 85% cross-validated accuracy 235 ms before movement onset and exhibit substantial variability across sessions and individuals. In contrast, our reward-driven linear decoder achieves higher accuracy slightly earlier—92%, 250 ms in advance. This study demonstrates the feasibility of framing neural event prediction as a reinforcement-learning task, to converge on self-initiated motor-preparatory signals that are both early and reliable. This offers a high-performing, label-free training strategy for asynchronous decoders of various cognitive tasks where the onset of the relevant neural state is unknown a priori.

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Poster

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Topic: F.05. Brain-Machine Interface

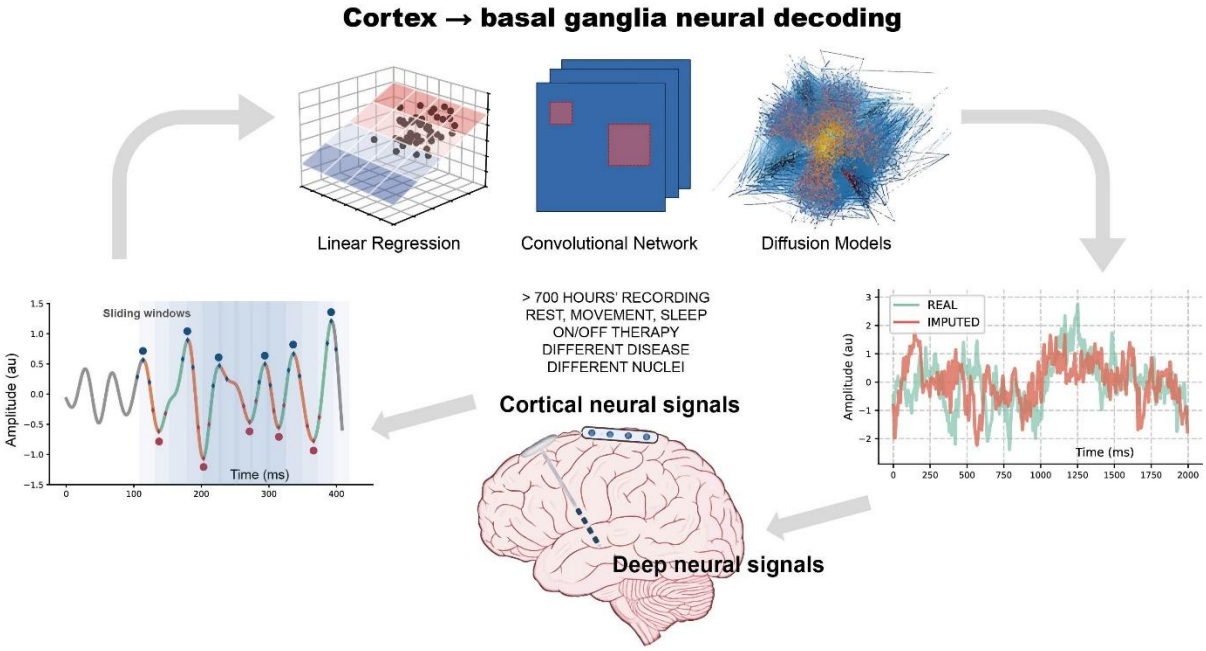
Support: National Nature Science Foundation of China (81830033)

Title: Deep learning enables minimally invasive monitoring of human basal ganglia activity

Authors: *Z. YIN[1,2];
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Abstract: Monitoring deep brain activity is crucial for understanding neural circuit dysfunction and advancing neuromodulation therapies, yet current approaches require invasive recordings.

Here we develop a deep learning framework combining spectral processing and diffusion models to decode subthalamic nucleus activity from cortical signals, validated across 723 hours of recordings from 49 patients with movement disorders. The framework demonstrates robust anatomical specificity, with decoding performance correlating with hyperdirect pathway density and predominantly capturing physiological motor-related oscillations. We establish broader clinical utility through successful generalization across disease conditions (Parkinson's disease, dystonia, Tourette syndrome), subcortical targets (subthalamic nucleus, globus pallidus, centromedian thalamus), and behavioral states, while maintaining efficacy during stimulation artifacts and movement. Notably, cortical-predicted signals significantly improve both sleep state classification and movement detection during basal ganglia recording failures. These findings establish a comprehensive and reliable approach for minimally invasive monitoring of deep brain activity, with direct implications for adaptive neuromodulation.



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Poster

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Moonshot R &D-MILLENNIA Program (JPMJMS2012)

Title: Scaling analysis of binary motor intention decoding accuracy with increasing intracranial EEG data in monkey: a machine learning Perspective

Authors: *D. SHIMIZU[1], H. YANG[3], R. FUKUMA[5], T. NAMIMA[2], S. NISHIMOTO[6], H. KISHIMA[7], T. YANAGISAWA[4];
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Abstract: Decoding motor intentions from intracranial electrocorticography (ECoG) in non-human primates poses significant challenges due to inherent signal variability, particularly in data collected intermittently over extended periods. A question is whether decoding accuracy systematically improves with accumulating discrete data, conforming to scaling laws, and which machine learning models effectively leverage such temporal dynamics in the domain of ECoG.This study aimed to characterise how binary motor intention decoding accuracy scales with increasing quantities of ECoG data collected over approximately one year (61 recording days) and identify optimal machine learning methods for direct signal analysis. We systematically evaluated multiple models, including EEGNeX, Two-Dimensional CNN, LSTM, One-Dimensional CNN, Support Vector Machine, Random Forest, Logistic Regression, Multilayer Perceptron, Gradient Boosting, k-Nearest Neighbours, and Decision Tree. After performing 10-fold cross-validation across the entire dataset, EEGNeX and One-dimensional Convolutional Neural Network (OneDCNN) emerged as the top-performing models and were subsequently selected to investigate how decoding accuracy scales with increasing data volume.Our findings demonstrate that decoding accuracy consistently increased with the volume of collected data up to a certain number of days, beyond which performance saturated, indicating practical limits to the benefits derived from additional data accumulation. Among tested models, EEGNeX exhibited the highest absolute decoding accuracy, whereas OneDCNN stood out for its exceptional balance between accuracy and stability, showing minimal variance across cross-validation folds.These results confirm the applicability of scaling laws to long-term unsteady ECoG recordings while highlighting a saturation effect beyond a certain data threshold. Furthermore, the robust performance and remarkable stability of the relatively simple OneDCNN underscore the advantages of directly leveraging raw temporal dynamics over complex architectures or sophisticated feature extraction methods. Our study thus provides practical insights into optimal data acquisition strategies and methodological choices crucial for developing efficient and effective neural decoding applications.

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Poster

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Title: Shared Control and Latent Neural Dynamics in a novel AI-iBCI system

Authors: *O. SAUSSUS[1], S. DE SCHRIJVER[2], P. SONG[1], I. CAPRARA[1], J. GARCIA RAMIREZ[1], T. DECRAMER[3], R. DETRY[1], P. JANSSEN[1];
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Abstract: Shared-control brain-machine interfaces (BCIs) that combine user-driven neural decoding with artificial intelligence (AI) assistance are emerging as promising tools for robust neuroprosthetic control. However, the mechanisms by which AI and user interact—and how this interaction shapes underlying cortical dynamics—remain poorly understood. Here, we provide a dual-level analysis of this interaction, combining behavioral metrics of AI-BCI coordination with latent state characterization of motor cortical population activity. Two macaque monkeys performed a navigation task in a 3D virtual reality (VR) environment using a closed-loop BCI that decoded neural activity from primary motor, dorsal and ventral premotor cortex to control a virtual sphere. In a subset of trials, decoded velocities were modulated by a real-time AI intention predictor. The tasks included three conditions designed to probe user-AI coordination: obstacle avoidance, sudden obstacle appearance, and mid-trial changes in movement intention. Performance was significantly higher in AI-assisted trials compared to no-AI trials in all obstacle avoidance tasks. Across both monkeys, success rate was on average 30% higher on AI-assisted trials vs. no-AI trials (Monkey 1: 81% compared to 49%, Monkey 2: 61% compared to 34%). We then quantified interaction dynamics using three metrics: AI intervention frequency (trial-wise and per-target), deviation from the pure BCI path, and the entropy of the AI's predicted action distribution. Entropy reflects the confidence of the AI model (low entropy corresponds to high certainty and increased AI weighting in control; high entropy means reduced AI influence). These analyses revealed that AI interventions clustered around decision-critical moments and entropy-based arbitration adapting to task demands. Next, we investigated the structure of the latent states driving decoder output. Latent activity during AI-assisted and no-AI trials remained confined to the same low-dimensional neural manifold, confirmed via principal angle analysis. Trajectory shape and timing, assessed via Procrustes disparity and canonical correlation, showed subtle within-manifold differences across conditions. These findings suggest that shared control modulates the decoder-relevant cortical dynamics without disrupting the underlying representational geometry. Together, they demonstrate that shared control operates within the brain's existing control framework, adapting to task demands without overriding user-generated cortical dynamics. Our results provide a foundation for cooperative human-AI systems in future neuroprosthetic applications.

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Poster

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UH3NS107714
U01NS108922
U01NS123125

Title: Rapid decoder calibration through few-shot manifold alignment

Authors: *B. DEKLEVA[1], W. HOCKEIMER[2], J. L. COLLINGER[1];
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Abstract: Intracortical brain-machine interfaces (iBCIs) provide a potential avenue for individuals to regain motor function lost due to injury or disease. iBCIs enable control of an end-effector (computer mouse, robotic limb, etc) via decoders, which create maps between motor intention signals recorded from the activity of populations of individual neurons and a desired behavioral output (kinematics, etc.). However, one of the challenges facing the development of clinically-viable brain-machine interfaces (BCIs) is the high degree of temporal instability in decoding performance observed in human iBCI, which necessitates recurring and often time-consuming calibration routines. Recent approaches have sought to create more stable decoders by either periodically or continuously re-aligning the recorded activity to an assumed stable dynamical structure within the low-dimensional "neural manifold". These approaches have shown promising results for cursor control in nonhuman primates, but it is unclear how well they will perform in the higher degree-of-freedom and data-limited regime of human iBCI. We investigated the potential for achieving rapid decoder recalibration through manifold alignment in two human participants with tetraplegia enrolled in an iBCI clinical trial. We recorded neural activity from microelectrode arrays implanted in the hand and arm area of the precentral gyrus as the participants attempted cued upper limb movements within the context of controlling either a computer cursor or virtual arm. We began with an extensive calibration session to fully characterize the task-relevant manifold/dynamics and create a manifold-to-behavior decoder. On subsequent sessions, we collected only a small subset of individual calibration trials and aligned them to the corresponding dynamics from the full calibration set. Offline analysis showed that decoder performance using activity re-aligned according to these small calibration sets rapidly approaches the levels of decoders created from exhaustive calibration sets. As an example, for a simple center-out task we recalibrated using just one trial in each of the four cardinal directions. These minimally re-calibrated decoders achieved offline decoding performance 72% that of fully calibrated decoders when tested across forty held-out trials in all directions. These results suggest that constrained alignment to known dynamics on a low-dimensional manifold can enable fast calibration of iBCI decoders and ease the burden of calibration for iBCI users.

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Poster

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Title: Learning high-performance neuroprosthetic control is associated with increasingly predictable mu-band traveling waves

Authors: *N. NATRAJ[1], R. MIAO[3], S. SEKO[4], E. F. CHANG[2], K. GANGULY[4];
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Abstract: Successful and proficient operation of brain computer interfaces (BCIs) requires neuroplasticity and consolidation. Specifically, there is neural adaptation to the BCI via real-time closed-loop neurofeedback. However, the exact spatiotemporal neural dynamics underlying such cortical reorganization is unclear. Uncovering the underlying mechanism can aid in the adoption and retention of BCIs. At the mesoscale level via electrocorticography (ECoG), an intriguing candidate sensorimotor feature are mu rhythms, known for movement encoding and motor learning. We thus characterized network-wide mu as cortical traveling waves and evaluated wave consistency across BCI sessions in two human participants. Both participants have severe tetraparesis and were implanted with a 253 channel grid over contralateral sensorimotor cortex. The BCI decoder in one subject (B3) served to control a virtual human hand, and in another subject (B1) served to decode whole body movements to a virtual robotic arm. Delta (0.5-4Hz, low frequency oscillations, LFOs), high gamma (70-150Hz) and beta (13-30Hz) were used as neural features. In both subjects, performance steadily increased with training, culminating in 93.75% accuracy in B3 and 95.57% accuracy in B1. Spectral analyses confirmed mu oscillations across the grid (7-9Hz in B1 and 8-10Hz in B3). We then used a 3D convolutional neural network based temporal autoencoder framework and cross-validation to predict the dynamics of cortical traveling waves. In both subjects, results revealed that traveling waves became increasingly more predictable across-sessions. Surprisingly, this occurred at the cost of the coupling of mu phase to high gamma amplitude (phase amplitude coupling, PAC), which steadily decreased across-days. To understand the neurophysiological relevance of this finding, we correlated the strength of mu-high gamma PAC to high gamma's ability to decode movements at individual channels of the grid. We found that an early negative relationship between PAC and high gamma decoding information transitioned to a null effect. In contrast, we found the emergence of a positive relationship between high gamma decoding information and delta - high gamma PAC. This was especially pronounced over primary motor cortex. Remarkably, the dynamics of mu traveling waves were most predictable over this cortical region.

For high-performance BCI control, our results thus suggest that mesoscale mu rhythms increase the consistency of their spatiotemporal wave patterns and decouple from high gamma, especially over areas where PAC between high gamma and LFOs exist and where concurrently high gamma decoding information emerges.

Disclosures: N. Natraj: None. **R. Miao:** None. **S. Seko:** None. **E.F. Chang:** None. **K. Ganguly:** None.

Poster

PSTR457: BMI: Decoding Methods

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.20/AA10

Topic: F.05. Brain-Machine Interface

Title: Planning-to-movement graph attention network for eeg-based grasp prediction

Authors: A. CETERA, A. RABIEE, Y. SHAHRIARI, ***R. ABIRI**;
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Abstract: Understanding how macroscopic neural dynamics evolve between the motor planning and execution phases is fundamental for advancing brain-computer interface (BCI) systems. For individuals with spinal cord injury (SCI), who retain cognitive motor intent despite the inability to produce voluntary movement, BCIs that operate during the planning phase offer a promising path toward restoring purposeful interaction. Although invasive studies have established distinct pathways for the ventral (object recognition) and dorsal (motor planning) streams during visuomotor tasks, how these pathways emerge within the vision-based grasping network remains unclear at the macroscopic level using electroencephalography (EEG). To address this, we introduce the Planning-to-Movement Graph Attention Network (P2M-GAT), a graph-based deep learning framework that aims to model how brain connectivity evolves from planning to movement execution. Rather than classifying isolated EEG snapshots, P2M-GAT learns to predict future movement-phase brain graph representations from planning-phase neural activity, offering a forward-looking approach to decoding motor intention. P2M-GAT is composed of three sequential modules: (1) a Planning Graph Encoder, which applies multi-head GAT layers to extract node embeddings during the motor planning phase; (2) a Movement Graph Predictor, which predicts movement-phase graph representations from planning-phase embeddings; and (3) a Predicted Graph Classifier, which applies GAT layers to the predicted movement graph to classify grasp type. Preliminary results included EEG data (16-channel, 256 Hz) collected from one participant performing 150 plan-to-grasp tasks, segmented into planning and execution phases. Each phase was represented as a brain graph with node features including power spectral density across five bands and time-domain statistics, and edge weights computed from top-5 Pearson correlations. Trained with a hybrid loss (cross-entropy + MSE), P2M-GAT achieved 73.3% accuracy (power grasp vs. no movement) on the held-out test set and showed the strongest predictive alignment in the beta band ($r = 0.15$), consistent with its known role in motor

planning. Future work will expand electrode coverage, analyze attention patterns for graph validation and neuroscientific interpretability, and integrate kinematics to capture visuomotor coordination. Our findings demonstrate that planning-phase brain connectivity—rooted in the vision-based grasping network—can be used to decode motor intent, advancing the potential for intuitive, neuroscience-informed BCI control strategies for individuals with SCI.

Disclosures: A. Cetera: None. **A. Rabiee:** None. **Y. Shahriari:** None. **R. Abiri:** None.

Poster

PSTR457: BMI: Decoding Methods

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.21/AA11

Topic: F.05. Brain-Machine Interface

Title: Scifi: a high-bandwidth wireless neural recording headstage with on-device computation for real-time brain-computer interfaces

Authors: M. ROSTOV, S. WALKER, R. SHARPE, H. PANG, G. MONTAGUE, ***E. ZHOU**, M. J. HODAK;
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Abstract: Advanced brain-computer interface (BCI) research requires high-bandwidth neural recording systems with real-time processing capabilities for closed-loop applications. Current wireless headstages face limitations in wireless data throughput, computational power and battery life that constrain experiments. Here we present the SciFi headstage, a wireless neural recording platform that addresses these challenges for next-generation BCI experiments. The SciFi headstage features WiFi 6E connectivity with TCP throughput of 1.4 Gbps. This enables streaming of >5200 channels of 12-bit broadband data at 32 kHz sampling rates with 2 Gbps total probe bandwidth. The compact device (56×66×17.5 mm) integrates 128 GB of high-speed internal storage providing 120 minutes of local recording capacity and ensuring data integrity during connectivity interruptions. The integrated Qualcomm QCS6490 processor delivers 12 TOPS of computational performance with the onboard Hexagon NPU, enabling real-time on-device neural feature extraction and decoding algorithms. Through the user-friendly Synapse API and comprehensive Synapse App SDK, researchers can deploy custom algorithms (Apps) directly on the headstage without managing data streaming, peripheral interfacing, or storage protocols. This enables the ultra-low latency closed-loop control essential for real-time BCI applications. SciFi incorporates a high-contrast AMOLED display for configuration and diagnostics, and a customizable RGB LED ring for remote status monitoring. Power management includes a 5.6 Wh battery providing 2-4 hours of active recording with comprehensive safety protections. Validation testing using Wifi 6e demonstrates reliable high-bandwidth wireless streaming with minimal packet loss across laboratory environments while successfully executing real-time spike detection and feature extraction algorithms on device.

Future work will focus on expanding the library of available tools for developing Synapse Apps to expand the ML toolbox available for adaptive BCI applications.

Disclosures: **M. Rostov:** A. Employment/Salary (full or part-time): Science Corporation. **S. Walker:** A. Employment/Salary (full or part-time): Science Corporation. **R. Sharpe:** A. Employment/Salary (full or part-time): Science Corporation. **H. Pang:** A. Employment/Salary (full or part-time): Science Corporation. **G. Montague:** A. Employment/Salary (full or part-time): Science Corporation. **E. Zhou:** A. Employment/Salary (full or part-time): Science Corporation. **M.J. Hodak:** A. Employment/Salary (full or part-time): Science Corporation.

Poster

PSTR457: BMI: Decoding Methods

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.22/AA12

Topic: F.05. Brain-Machine Interface

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Title: Image retrieval based on imagery in a closed-loop condition using electrocorticograms

Authors: ***R. FUKUMA**[1,2], T. YANAGISAWA[1,2,3], H. SUGANO[4], K. TAMURA[5], S. OSHINO[1], N. TANI[1], Y. IIMURA[4], H. KHOO[1], H. SUZUKI[4], H. YANG[6], T. IWATA[1], M. NAKAJIMA[4], S. NISHIMOTO[6,7], Y. KAMITANI[8,2], H. KISHIMA[1,3];
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Abstract: Objectives: Recent advances in brain-computer interface (BCI) technology utilising motor cortical activity have enabled the restoration of communication function in patients with severe paralysis, including those with amyotrophic lateral sclerosis (ALS). However, it is known that motor cortical activity deteriorates in patients with severe ALS. Therefore, we propose a BCI that uses visual cortical activity to infer images being viewed from a large image dataset, and which is controlled by the patient's visual imagery in a closed-loop configuration. Methods: The developed BCI uses a linear decoder to infer latent vectors (real-time vectors) from high-gamma power (80-150 Hz) of electrocorticographic signals and selects feedback images from a dataset of 2.3 million images based on cosine similarity. The latent vectors were extracted using either the contrasting language-image pre-training (CLIP) model or the AlexNet

model. Participants were given one of two instructions (e.g. 'animals' vs. 'tools') and were instructed to imagine and display feedback images that represented the meaning of the instruction. Controllability was evaluated based on the similarity, within each trial, between the real-time vectors and latent vectors corresponding to the target and non-target instructions.
Results: All three subjects performing online tasks using the CLIP latent space were able to control the feedback images in a two-choice manner, achieving a maximum accuracy of 92.50%. In contrast, the three subjects who used the AlexNet latent space failed to control the feedback images.
Conclusion: This study demonstrated that image retrieval based on CLIP vectors decoded from the visual cortex can achieve over 90% accuracy in searching for intended categories of images from a set of 2.3 million images under closed-loop conditions in a two-choice manner. Interestingly, controllability of the feedback images was suggested to depend on the latent space chosen to represent the images. Furthermore, it has been suggested that imagery, particularly the semantic aspects of imagery, alters the neural activity of the higher visual cortex during the online task, thereby causing inferred vectors in the CLIP latent space to move closer to the instructed meaning.

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Poster

PSTR458: Respiratory Control

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.01/AA13

Topic: F.08. Respiratory Regulation

Title: Neural and autonomic responses during prolonged breath-holding: An EEG study in elite freedivers

Authors: *O. YILMAZ;
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Abstract: Freedivers hold their breath voluntarily during their performances. In static breath-hold discipline elite athletes can hold their breath around 9 minutes without exhibiting any cognitive damage. This is a curious process of conscious suppression of a vital autonomic function. Therefore, we aim to examine the changes during voluntary prolonged breath-hold with a particular focus on cardiac autonomic activity and EEG oscillations. Analyses mainly focused on the struggle phase and its comparisons to reveal a neurophysiological explanation for prolonged breath-holding. Electrocardiography (ECG), electrodermal activity (EDA) and electroencephalography (EEG) were recorded during resting condition for baseline and during breath-hold periods. Initiation of the struggle phase was aligned to first diaphragm contraction.

Frequency analyses carried out on EEG oscillations. EEG was filtered and divided into baseline, pre-struggle and struggle phases. Alpha, theta mean powers and mean EDA and HRV parameters were presented in between these 3 phases. Recordings have been obtained from10 freedivers so far. In our preliminary results, observable differences in the mean values suggest a marked distinction between the struggle phase and the pre-struggle phase. There is a decrease in alpha power in struggle phasewhich suggests the relationship of top-down cortical inhibition of breathing reflex in line with Steinberg et al. (2017). EDA change is consistent with the literature and decreases in pre-struggle phase but then increases with emotional stress in the begining of struggle phase (even before diaphragm contractions) as we expected. Interpreting the changes in HRV remains, since the data collection, futher analyses and statisctical conclusions is still ongoing in our project. Upon completion of our project, the results will provide more valuable insights into the neurophysiological effects of cortical inhibition and autonomic control during prolonged breath-holding.

Disclosures: O. Yilmaz: None.

Poster

PSTR458: Respiratory Control

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.02/AA14

Topic: F.08. Respiratory Regulation

Title: Covid-19 induces structural and microstructural changes in brainstem subfields and arousal nuclei

Authors: *A. QUDDUS[1], M. AL AMIN[2], S. MAHARJAN[3];
[1]Natl. Univ. Bangladesh, Gazipur, Bangladesh; [2]Dept. of Med. and Mol. Genet., Dept. of Med. and Mol. Genet., Indianapolis, IN; [3]Weill Cornell Med. college, New York, NY

Abstract: Respiratory failure remains the leading cause of mortality in coronavirus disease 2019 (COVID-19), and the brainstem a critical hub for respiratory regulation, implicated in this outcome. Prolonged unresponsiveness and delayed arousal in COVID-19 patients further suggest brainstem dysfunction. However, structural and microstructural changes in specific brainstem subfields and ascending arousal nuclei remain poorly characterized, despite their potential role in these clinical manifestations. We analyzed T_1-weighted structural and diffusion-weighted magnetic resonance imaging (MRI) data from 73 COVID-19 patients (mean age: 42.1) and 27 age-matched healthy controls (mean age: 42.8), obtained from the OpenNeuro repository (accession: ds005364). Brainstem subfields and ascending arousal nuclei were segmented using the *segment subregions* and *SegmentAAN* packages following preprocessing and whole-brain parcellation. COVID-19 patients exhibited distinct structural alterations: increased volume in the superior cerebellar peduncle (SCP) and reduced volumes in the ventral tegmental area (VTA) and periaqueductal gray (PAG). Diffusion metrics revealed microstructural disruptions: the SCP showed lower fractional anisotropy (FA) and axial diffusivity (AD) with elevated radial (RD)

and mean diffusivity (MD), suggesting edema or axonal disorganization. Conversely, the VTA displayed higher FA and lower RD, indicating compensatory microstructural adaptation despite tissue loss. The PAG exhibited elevated RD, consistent with neuroinflammatory processes. These changes correlated with anxiety symptoms, implicating COVID-19 in disrupting neural circuits governing emotional regulation through direct tissue damage and secondary mechanisms. Our findings identify COVID-19-associated alterations in key brainstem regions, linking structural and microstructural changes to clinical symptoms. The SCP's increased volume and diffusivity abnormalities may underlie respiratory dysfunction, while VTA adaptations could contribute to prolonged unresponsiveness. PAG atrophy and inflammation may drive anxiety and headaches. These insights bridge observed neuroimaging changes to clinical outcomes, offering a foundation for targeted therapeutic strategies to mitigate COVID-19's neurological sequelae.

Disclosures: A. Quddus: None. **M. Al Amin:** None. **S. Maharjan:** None.

Poster

PSTR458: Respiratory Control

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Program #/Poster #: PSTR458.03/AA15

Topic: F.08. Respiratory Regulation

Support: FAPESP 2021/06886-7
CNPQ 313719/2020-9

Title: Ventral medullary parvalbuminexpiratory neurons control respiratory pattern formation and active expiration

Authors: *D. J. MORAES[1], N. SALIM[2], R. MARTINS SÁ[2], J. REIS SOUZA[3];
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Abstract: Parvalbumin (PV) is a marker of inhibitory neurons. Previous studies described the presence of PV neurons in the ventral medullary region of rats, closely associated with the location of Bötzinger Complex (BötC) expiratory neurons. Herein, we addressed whether PV is expressed by BötC inhibitory expiratory neurons. We also evaluated the role of BötC PV neurons in the control of ventilation (VE) and respiratory pattern formation. Mice expressing Cre-recombinase in PV neurons were used to analyze the expression of PV in physiologically identified BötC expiratory neurons and their projection, as well as to evaluate the effects of inhibition and activation of BötC PV neurons on respiratory pattern formation and pulmonary ventilation (VE) during resting and high chemical drive. BötC post-inspiratory (PI) glycinergic neurons express PV. By projecting to preBötzinger Complex, PV-PI+ are involved in the respiratory pattern formation, by controlling Hering-Breuer reflex expiratory response, PI glottal adduction and VE. On the other hand, PV-PI+ neurons inhibit active expiration during resting, as

well as control its incidence and ventilatory responses to hypercapnia/acidosis by projecting to lateral parafacial region. The target-specific of glycinergic inhibition from BötC PV+ neurons to different respiratory cells is another mechanism controlling inspiration and expiration.

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Poster

PSTR458: Respiratory Control

Location: SDCC Halls B-H

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Program #/Poster #: PSTR458.04/AA16

Topic: F.08. Respiratory Regulation

Support: CIHR Project Grant PJT 190098
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Title: A midbrain circuit synchronizing breathing with behaviors

Authors: *K. BAKER[1,2], C. S. SCARPELLINI[2], G. MONTANDON[1,2];
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Abstract: One of the universal behaviors present in most animals is the threat response, which is critical for continued survival. A key feature of this response is the accelerated breathing to meet metabolic demand in cases of intense locomotor activity. Although breathing is mostly an automatic process, it is highly flexible and can be synchronized with behaviors, such as nociceptive and locomotor responses. Respiratory neural circuits receive projections from various cortical and subcortical regions to modulate respiratory muscles. For instance, the periaqueductal grey matter (PAG), located in the midbrain, sends projections to respiratory medullary circuits. While the PAG is not involved in the automatic production of breathing, it coordinates breathing with behaviors such as locomotor activity; however, the identity of PAG neurons modulating breathing remains unclear. Somatostatin (SST) is an inhibitory neuropeptide expressed in the PAG, and its expression is mostly restricted to the ventrolateral PAG (vlPAG). The vlPAG has been shown to have strong projections to the medulla, and SST vlPAG cells may modulate breathing. We aim to determine the role of SST vlPAG neurons in modulating respiratory activity and their role in motor behaviors such as motor response to nociception, which is involved in the the fight or flight and the threat response. To this aim, we used optogenetics to selectively activate SST vlPAG cells in mice expressing the opsin channelrhodopsin in SST cells. Respiratory activity was measured using whole-body plethysmography, and motor behaviors were assessed using video recording in freely behaving mice. Photostimulation of SST vlPAG cells stimulated breathing while the mouse was inactive. When the mouse was active, there was a mild decrease in respiratory rate during photostimulation. Activating SST vlPAG cells also causes a simultaneous increase in locomotor activity. Additionally, as the PAG is a key region in the descending pain pathway, we found that activating SST vlPAG cells significantly decreased the latency to tail flick, thereby facilitating

the nociceptive response. To determine whether changes in respiratory activity were due to increased motor activity, we activated SST vlPAG cells in anesthetized mice and found that photostimulation of SST vlPAG neurons increased respiratory activity in the absence of behaviours. Our results suggest that stimulation of SST vlPAG neurons independently modulates respiration, motor activity, and nociception. As such, SST vlPAG neurons may constitute a key circuit coordinating non-respiratory behaviours such as nociception and locomotor responses with breathing.

Disclosures: K. Baker: None. **C.S. Scarpellini:** None. **G. Montandon:** None.

Poster

PSTR458: Respiratory Control

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.05/BB1

Topic: F.08. Respiratory Regulation

Title: Dynamic interactions between respiratory rhythms and beta oscillations during self-initiated locomotion in mice

Authors: E. NEUBERG[1], K. DEHDAR[1], *B.-M. GU[2,3];
[2]Neurosci. Inst., [1]HMH JFK Univ. Med. Ctr., Edison, NJ; [3]Hackensack Meridian Sch. of Med., Nutley, NJ

Abstract: Initiating voluntary locomotion is a fundamental yet complex behavior that requires coordination across multiple systems, including motivational processes and widespread muscle activation. Respiratory rhythms are also critically involved in locomotor behaviors, as gait and respiration are tightly related - a phenomenon known as locomotor-respiratory coupling. Beta oscillations (13-30Hz), a hall mark of behavioral inhibition, typically decrease prior to and during movement initiation. In Parkinson's disease (PD), excessive beta synchrony in basal ganglia circuits contributes to bradykinesia and gait abnormalities. Interestingly, respiratory dysfunction is also prevalent in PD, raising important questions about the systematic interplay between respiratory rhythms and beta synchrony. Despite this overlap, the dynamic interplay between these rhythms during voluntary movement remains poorly understood. In this study, we examined how beta oscillations and respiratory rhythms interact during self-initiated locomotion in mice. We simultaneously recorded local field potentials (LFPs) from the motor cortex and substantia nigra pars reticulata (SNr), a key basal ganglia output nucleus, in addition to diaphragm electromyography (EMG) to monitor respiration. As expected, beta power significantly decreased prior to locomotion onset and maintained suppressed throughout the movement. To quantify cross-frequency interactions between respiratory and beta rhythms, we calculated the modulation index (MI) between the amplitude of beta oscillations and the phase of respiration rhythm. Our results revealed strong respiratory modulation of beta activity during immobility, which declined seconds before and during locomotion initiation. These findings demonstrate a dynamic interaction between respiratory rhythms and beta oscillations,

highlighting the importance of coordinated brain-body rhythms in initiating voluntary locomotive behaviors.

Disclosures: E. Neuberg: None. **K. Dehdar:** None. **B. Gu:** None.

Poster

PSTR458: Respiratory Control

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.06/BB2

Topic: F.08. Respiratory Regulation

Title: Ion channel targets of μ-opioid receptor signaling in the preBötzinger Complex

Authors: *E. J. KALAJIAN, M. K. STETTLER, C. A. DEL NEGRO, G. D. CONRADI SMITH;
Applied Sci., William & Mary, Williamsburg, VA

Abstract: Opioid-induced respiratory depression is a leading cause of death following overdose of oxycodone, heroin, or fentanyl, yet molecular mechanisms by which μ-opioid receptor (μOR) activation disrupts breathing remain unclear. The preBötzinger Complex (preBötC) is a mammalian brainstem nucleus containing excitatory neurons that generate breathing rhythm, and inhibitory neurons that modulate respiratory frequency and amplitude. This study aims to 1) quantify μOR mRNA (*Oprm1*) expression in preBötC glutamatergic, GABAergic, and glycinergic neurons and 2) identify ion channel targets of μOR signaling in these populations. Using RNAscope *in situ* hybridization in adult C57BL/6 mice, we label *Oprm1* and neurotransmitter-specific mRNA transcripts (N = 3 per cell type). *Oprm1* expression is evaluated by 1) transcript density (transcripts per unit somatic area, μm^2; mean ± SD): glutamatergic 0.021 ± 0.009, GABAergic 0.016 ± 0.006, glycinergic 0.011 ± 0.004; and 2) proportion of cells of each phenotype expressing ≥1 *Oprm1* transcript: 77% glutamatergic, 74% GABAergic, 67% glycinergic. While RNAscope provides insight into μOR expression across preBötC cell types, *in vitro* electrophysiology more reliably measures opioid effects. Whole-cell patch-clamp recordings in slices from a neonatal Vglut2-reporter mouse reveal that 30 nM [D-Ala^2, N-MePhe^4, Gly-ol]-enkephalin (DAMGO) increases inwardly rectifying K^+ channel conductance in glutamatergic neurons (41.191 $\pm$ 51.511% increase, Wilcoxon signed rank test, p = 7E-6, n = 18), resulting in a 6.930 $\pm$ 4.432 mV hyperpolarization (paired t-test, p = 4E-6, n = 18). These effects are occluded by Ba^{2+} (n = 9). On-cell patches from glutamatergic neurons show single-channel currents with conductance of 36.834 $\pm$ 6.098 pS and open-time constant of 1.288 ± 0.471 ms (n = 32), consistent with Kir3 channels. In ~50% of non-glutamatergic neurons, we measure a hyperpolarization-activated current that is downregulated by DAMGO in the subset of cells we tested (36.783 $\pm$ 18.359% decrease, paired t-test, p = 0.032, n = 5). These findings reveal μOR signaling differences in glutamatergic and non-glutamatergic preBötC neurons. These data highlight components of the signaling pathway and ion channels as potential therapeutic targets for reversing opioid-induced apnea.

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Poster

PSTR458: Respiratory Control

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Program #/Poster #: PSTR458.07/BB3

Topic: F.08. Respiratory Regulation

Title: The NR1 Subunit Is Expressed at Twice the Level of GluA2 in the pre-Bötzinger Complex

Authors: *C. A. OLMOS-PASTORESA[1], E. VAZQUEZ-MENDOZA[1], O. VÁZQUEZ[2], L. BELTRAN-PARRAZAL[1], C. MORGADO-VALLE[1];
[1]Inst. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Mexico; [2]Lab. de Fisiología Celular, Inst. De Neurobiología. Univ. Nacional A, Queretaro, Mexico

Abstract: The pre-Bötzinger Complex (preBötC), a cluster of excitatory interneurons in the ventrolateral medulla essential for respiratory rhythm generation, is primarily driven by glutamatergic neurotransmission mediated by AMPA receptors (AMPARs). Under physiological conditions, NMDA receptors (NMDARs) contribute modestly to synaptic charge due to their voltage-dependent Mg^{2+} block. However, in *in vitro* experiments using Mg^{2+}-free solutions, NMDAR-mediated synaptic charge increases dramatically, unveiling a previously silent population of Mg^{2+}-blocked NMDARs that, when disinhibited, can drive respiratory rhythm independently of AMPAR activation. To further investigate the distribution of AMPAR and NMDAR subunits in the preBötC, we performed double immunofluorescence and confocal microscopy to quantify GluA2-positive ($GluA2^+$) and NR1-positive ($NR1^+$) puncta —essential subunits of AMPARs and NMDARs, respectively— in 3-month-old male Sprague-Dawley rats ($n = 4$). We found that the percentage and density of $NR1^+$ puncta were approximately twice those of $GluA2^+$ puncta and significantly higher than those of colocalized $NR1^+$-$GluA2^+$ puncta. The $GluA2^+/NR1^+$ ratio was ~0.5, supporting this twofold difference. Additionally, $NR1^+$ puncta exhibited a larger average area, while colocalized $NR1^+$-$GluA2^+$ puncta showed greater circularity compared to either marker alone. These findings suggest that although NMDARs are not required for rhythm generation *per se*, their higher abundance and distinct spatial distribution may support integrative processes that modulate respiratory rhythm in response to changing physiological and cognitive states. The low degree of colocalization between $GluA2^+$ and $NR1^+$ puncta further suggests differential compartmentalization, with AMPARs likely localized to synaptic regions and NMDARs predominantly extrasynaptic.

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Poster

PSTR458: Respiratory Control

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Topic: F.08. Respiratory Regulation

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Title: Molecularly-defined inhibitory microcircuits in Bötzinger Complex

Authors: *J. SKACH[1], K. KAM[2];
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Abstract: The Bötzinger Complex (BötC) has historically been described as a density of glycinergic and GABAergic cells with expiratory modulated activity located ventral to the nucleus ambiguous (NA), caudal to the facial nucleus (VII), and rostral to the preBötzinger Complex. Sitewide functional and anatomical investigations have led to a suite of proposed roles for these neurons including inspiratory gating, respiratory phase switching, and coordination across orofacial motor behaviors. The wide range of functionality exhibited by BötC neurons points to distinct BötC microcircuits or subdivisions with unique contributions to the breathing motor program. To investigate this possibility, we used double reporter transgenic mice of both sexes to characterize the pairwise spatial distribution, level of co-expression, and spinal cord projections of BötC neurons expressing either tdtomato or EGFP in glycinergic (GlyT2+) or GABAergic (GAD1+ or GAD2+) neurons or in Dbx1-derived (Dbx1+) neurons, a subpopulation critical for breathing. We found the majority of neurons within the anatomically defined BötC region to be GlyT2+ and have a ventromedial spatial bias relative to NA. GAD2+ neurons appear to have no spatial bias and are evenly distributed ventral to NA. GAD1+ neurons are the most spatially restricted cell type and are confined to the region directly ventral to NA and caudal to VII. The majority of GAD1+ neurons also expressed GlyT2 and GAD2. To determine if molecularly-defined BötC subpopulations could be distinguished based on connectivity, we injected the retrograde tracer fast blue into the phrenic motor nucleus, a known spinal target of BötC. We found that almost all phrenic-projecting neurons within the BötC were GlyT2+ but not GAD1+, and located ventromedial to NA. We therefore suggest that BötC may be divided into a rostral GAD1+/GlyT2+/GAD2+ subpopulation, a ventromedial GlyT2+/GAD2+ subpopulation, and a ventrolateral GAD2+ subpopulation. In conclusion, our observations point to anatomically- and molecularly-distinct BötC microcircuits that make unique contributions to the breathing motor program.

Disclosures: J. Skach: None. **K. Kam:** None.

Poster

PSTR458: Respiratory Control

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.09/BB5

Topic: F.08. Respiratory Regulation

Support: F31 HL176159-01
R01 HL108609
UVA Wagner Fellowship

Title: Expression of PACAP in the neonatal retrotrapezoid nucleus is regulated by changes in arterial CO_2

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Abstract: At the time of birth, respiratory efforts must be initiated promptly and efficiently for the infant to successfully transition to extrauterine life. Thereafter, this vital physiological process must remain robust and flexible to maintain homeostatic levels of blood gases throughout life. The retrotrapezoid nucleus (RTN) comprises a group of brainstem neurons that detect and respond to elevated levels of arterial CO_2 (PCO_2) and provide critical drive to the respiratory circuits to maintain blood gas homeostasis. The ability of RTN neurons to intrinsically detect and respond to acute elevations in PCO_2 is attributed to two molecular pH sensors: GPR4, a proton activated GPCR, and TASK-2, an alkaline activated K^+ channel. The acute response of RTN neurons to brief elevations of PCO_2 has been well characterized, but it is less understood how changes in PCO_2 may lead to adaptive changes in the phenotype or function of RTN neurons, particularly in the vulnerable neonatal stage. In previous work from our laboratory, we found that deletion of PACAP, a neuropeptide associated with sudden infant death syndrome (SIDS), from RTN neurons of neonatal mice (P2-P12) results in blunted CO_2-stimulated breathing and increased respiratory instability under thermal stress. Additionally, we reported a striking upregulation of PACAP expression by the RTN following the onset of breathing at birth. The current work aims to uncover the physiological mechanisms which underlie this PACAP upregulation in the RTN at birth and determine if PACAP expression is necessary to properly initiate and sustain early neonatal respiratory efforts. Preliminary data suggests decreasing PCO_2 in the neonate via hypoxia-induced hyperventilation disrupts the normal upregulation of PACAP expression in the RTN at birth, while maintaining elevated PCO_2 levels during hypoxia-induced hyperventilation restores the increased PACAP expression typical of RTNs. Together these results suggest that early postnatal activation of this peptidergic system is due, in part, to changes in PCO_2. Ongoing experiments aim to determine if the expression pattern of PACAP in neonatal RTN neurons is dependent on direct CO_2 sensing via GPR4 and TASK-2. Further work aims to determine if PACAP is necessary for protecting respiratory activity during external stressors in the immediate neonatal period. Collectively these studies provide novel insight regarding the molecular mechanisms which regulate PACAP gene expression in the RTN, as well as the molecular signals which are vital for protecting neonatal respiration during this vulnerable developmental period.

Disclosures: R.T. Clements: None. **Y. Shi:** None. **S.M. Baca:** None. **D.A. Bayliss:** None.

Poster

PSTR458: Respiratory Control

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.10/BB6

Topic: F.08. Respiratory Regulation

Support: NIH Grant AG44615

Title: Impact of Aging onBDNF/TrkB.FL Signaling and Mitochondrial Biogenesisin Phrenic Motor Neurons

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Abstract: Brain-derived neurotrophic factor (BDNF) is a key member of the neurotrophin family and plays a critical role in neuronal survival, plasticity, and function. BDNF signals through its high-affinity full-length tropomyosin receptor kinase-B (TrkB.FL). Previously, we showed that BDNF/TrkB.FL signaling activates pCREB^{S133} phosphorylation and its nuclear translocation where pCREB^{S133} transcriptionally activates PGC1α and downstream TFAM expression, promoting mitochondrial biogenesis. Previous ly, we reported that BDNF/TrkB.FL signaling improves neuromuscular transmission at the diaphragm muscle (DIAm), an effect that is absent in older rats. In the present study, we hypothesized that aging reduces BDNF/TrkB.FL signaling in PhMNs, leading to impaired downstream pCREB^{S133} reduced PGC1α and TFAM expression and reduced mitochondrial biogenesis. In young (6 months old) and old (24 months old) Sprague Dawley rats (n=3 females and 3 males in each age group), PhMNs were retrogradely labeled and imaged using high-resolution 3D confocal microscopy. Consistent with our previous results, we found a significant reduction in the number of large PhMNs in older rats. In the cervical ventral horn, we found that total BDNF levels were unchanged with aging. BDNF-induced TrkB.FL autophosphorylation at pTrkB^{Y817} and pCREB^{S133} phosphorylation were reduced in older rats. Downstream, BDNF-induced expression of PGC1α and TFAM were also reduced in older rats. The BDNF-induced increase in mitochondrial DNA (mtDNA) copy number (reflecting mitochondrial biogenesis) was also reduced in older rats. Our results found a reduced expression of BDNF and TrkB.FL expression in the aged cervical spinal cord. These results support our hypothesis that age-related PhMN loss is associated with diminished BDNF/TrkB.FL signaling and reduced mitochondrial biogenesis. Reduced BDNF/TrkB.FL signaling may compromise neuromotor control of the DIAm in old age especially in accomplishing higher force airway clearance and expulsive behaviors that require recruitment of larger PhMNs.

Disclosures: G.A. Hernandez Vizcarrondo: None. **D. Dasgupta:** None. **M.J. Fogarty:** None. **C.B. Mantilla:** None. **G.C. Sieck:** None.

Poster

PSTR458: Respiratory Control

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.11/BB7

Topic: F.08. Respiratory Regulation

Support: HL 146114

Title: Alterations in phrenic motor neuron perineuronal nets following cervical spinal hemisection

Authors: S. CHEUNG[1], M. J. FOGARTY[2], W.-Z. ZHAN[3], M. C. BELLINGHAM[5], P. G. NOAKES[6], *G. C. SIECK[4];
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Abstract: Phrenic motor neurons (PhMNs) innervate the diaphragm muscle (DIAm), which is essential for ventilation and airway defence maneuvers (e.g., cough/sneeze). 'Inspiratory drive' for PhMNs arises primarily from ipsilateral, descending glutamatergic inputs originating from the medulla. Unilateral cervical hemisection (C2SH) disrupts this drive, reducing ventilatory DIAm activations on the injured side. Neuroplastic changes, increasing synaptic signaling via spared pathways, can enhance the spontaneous recovery from C2SH. However, synaptic neuroplasticity is highly regulated by the perineuronal net, an extracellular matrix structure. Here, we evaluated perineuronal nets on PhMNs bilaterally, in sham and injured rats. Prior to C2SH, PhMNs were retrogradely labeled intrapleural injection of CTB. During and following C2SH, DIAm EMG activity was assessed and remained diminished on the injured side. After 7 days, rats were euthanized and perfused with paraformaldehyde and the cervical spinal cord was extracted and then processed to perform free-floating immunolabeling. Horizontal sections of the cervical spinal cord were probed with antibodies against aggrecan and ChAT. Three-color confocal images (2 μm z-steps) of PhMNs (alexa-647nm-conjugated CTB), aggrecan (488 nm) and ChAT (594 nm) were obtained at 60x. A total of 292 sham and 386 C2SH PhMNs were imaged. Aggrecan intensity was quantified around the soma of PhMNs with ChAT serving as the somal boundary. Overall, less aggrecan was present on the injured ipsilateral side of C2SH rats. In control rats, the aggrecan intensity was comparable across PhMNs ov varying size. In C2SH rats, aggrecan intensity was directly dependent on PhMN size, consistent with increased reconfiguring of the ipsilateral PhMN neural network. These findings have important implications for neuroplastic mechanisms following cervical spinal cord injury.

Disclosures: S. Cheung: None. **M.J. Fogarty:** None. **W. Zhan:** None. **M.C. Bellingham:** None. **P.G. Noakes:** None. **G.C. Sieck:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.01/BB8

Topic: G.03. Stress and the Brain

Support: SECIHTI Graduate Scholarship 1321385

Title: Characterization of a murine model of early life stress

Authors: *P. I. ESCALANTE GONZÁLEZ[1], L. MENDOZA VIVEROS[2];
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Abstract: Early life stress (ELS) is a risk factor for developing psychiatric disorders such as depression and generalized anxiety. ELS is associated with neurological changes that can have a lasting impact in adulthood, due to the persistent dysregulation of the hypothalamic-pituitary-adrenal axis. The Limited Bedding and Nesting Material Limitation (LBN) model is an experimental strategy that seeks to mimic conditions of poverty, abuse and neglect in humans in model organisms, persistently affecting stress response in offspring. The aim of this work was to establish a model of ELS using the LBN paradigm, and to validate its effects on anxiety-related traits, learning and memory, and circadian behavior on the offspring. Maternal behavior was assessed through thirty-minute recording sessions at two points of the day. Behavioral tests on nine-week-old offspring of both sexes consisted of the open field test, the light box, light-dark box test, novel object recognition, and forced swimming. Locomotor behavior was evaluated using a constant monitoring system with infrared/PIR sensors. The results showed a tendency for mothers subjected to the ELS model to develop anxious hypervigilance behavior. In addition, the results of behavioral tests in the ELS progeny indicate that there is a sex-specific alteration in long-term memory, as well as anxious behavior. Interestingly, disturbances in risk perception were identified in the ELS groups, observed as an increase in the time spent in open and illuminated areas. The evaluation of locomotor behavior showed that ELS decreases activity in females. This work contributed to the implementation and validation of an ELS model with lasting effects in progeny, through behavioral tests and circadian rhythm analysis.

Disclosures: P.I. Escalante González: None. **L. Mendoza Viveros:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.02/BB9

Topic: G.03. Stress and the Brain

Support: CDMRP Grant W81XWH-22-1-0840

Title: Synergistic effects of early life adversity and adult traumatic brain injury: Microglia as potential mediators of long-term outcomes

Authors: *A. ZALETA LASTRA[1], R. BOLAND[2], P. PURYEAR[1], M. MCDONALD[1], M. MOHAMED[1], Z. R. ZIMOMRA[2], C. J. COTTER[2], S. HOULE[4], O. KOKIKO-COCHRAN[3], K. M. LENZ[1];
[1]Psychology, [3]Neurosci., [2]The Ohio State Univ., Columbus, OH; [4]Neurosci., the Ohio State Univ., Columbus, OH

Abstract: Background: Early life adversity (ELA), ranging from neglect to physical mistreatment, is a public health concern. 64% of adults in the U.S. have a history of ELA, and ELA is linked to 30% of later-life psychiatric conditions (Kessler et. al., 2010). Traumatic brain injury (TBI) affects approximately 2 million Americans per year. TBI survivors have an increased risk of developing depression, anxiety, and substance misuse. Work with veterans shows that a TBI following ELA increases risk for mood disorders developed after a TBI, suggesting that these two insults synergize to affect long term outcomes. ELA in rodent models perturbs microglia, the brain's primary immune cells, to impact neurodevelopment. ELA can lead to microglia priming, which may alter their response to secondary insults, including TBI. We investigated whether ELA and TBI synergistically influence behavioral outcomes, and if microglia turnover after ELA mitigates the effects of ELA alone or in combination with adult TBI.
Methods: Male and female mouse pups underwent 4 hr/day of maternal separation stress (MSS), a rodent model of ELA, from postnatal day (P)1-14 or were left undisturbed (n=6-8). MSS dams underwent daily unpredictable stress from P1-14. At weaning, mice were treated for 7 days with CSFR-1 inhibitor, PLX5622, in chow, to induce forced turnover of microglia, or control chow. In adulthood (~P80), mice received a sham procedure or a lateral fluid percussion injury. Behavioral testing was conducted for 7-14 days post injury (DPI), including elevated plus maze, sucrose preference test, y-maze, open field, forced swim, and HPA function testing. Mice were euthanized 14DPI and brains were processed to assess microgliosis and microglia engulfment of synaptic elements in the prefrontal cortex, basolateral amygdala, and ventral hippocampus.
Results: In the elevated plus maze, ELA induced a risk taking phenotype in males and an anxiety-like phenotype in females, regardless of injury. Microglia turnover normalized risk taking behavior in males. In the forced swim test, ELA reduced active stress coping in males, regardless of TBI. No effects were seen on anhedonic behaviors. Ongoing analyses are assessing microglial interactions with synaptic elements via high resolution microscopy in mood-regulating brain regions.
Conclusions and Future Directions: ELA programs long term mood-related behavioral changes which were rescued by microglia forced turnover at weaning. Further work is needed to explore the synergistic effects of TBI following ELA. Overall, this work lends important insight into how a life history of stress alters risk for psychiatric complications after adult brain injury.

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Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.03/BB10

Topic: G.03. Stress and the Brain

Support: NSF PRFB 2208822
NIDA R01 DA049837
NIDA R01 DA056534
2024 National Institute on Drug Abuse Summer Internship
Mollecular Basis of Disease Fellowship

Title: Acute Predator Odor Exposure in Neonatal Rats: Impact on Maternal Behavior

Authors: *M. STRICKLIN[1], D. A. BANGASSER[2], A. CUARENTA[3];
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Abstract: Early-life adversity (ELA) can have major impacts on offspring development and some of these effects are mediated by maternal care. This ELA can be linked to a higher likelihood of developing psychiatric disorders, including depression, anxiety, and substance use disorder. We model ELA in rats using a neonatal predator odor exposure (POE) paradigm. During POE, we expose neonatal pups for 5-min on three consecutive days starting on pup postnatal day (PND) 1 to PND-3. Pups are separated from their dams and placed in an odor exposure chamber, where they sit on a perforated platform above bedding. Control pups are exposed to clean bedding for five minutes each day, while the POE group is exposed to bedding infused with predator urine. Previously, we found POE reduces social play in the juvenile period and alters reward-related behaviors in adulthood. What remains unknown is how dams respond to pup reentry after exposure and whether there are changes in maternal care. Therefore, we are investigating the impact of pup POE on maternal behavior. After odor or control exposure, pups are returned to their home cage, where they are placed on the opposite side from the nest. Maternal care scoring begins as soon as pups are reintroduced to the cage. Our preliminary results demonstrate a trending effect for sniffing with dams with control pups sniffing their pups for a longer duration than dams with POE pups. We also observe a trending effect of on-nest behavior with dams with POE pups spending more time on the nest than those with control pups. These results suggest that even though the dam never experiences ELA herself, there are behavioral changes she's exhibiting in response to the pups. Altogether, we are developing a nuanced understanding of this model and how it impacts maternal behavior. This will allow us to determine how maternal care mediates the effects of offspring stress.

Disclosures: M. Stricklin: None. **D.A. Bangasser:** None. **A. Cuarenta:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.04/BB11

Topic: G.03. Stress and the Brain

Support: Colorado College Research and Development Grant
Colorado College Faculty/Student Collaborative Grant

Title: Early life adversity: effects on the gut microbiome and behavior, and mitigation with dietary inulin and psyllium

Authors: *L. L. DRISCOLL;
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Abstract: Early life adversity can disrupt gut health and impair brain development and subsequent behavior. The purpose of this study was to determine if the impacts of maternal separation (MS), a rodent model of early life adversity, on the composition of the gut microbiome and anxious, depressive, and social behaviors could be reduced by an intervention of dietary inulin and psyllium. Animals received regular purified chow (AIN-93G) or AIN-93G in which some cornstarch was replaced with equivalent weight (5%) inulin powder and (5%) psyllium husk. Newborns from both diet groups were assigned to control or maternal separation (MS) conditions, in which pups were isolated in a separate room for 5h per day from postnatal days 2-18. Caecal samples were obtained in a subset of pups at postnatal day 21 for 16s ribosomal bacterial sequencing. The other pups were administered the elevated plus maze test to assess anxious behaviors, social preference and social interaction tests, and the forced swim test to assess depressive behaviors. Following behavioral testing, serum brain derived neurotrophic factor (BDNF) was assayed using ELISA. Pups consuming the inulin/psyllium diet had significantly higher serum BDNF levels than their control diet counterparts. Maternal separation changed caecal beta diversity and behavior, both of which were partially rescued by inulin/psyllium supplementation. These data provide evidence for the role of both early life adversity and dietary prebiotic supplementation in shaping social and emotional behaviors later in life.

Disclosures: L.L. Driscoll: None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.05/BB12

Topic: G.03. Stress and the Brain

Support: NIH Grant R21ES035818
Khan Family Fellowship
UNE Research Infrastructure Fund

Title: Short- and Long-Term Effects of 10ppb Embryonic Arsenic Exposure in a Zebrafish Model

Authors: *T. MCGOLDRICK[1], G. STOEHR[2], M. A. BURMAN[3];
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Abstract: Arsenic is commonly found in drinking and well water, with EPA action levels and WHO safe drinking limit set at 10 ppb. Evidence is emerging that exposure to even this level has lasting effects on stress resilience and mental health. These effects may be exacerbated in vulnerable populations exposed to early life stress (ELS) and trauma. We examined the effects of exposure to 10 ppb arsenic, early life stress, or both for the first 5 days of life in zebrafish. ELS protocol involved embryos being exposed daily to alternating light-dark cycles, as well as a vibration stimulus from day post fertilization (dpf) 0-4 and 0-5. Following this, phototaxic-induced locomotion behavior was recorded. Both arsenic exposure and ELS resulted in reduced baseline and phototaxis-induced locomotion. There appeared to be an additive effect when these factors were combined, with a greater decrease in locomotion observed when exposed to ELS and arsenic than with individual treatments, possibly indicating different, non-mutually exclusive mechanisms of action. The long-term effects of early-life arsenic on the stress response were then investigated in adult fish. We tested the possibility of a two-hit model of stress, where fish are exposed to an adverse event early in life which then leaves them especially vulnerable to a later-life (secondary) stressor as adults. We did this in two ways. Experiment 1 involved social isolation during the juvenile period - which turned out to produce resiliency. Adult zebrafish subjected to social isolation or early life arsenic appeared to have increased boldness and locomotion in a light-dark box, in which fish demonstrated an increased willingness to explore the light side. We followed up with a net chase protocol in adulthood. In addition to social preference, novel tank, and predator response behaviors were investigated. Examining cortisol levels as a proxy for stress, arsenic fish have higher cortisol levels than controls at baseline; however, when exposed to stressful behavioral tests, there was no effect of arsenic on evoked cortisol.

Disclosures: T. McGoldrick: None. **G. Stoehr:** None. **M.A. Burman:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.06/BB13

Topic: G.03. Stress and the Brain

Support: NIDA-(R01DA057310)

Title: Sex-specific Effects of Prenatal Cosmetic Product Exposure on Early Childhood Temperament: The Moderating Role of IL-6

Authors: *I. KHAN[1], C. BRABANDER[3], D. DEINGENIIS[4], S. RAMJAN[4], Z. WANG[5], S. ISKANDER[2], M. BALDYGA[2], L. AZIZ[6], K. VEMU[7], S. SIE[8], Y. NOMURA[9];
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Abstract: Endocrine-disrupting chemicals (EDCs), like parabens and phthalates in cosmetic products, can cross the placenta during pregnancy and disrupt fetal brain development. Prenatal EDC exposure has been linked to sex-specific effects on children's emotion regulation, potentially shaped by inflammatory pathways. Interleukin-6 (IL-6), an inflammatory marker linked to brain development, may heighten fetal sensitivity to EDCs, though sex-specific effects remain unclear. This study examined the sex-specific effects of prenatal cosmetic use on early childhood temperament and if maternal IL-6 levels moderate those associations. This study evaluates a sample of participants (n=270; 51% female) from the longitudinal Stress in Pregnancy study. Prenatal EDC exposure was assessed via self-reported cosmetic use, IL-6 levels were quantified from umbilical cord blood using Luminex assays, and mothers reported child temperament from 6 to 36 months using the Infant/Early Childhood Behavior Questionnaire. Sex-stratified Generalized Estimating Equations models examined the main effects of prenatal cosmetic product exposure and IL-6 levels, and their interaction on child emotion regulation over time. Prenatal EDC exposure was associated with increased emotion regulation (p =.05) only in males. There was no main effect of IL-6 on emotion regulation in either sex. A formal test of interaction confirmed evidence for interaction between prenatal EDC exposure and IL-6 levels on emotion regulation in males (p=.041), where EDC exposure was linked to decreased emotion regulation when IL-6 levels were high. The opposite pattern occurred with IL-6 levels. High IL-6 levels intensified the adverse impact of prenatal EDC exposure on emotion regulation in males only. Independent of inflammation, EDC exposure may conversely improve emotion regulation skills by blocking testosterone production, which prior work shows decreases aggression. However, when combined with IL-6, EDCs may disrupt androgen signaling and alter testosterone production, essential for brain masculinization, potentially rendering males more vulnerable to decreased emotion regulation. More research is needed to clarify how androgen signaling is disrupted and how inflammation shapes these sex-specific effects. These findings stress the need to educate pregnant individuals about the neurodevelopmental risks of cosmetic use, especially for male offspring.

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Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.07/BB14

Topic: G.03. Stress and the Brain

Support: NIH Grant HD099338

Title: Timing matters: the effects of early life stress on unconditioned response plasticity in adolescence and adulthood

Authors: *M. SMITH[1], D. WANG[2], B. G. SCHREURS[3];
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Abstract: Adverse childhood experiences (ACEs) are faced by over 60% of children and are especially prevalent in Appalachia due to high levels of poverty. As these children move toward adulthood, only some display maladaptive physiology and behavior, including hyperarousal as seen in post-traumatic stress disorder (PTSD). This mismatch suggests differences between individuals in resilience to developing these maladaptive behaviors. PTSD is a disorder of learning and memory, in that an exposure to a stressful stimulus leads to maladaptive responding to both novel and previously encountered stimuli. Most animal models designed to study PTSD fail to measure both the learning-related and the hyperarousal symptoms seen in PTSD—however, by presenting rats with a series of periorbital pulses varying in intensity and duration, both before and after delay eyeblink conditioning (dEBC), we provide a way to quantify changes in unconditioned responding (UR) as a result of conditioning, or conditioning-specific reflex modification (CRM). We hypothesize that early life stress (ELS) in the rat predisposes individuals to CRM through aberrant regulation of perineuronal net (PNN) plasticity during the critical period of development in the sensorimotor integration center of the deep cerebellar nuclei (DCN). This may result in altered plasticity regulation of not only the circuitry underlying dEBC learning and memory, but of the UR itself as well. and on through adolescence and adulthood during learning. To model ACEs/ELS, we exposed rat pups to daily maternal deprivation (MD) from post-natal day 1 (P1) to P12. We then assessed for differences in dEBC behavior and CRM during conditioning at P40 and P90. We expect MD-exposed rats receiving paired conditioning to display greater plasticity of UR frequency, amplitude, peak latency, and area when compared to normally-raised controls. To explore ELS-induced changes to PNN plasticity in the DCN, we stained DCN tissue for neurons and PNN in MD and control animals; we expect a lower density and more diffuse distribution of DCN PNN in MD subjects, indicative of elevated plasticity. These studies will delineate a connection between ACEs and reflex plasticity, as well as a neurobiological mechanism for the ELS-related differences in unconditioned responding through differential regulation of PNN in the DCN.

Disclosures: M. Smith: None. **D. Wang:** None. **B.G. Schreurs:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

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Program #/Poster #: PSTR459.08/BB15

Topic: G.03. Stress and the Brain

Support: TCU College of Science & Engineering Research Center (SERC) Grant

Title: Exploring the interaction between diet quality and food source reliability on behavior and inflammation in a model of food insecurity in C57BL/6J mice

Authors: *L. P. GUNDERSON[1], G. W. BOEHM[2], M. J. CHUMLEY[3];
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Abstract: Food insecurity affects more than 6 million households with children in the U.S., the majority of which are insecure without hunger, and is associated with significant negative health outcomes, such as impaired immune function, anxiety/eating disorders, malnutrition, and delayed language acquisition. To explore the connection between a food insecure environment and the associated cognitive and physiological impairments, prior studies have attempted to model food insecurity in rodent models. An ideal study design to answer this question would expose mice to a food source that is truly unpredictable and of poor nutritional value for an extended period and assess their behavior for any significant changes. However, most of the prior work has either not been able to make a truly unpredictable food source or not utilized a food source that is both unpredictable and less-than-healthy, thus limiting the generalizability of their findings. To address these limitations, the present study aimed to ensure that the rodent's food source was truly unpredictable by randomly assigning periods of limited food access across each week of the study. At weaning, male and female C57BL/6J mice were either given ad libitum food access or were food insecure, where their otherwise full food-hopper would be reduced to 25% of their baseline consumption three randomly selected nights each week until the following morning. Additionally, mice were also randomly assigned to be fed either a standard chow, a “typical American diet” chow, or a high-fat/high-sugar chow. At 7 months, the mice underwent a battery of behavioral tests, including the open field test, elevated-zero maze, and novel object location task, to assess anxiety-like behavior and spatial memory capabilities. Tissue was also collected from the hippocampus, prefrontal cortex, and cerebellum for subsequent analysis of the inflammatory response as noted by changes in TNF-α and IL-6 expression, in particular. Taken together, this study provides a more complete analysis of the behavioral changes due to a truly unpredictable and nutritionally poor food source, which more closely represents the environment of those living with food insecurity.

Disclosures: L.P. Gunderson: None. **G.W. Boehm:** None. **M.J. Chumley:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.09/CC1

Topic: G.03. Stress and the Brain

Support: NSF GRFP

Title: Early Life Adversity Modulates Methamphetamine-Induced Place Preference and Extinction: Implications for Dopamine Dynamics in the Nucleus Accumbens

Authors: *B. L. WILLIAMS[1], H. R. HYLAND[3], K. G. BATH[2];
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Abstract: Experiencing early life adversity (ELA) increases the risk of substance use disorders (SUDs) and stress-induced relapse following abstinence. Among SUDs, methamphetamine (MA) use and abuse has been steadily increasing and has emerged as a major public health concern with profound psychiatric, medical, and psychosocial complications. In 2021 alone, over 64% of MA users met criteria for MA-SUDr for which there are currently no approved pharmacological treatments. Psychostimulants such as MA primarily exert their effects by increasing extracellular dopamine (DA), and the pursuit of reward and reinstatement (a model of relapse) has been shown to be mediated by DA release.

Conditioned place preference (CPP) is an established model to study reward-related behaviors and the association of drugs of abuse with contextual cues, which has been implicated in context-induced craving and relapse. This association can be extinguished, and either drug injection or stress can elicit reinstatement of CPP. Prior studies have shown that entry into a drug-paired context evokes robust DA release in the nucleus accumbens (NAc) and activation of the D1R-mediated direct pathway. However, the impact of ELA on MA-induced CPP, extinction, and the underlying DA dynamics remains unclear.

Using an 8-day CPP paradigm, we found that both control and ELA animals develop robust preference for the MA-paired chamber after 4 days of conditioning. At 1 mg/kg MA, CPP was comparable between groups, but at 2 mg/kg, ELA animals showed heightened preference relative to controls ($p=0.04$), while controls trended toward aversion (1 vs 2 mg/kg, $p=0.075$). During extinction, ELA animals showed faster reduction in CPP than controls (Day 4, $p=0.008$), but both groups reinstated to post-test levels after MA re-exposure (n.s.). These findings suggest ELA alters behavioral sensitivity to MA dose and extinction dynamics, potentially via changes in NAc DA signaling.

In my ongoing work, I will employ fiber photometry and a genetically encoded DA sensor to directly assess how ELA modulates DA release during MA-induced CPP and extinction. Together, these results may shed light on mechanisms underlying SUD risk in vulnerable populations and inform new intervention strategies.

Disclosures: B.L. Williams: None. **H.R. Hyland:** None. **K.G. Bath:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.10/CC2

Topic: G.03. Stress and the Brain

Title: Effects of maternal stress during gestation on offspring neurodevelopment and anxiety

Authors: *P. TORRES, J. M. IBARRA HERNÁNDEZ, A. GARCIA, F. SIERRA, F. GUZMAN DE LA GARZA;
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Abstract: Stress is a physiological response to adverse stimuli that can become detrimental when intense or prolonged. Currently, an increase in stress levels has been reported in women, influenced by factors such as work overload, economic instability, and insecurity, which may affect the neurodevelopment and anxiety of their offspring. This study aimed to evaluate the impact of gestational stress on neurodevelopment and anxiety in Wistar rat offspring. Male and female Wistar rats were used, born to control mothers or to mothers exposed to a chronic stress battery during gestation. During the lactation period, offspring were evaluated using a neurodevelopmental test battery, which included assessments of forelimb and hindlimb grip, righting reflex, hindlimb placement, cliff avoidance, gait, auditory startle, body posture, eye opening, and accelerated righting reflex. At one and a half months of age, anxiety-like behavior was assessed using the elevated plus maze, recording time spent in open and closed arms. A significance level of $P<0.05$ was considered. Offspring from the gestational stress group showed significantly earlier onset of certain reflexes during the first postnatal week: cliff avoidance, dorsiflexion, and righting reflex. Moreover, male offspring exposed to gestational stress spent significantly more time in the closed arms compared to non-stressed controls ($P<0.001$). In conclusion, gestational stress appears to accelerate early neurodevelopment in both sexes, possibly as an early adaptive response of the nervous system to adverse environments. However, it also significantly increases anxiety-like behavior exclusively in male offspring exposed to gestational stress.

Disclosures: P. Torres: None. **J.M. Ibarra Hernández:** None. **A. Garcia:** None. **F. Sierra:** None. **F. Guzman de la garza:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.11/CC3

Topic: G.03. Stress and the Brain

Support: College of Arts and Sciences, Quinnipiac University
Biomedical Sciences, Quinnipiac University

Title: The effects of maternal separation on learning and memory in aged rodents

Authors: *A. J. BETZ[1], M. ENOS[2], S. AZERRAD[3], C. CHARPENTIER[4], T. PANTALENA[5], N. SYME[6];
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Abstract: An increase in aging populations across the globe makes research on the factors that affect the aging brain increasingly important. Early life stress, such as maternal separation (MS), has long-lasting effects on neurodevelopment, yet its interaction with aging remains poorly understood. This study investigated the impact of MS on learning, memory, and molecular markers of synaptic function in aged rodents. Using a trace fear conditioning paradigm, we evaluated behavioral responses in two-year-old male and female rats with or without a history of MS. We further examined total tau, phosphorylated-tau and extracellular signal-regulated kinase (ERK), expression in cellular compartments from the hippocampus and prefrontal cortex, two regions critical for memory and stress regulation. MS significantly altered freezing behavior during specific trace fear conditioning phases, particularly in male rats. Western blot analysis revealed sex-specific differences in tau and ERK distribution, with limited effects of MS on total tau expression but a significant MS-induced reduction of ERK in the male prefrontal cortex cytosolic fraction. These findings suggest that MS contributes to subtle, sex-dependent cognitive and molecular alterations in aging, potentially increasing vulnerability to age-related neurodegeneration.

Disclosures: A.J. Betz: None. **M. Enos:** None. **S. Azerrad:** None. **C. Charpentier:** None. **T. Pantalena:** None. **N. Syme:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.12/CC4

Topic: G.03. Stress and the Brain

Support: VA BLRD Merit Award 1I01BX006155
DoD PRP HT9425-24-1-0775

Title: Behavioral signatures of a neurotrauma-induced Parkinson's disease model: Defining a sensitive window for therapeutic intervention

Authors: *C. J. TINSLEY[1], L. DOVEK[4], K. MCDANIEL[2], L. NUNGARAY[1], N. MCGUIRE[1], P. T. WICKHAM[5], G. SCOTT[5], C. K. MESHUL[6], J. J. ILIFF[7], J. E. ELLIOTT[3], M. M. LIM[5]; [1]Oregon Hlth. and Sci. Univ., Portland, OR; [2]Oregon Hlth. and Sci. Univ., portland, OR; [3]Neurol., Oregon Hlth. and Sci. Univ., Portland, OR; [4]Biomed. Sciences/ MCSB, Oregon Hlth. & Sci. Univ., Portland, OR; [5]OHSU, Portland, OR; [6]Neurocytology Lab/Bldg 101, Room 520, OHSU, Tigard, OR; [7]Univ. of Washington, Lynnwood, WA

Abstract: Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are linked to increased risk for neurodegenerative diseases such as Parkinson's disease. Identifying when behavioral impairments emerge after neurotrauma can inform early treatment strategies. In this preclinical study, subjects were exposed to Single Prolonged Stress (SPS) and Controlled Cortical Impact (CCI) to model PTSD and TBI, respectively. Gait, anxiety-like behavior, and cognition were assessed at 2, 4, and 12 weeks post-injury to examine the time course of dysfunction. Cognitive and motor deficits appeared as early as 2 weeks and persisted through 12 weeks, while changes in anxiety-like behaviors emerged later. These findings establish a timeline of behavioral changes following neurotrauma, offering insight into early indicators of neurodegenerative disease risk and informing potential therapeutic targets.

Disclosures: C.J. Tinsley: None. **L. Dovek:** None. **K. McDaniel:** None. **L. Nungaray:** None. **N. McGuire:** None. **P.T. Wickham:** None. **G. Scott:** None. **C.K. Meshul:** None. **J.J. Iliff:** None. **J.E. Elliott:** None. **M.M. Lim:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.13/CC5

Topic: G.03. Stress and the Brain

Support: NIEHS Intramural ES100221

Title: Prenatal corticosterone exposure alters hippocampal area CA2's molecular profile and connectivity.

Authors: D. I. COATES[1], P. N. SIEGLER[2], G. M. ALEXANDER[2], *S. M. DUDEK[2]; [1]Neurobio. Lab., Natl. Inst. of Enviornmental Hlth. Sci., Research Triangle Park, NC; [2]Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC

Abstract: Stress is the body's response to a challenge or threat and is universally experienced across species. Upon experiencing stress, in mammals the Hypothalamic-Pituitary-Adrenal (HPA) axis is activated starting a hormonal cascade that ultimately produces glucocorticoids. These glucocorticoids—cortisol in humans and corticosterone (CORT) in rodents— then act on target tissues, like the limbic areas of the brain. In humans, prenatal stress is known to change the structure and connectivity of brain regions including the hippocampus , and it is also known that chronic stress experienced at key times in development (i.e. prenatal and early life) increases

susceptibility for neurodevelopmental disorders - like autism, bipolar disorder, or schizophrenia - that are often hallmarked by social deficits. Within the hippocampus, expression of the glucocorticoid and mineralocorticoid receptors (GR and MR) is enriched in areas CA1 and CA2, respectively. MRs in hippocampus within humans can be found as early as 24 weeks of gestation, and in mice by embryonic day 15 - before GRs are expressed (postnatal day 7). This suggests that MRs are likely the primary target of glucocorticoids in the prenatal brain. Previously, our lab found that a 7-day treatment of CORT in adult mice reduces CA2 expression of MRs and an MR-dependent CA2 protein. In addition, an MR conditional knockout mouse model resulted in a loss of CA2's unique molecular profile, and prenatal treatment with the MR antagonist, spironolactone (SPIRO), caused decreased staining of vesicular glutamate transporter 2 (vGluT2), which labels synaptic terminals originating from the supramammillary nucleus (SuM). Our current question is how prenatal exposure to CORT influences area CA2's development and connectivity to other social brain regions. To isolate the effects of CORT from other hormones, we treated pregnant dams from gestational day 9.5 to littering with either a vehicle, a low (35µg/ml), or high (50µg/ml) concentration of CORT via the home cage drinking water. Animals were euthanized at several developmental ages, and their brains processed for immunofluorescence (IF). We found that prenatal CORT increased GR IF in area CA1 at P60, and increased staining for vGluT2 in CA2 and dentate gyrus, suggesting altered connectivity to SuM. These results suggest that excessive prenatal glucocorticoids impact hippocampal circuitry. Ongoing work using a viral strategy is being used to better understand how CA2 input circuits are altered with a prenatal treatment of CORT or SPIRO.

Disclosures: D.I. Coates: None. **P.N. Siegler:** None. **G.M. Alexander:** None. **S.M. Dudek:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.14/CC6

Topic: G.03. Stress and the Brain

Support: NIEHS ES 100221

Title: Prenatal corticosterone exposure alters hippocampal area CA2's development and related behaviors at different developmental stages

Authors: *P. N. SIEGLER[1], D. COATES[3], G. M. ALEXANDER[2], S. M. DUDEK[4];
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Abstract: In humans, prenatal stress is associated with an increased risk of neurodevelopmental and psychiatric disorders—such as autism, schizophrenia, or bipolar disorder—many of which

involve social deficits, and these disorders are also linked to altered structure and connectivity of various brain areas, including hippocampus. Glucocorticoid and mineralocorticoid receptors (GR and MR, respectively), the two primary stress hormone receptors, are enriched in hippocampus of adult human and mouse. Within CA2 of hippocampus, MR shows the greatest enrichment, and GR is minimally expressed. Developmentally, MR is richly expressed in human hippocampus as early as 24 weeks of gestation and in mouse hippocampus around embryonic day 15, whereas GR is only minimally expressed prenatally in human and is not expressed until at least postnatal day 7 in mouse. Therefore, MR is likely the primary target of glucocorticoids during the prenatal period. Previously, our lab found that a 7-day treatment of the glucocorticoid corticosterone (CORT) in adult mice reduced CA2 expression of MR, as well as an MR-dependent CA2 protein. Additionally, in MR conditional knockout mice, the distinct molecular profile of CA2 is lost. These findings led us to ask how prenatal stress, specifically elevated CORT associated with stress, influences hippocampal development and related behaviors. To isolate the effects of CORT from other hormones, we treated pregnant dams from gestational day 9.5 to littering with either a vehicle, a high (50 µg/ml) or low (35 µg/ml) concentration of CORT via the homecage drinking water. Animals were euthanized at various developmental timepoints, and their brains were preserved for mass spectrometry and immunofluorescent (IF) staining. Mass spectrometry revealed increased CORT and decreased aldosterone at birth for CORT-treated animals relative to vehicle-treated animals, and elevated aldosterone at P14 of CORT-treated animals. IF staining for proteins, receptors, and extracellular structures unique to area CA2 (i.e. staining for perineuronal nets) was performed. CORT and vehicle-treated animals at various ages also underwent behavioral analyses for assessment of social memory, novel object reactivity, anxiety, and home cage behavior. Findings reveal treatment and sex dependent effects, including CORT-treated males exhibiting heightened novelty reactivity and anxiety-like behaviors. Our results suggest that excessive prenatal exposure to glucocorticoids affects postnatal hormone levels, hippocampal circuitry, and CA2-related behaviors.

Disclosures: P.N. Siegler: None. **D. Coates:** None. **G.M. Alexander:** None. **S.M. Dudek:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

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Program #/Poster #: PSTR459.15/CC7

Topic: G.03. Stress and the Brain

Support: NIMH Silvio Conte Center 1P50MH094271
JPB Foundation
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JSPS KAKENHI 20A303
JSPS KAKENHI 23K06010

Title: Early adversity disrupts optimal dopamine receptor activity in the anterior cingulate cortex to impair attention

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Abstract: Early life adversity can lead to long-lasting neural and behavioral impairments. Attentional function is particularly susceptible to early life stress (ELS), especially in males, associated with an increased risk of attention deficit hyperactivity disorder (ADHD). Our recent findings show that ELS from postnatal day 2-9 in male mice increases dopamine D2 receptor (D2R) expression and decreases D4 receptor (D4R) expression in the anterior cingulate cortex (ACC), resulting in impaired attention [1]. On the other hand, previous work also shows that blockade of D2R activity could impair some aspects of attention, complicating interpretation of how elevated D2R expression by ELS leads to attentional deficits. Here, we investigated how varying levels of D2R activity in the ACC affect attention and how this relationship is altered by ELS in male mice. In normally-reared mice, local ACC infusion of increasing doses of the D2R agonist quinpirole progressively impaired attention on a two-choice visual attention task. Interestingly, increasing doses of the D2R antagonist raclopride also impaired attention in a dose-dependent manner. These results suggest an inverted U-shaped dose-response curve between D2R activity and attentional performance, with normally-reared mice positioned near the peak. In contrast, in mice after ELS by fragmented maternal care at P2-9, increasing doses of the D2R antagonist initially improved and then impaired attention. This indicates that ELS-exposed mice are positioned beyond the peak of dose-response curve due to the expressional increase of D2R, and while low-dose antagonist restores D2R activity toward the optimal point to improve attention, further doses overshoot it to impair attention again. Our findings are consistent with the well-established inverted U-shaped relationship between cortical dopamine signaling and cognitive performance [2] and further reveal that ELS displaces D2R activity in the ACC from the optimal point, leading to attentional deficits in males. **References**: [1] Makino, Y. et al. (2024). Sci. Transl. Med. 16: eadh9763. [2] Goldman-Rakic, P.S. et al. (2000). Brain Res. Rev. 31: 295-301.

Disclosures: Y. Makino: None. **T.K. Hensch:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

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Topic: G.03. Stress and the Brain

Support: NIH grant R01MH131592
NIH grant F31MH136684

NIH grant T32AG055378
Portland VA Research Foundation

Title: Social chemistry in monogamous rodents is modulated by early-life sleep experience

Authors: *L. S. BUENO-JUNIOR[1], N. E. P. MILMAN[2,3], C. J. TINSLEY[2,3], A. GHIMIRE[1], P. T. WICKHAM[2,3], Y. HU[4], B. YE[1], M. M. LIM[3,2], B. O. WATSON[1];
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Abstract: Studies of human sociability indicate stronger affinity in matched-neurotype dyads (e.g., two individuals with autism or two without) compared to mixed-neurotype dyads (e.g., one individual with autism paired with one without). Is this "social chemistry" phenomenon also quantifiable in non-human animals? Using deep learning tools, we analyzed dyadic male-female interactions in prairie voles, a highly social rodent species. To simulate "neurotypes", voles were exposed to either control conditions or early-life sleep disruption (ELSD) during a critical neurodevelopmental period (postnatal days 14-21), recapitulating two features of human autism: developmental sleep disruption and later-life atypical sociability. Analogous to human studies, voles showed signs of reduced affinity in mixed compared to matched dyads, including sex-specific changes in body orientation and aggression. These findings advance our evolutionary and clinical understanding of social affinity in humans, and provide a framework for future studies across species.

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

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

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Topic: G.03. Stress and the Brain

Support: Inflammation Healing Foundation
1R01MH131592-01A1

Title: Developmental Cell-Type Specific Alterations in MMP9 Expression in the Hippocampus of Prairie Voles Following Early-Life Sleep Disruption

Authors: *J. J. BABU[1], C. J. TINSLEY[4], N. E. MILMAN[5], B. GISABELLA[2], M. M. LIM[6], H. PANTAZOPOULOS[3];
[1]Psychiatry, [2]Dept. of Psychiatry and Human Behavior Div. of Neurobio. and Behavior Res., [3]Psychiatry and Human Behavior, Univ. of Mississippi Med. Ctr., Jackson, MS; [4]Behavioral

Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [5]Behavioral Systems Neurosci., OHSU, Portland, OR; [6]Veterans Affairs Portland Hlth. Care Syst., Portland, OR

Abstract: Background: Early-life sleep disruption (ELSD) is a significant environmental risk factor for autism spectrum disorders (ASD). Previous studies from our group demonstrated that ELSD resulted in impaired behaviors in adult prairie voles, including reduced partner preference and novel object recognition, a hippocampal-dependent behavior. Spatial memory deficits are also common in people with ASD. Prior work from our lab demonstrated decreased perineuronal nets (PNNs) in the hippocampal sector CA1 of ELSD prairie voles and elevated MMP9 expression in the hippocampus of children with ASD. MMP9, a matrix metalloproteinase, modulates synaptic plasticity and degrades extracellular matrix structures, including PNNs. PNNs are ECM structures composed of chondroitin sulphate proteoglycans (CSPGs) involved in neuronal maturation and synaptic plasticity implicated in neurodevelopmental disorders. Here, we tested the hypothesis that ELSD alters the developmental trajectory and cellular specificity of MMP9 expression in hippocampal CA1 in prairie voles.**Methods**: We analyzed hippocampal sections from juvenile (P17-P20) and adult (P150-160) male and female prairie voles with and without ELSD (n = 24). Immunohistochemistry for MMP9 was performed, and stereology-based microscopy was used to quantify labelled neurons, glia, and PNNs across CA1 subregions (stratum oriens, pyramidale).**Results**: In adult CA1, most MMP9+ cells were neurons (80.5% in stratum oriens, 89% in stratum pyramidale), with smaller proportions of MMP9+ glia (17.7% in stratum oriens, 8.9% in stratum pyramidale. We also observed unexpected MMP9 labeling in PNNs, which colocalized with wisteria floribunda positive PNNs surrounding parvalbumin neurons. Analysis of the data collected thus far revealed that adult ELSD voles display significantly reduced densities of MMP9+ neurons in both stratum oriens and stratum pyramidale ($p<0.03$). In comparison, MMP9+ PNNs are increased in stratum oriens ($p<0.05$) of adult ELSD voles. Across development, MMP9+ PNNs increased with age in both groups, while MMP9+ neurons remained stable in control voles but declined sharply in ELSD voles.**Conclusion:** These findings represent the first cellular-level mapping of MMP9 expression in the prairie vole hippocampus and demonstrate unexpected MMP9 labeling within PNNs. Furthermore, ELSD disrupts normal MMP9 developmental patterns, potentially impairing hippocampal ECM remodeling and synaptic integrity, which has been implicated in children with ASD. These data support a mechanism by which ELSD contributes to neurodevelopmental vulnerability through cell-type specific ECM dysregulation.

Disclosures: J.J. Babu: None. **C.J. Tinsley:** None. **N.E. Milman:** None. **B. Gisabella:** None. **M.M. Lim:** None. **H. Pantazopoulos:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

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Topic: G.03. Stress and the Brain

Support: George E. Hewitt Foundation for Biomedical Research (Postdoctoral Fellowship)
Swiss National Science Foundation (Postdoc.Mobility fellowship)
National Institutes of Health (MH096889)

Title: Peptide signaling in the paraventricular thalamus contributes to early-life adversity-induced disruptions of adult reward behaviors

Authors: *A. FLORIOU-SERVOU[1], R. WEBER[3], H. LIANG[1], C. KOOIKER[2], M. T. BIRNIE[5], M. GANTUZ[4], G. ANGELES[3], R. ROBERTS[6], A. MORTAZAVI[1], T. BARAM[3]; [2]Anat. and Neurobio., [1]UC Irvine, Irvine, CA; [4]UCIMIND, [3]Univ. of California, Irvine, Irvine, CA; [5]Dept. of Pediatrics, Univ. of California-Irvine, Irvine, CA; [6]Exptl. Pathology, Univ. of California Irvine, Irvine, MD

Abstract: Background: Early-life adversity (ELA) is associated with cognitive and mental health problems later in life, and evidence in rodents points to a causal role of ELA, with structural and functional changes in the brain's reward circuitry. However, the mechanisms through which ELA changes the brain remain poorly understood. An emerging key node of the reward circuit is the paraventricular thalamus (PVT). The PVT is strongly and almost exclusively activated in the mouse brain early in life, it is re-activated during reward in adulthood, and inhibiting specific PVT domains alleviates ELA-induced reward deficits in a sex-specific manner. Therefore, the ELA experience could be encoded in the PVT and influence the PVT's response and function during reward behaviors later in life. Here, we screen the translatome of PVT cells activated early in life at rest and in the context of reward and identify genes that are regulated by reward in a sex-specific way. One of these genes is the corticotropin-releasing hormone receptor type 1 (*Crhr1*), that senses CRH, a stress-related peptide that is significantly influenced by stress. Importantly, CRHR1 is expressed in a higher proportion of activated cells in the PVT of ELA mice compared to CTL, so it could mediate some of the effects of ELA on reward behavior. Therefore, we use the CRISPR/Cas9 technology to delete *Crhr1* specifically in PVT cells activated during ELA and we assess reward behaviors before and after the deletion. **Methods**: To isolate and sequence the translatome of early life (P6-P8) activated PVT cells we crossed mice expressing Fos-Cre^{ERT2} for activity-dependent genetic labeling, with mice expressing a Cre-dependent ribosomal tag for translating ribosome affinity purification. To delete *Crhr1* specifically from early life activated PVT cells, we crossed the Fos-Cre^{ERT2} mice with LSL-FLP mice and delivered a FLP-dependent AAV that expressed Cas9 and RNA guides for *Crhr1* in adult mice. **Results**: A. Strong enrichment in genes that are highly expressed in the PVT such as *Snca* and *Calb2*, and a reduction in genes that are less expressed in the PVT, confirmed that the isolated RNA was mainly from PVT cells. B. Few genes were differentially expressed in adult ELA vs control mice at rest, but exposure to reward induced very different translatomic responses in ELA, in a sex-dependent manner. C. *Crhr1* deletion ameliorated the sex-dependent ELA reward phenotype. **Conclusions**: Our results 1) indicate that ELA primes the PVT, influencing the way that the PVT responds to reward, 2) highlight PVT's sexually dimorphic nature and 3) point to a critical role of the CRH system in the dysregulation of reward behavior by ELA.

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Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

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Program #/Poster #: PSTR459.19/CC11

Topic: G.03. Stress and the Brain

Support: NIH R01 MH133456
NIH BRAIN Initiative R00MH124434
NIH BRAIN Initiative 3R00MH124434
BBRF NARSAD
Goldstein Innovation Award

Title: Impaired social behavior following early life adversity coincides with changes in blood metabolome and genetic profile of the basolateral amygdala

Authors: *C. A. MEDINA[1], I. MCKIE[1], N. ISABELLAH[2], M. OPENDAK[3];
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Abstract: Early life adversity (ELA) is a major risk factor for neuropsychiatric disorders such as anxiety and depression. Previous work using the scarcity adversity via limited bedding (LB) model of ELA suggests that the long-term behavioral consequences of ELA, such as impaired social behavior and threat processing, involve dysfunction of the basolateral amygdala (BLA) and changes in peripheral signalling. However, the specific mechanisms translating early experience to social impairments remain poorly understood. Here, we use a novel model of ELA called the Deconstructed Adversity Model in combination with metabolomics, and RNA-sequencing of the BLA to identify links between ELA and infant/adolescent social behavior, finding that levels of metabolites involved in bile acid synthesis are altered following social and non-social adversity. To explore this further, we supplemented rat pups with the primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) during scarcity adversity in early life before assessing social behavior at infancy (PN13) and adolescence (PN45). Our findings suggest that bile acid supplementation may mitigate social deficits associated with ELA, highlighting a potential therapeutic value.

Disclosures: C.A. Medina: None. **I. McKie:** None. **N. Isabellah:** None. **M. Opendak:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.20/CC12

Topic: G.03. Stress and the Brain

Support: R01 – 20-4440-9200-113620-0324-01

Title: Social conditioning increases exploratory behavior and bla-pvt activity in juvenile rats

Authors: *N. ISABELLAH;
Kennedy Krieger Institute., Baltimore, MD

Abstract: The development of social behavior reflects changes in age, environmental demands, and responses to early care. Indeed, the caregiver-infant social dyad provides a lasting template for lifelong social behavior patterns. However, the specific neural mechanisms translating early social experience to long-term reorganization of social behavior remain poorly understood. We modeled early life stress in infant rat pups (PND 8-12) and assessed social investigation behavior and social conditioned place preference (SCPP) in juveniles (PND 21-35). Neural measures included calcium dynamics (photometry) and IEG expression. Given the choice of two novel beddings in a SCPP apparatus, all pups showed a robust baseline preference for specific novel bedding, but these preferences were bimodally distributed. We observed that adversity-reared pups demonstrated lower exploratory behavior at baseline than controls, which was restored to control-levels after social conditioning. This behavior was associated with elevated c-Fos expression in the basolateral amygdala (BLA) and paraventricular thalamus (PVT). During social behavioral tests with partners of different sexes, we observed significant changes in amplitude of calcium signaling. These changes occurred in concert with proximity to social stimuli and with stress behaviors, such as freezing and grooming. Together, these measures reflect impacts of learning, development, and adversity on social circuit function in development.

Disclosures: N. Isabellah: A. Employment/Salary (full or part-time): Kennedy Krieger Institute, Johns Hopins University.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.21/CC13

Topic: H.06. Anxiety Disorders

Title: Effects of peri-natal exposure to bisphenol A in anxiety levels in high- and low- yawning sublines rats.

Authors: *H. AQUINO[1], C. CORTES[2], J. R. EGUIBAR, Sr.[3];
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Abstract: Anxiety prevalence has increased significatively around the world in the last two decades and even worsened after COVID-19 pandemia. Anxiety is a behavioral and physiological condition induced by a potential or real threat for individual survival and it is characterized by fear-like behavioral responses. Anxiety can be induced by several factors, such as environmental pollutants. Bisphenol A (BPA) is a synthetic plastic found in food and drink containers and ingested in a regular manner. In fact, BPA levels are associated with higher anxiety levels due to endocrine disrupting mechanisms with short and long-term effects. We have two sublines named *high-yawning* (HY) and *low-yawning* (LY) with 20 yawns/h and 2 yawns/h, respectively. HY are resilient and LY are more anxious in different psychobiological tests. The aim of this study was to evaluate BPA effects in anxiety levels in both sublines using the open-field arena (OFA) between 8000 and 1000 h. We analyzed 65 HY and 57 LY of both sexes which are maintained under standard conditions. The BPA was administrated via drinking water 250 μg/kg/day during the gestation and lactation periods. The litters were curled to 4 male/4 female, maintained to 90 ± 2 postnatal days and then evaluated the behavioral display in OFA. Our results showed an opposite tendency in anxiety levels between sublines after exposition to BPA, because HY males and females exposed to BPA had less rearings with respect to control subjects. On the other hand, LY males and females exposed to BPA had more rearings with respect to non-exposed rats. These results showed that exploratory behavior decreased in HY and increased in LY subjects exposed to BPA, indicating an increased and decreased in their anxiety levels, respectively. In conclusion, BPA modifies anxiety in an opposite way depending on basal anxiety level. Our results clearly show that the genetic background determines anxiety in OFA.

Disclosures: H. Aquino: None. **C. Cortes:** None. **J.R. Eguibar:** None.

Poster

PSTR459: The Nature and Neurobiology of Early-Life Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.22/CC14

Topic: H.04. Emotion

Support: NSERC PGSD3 - 557532
NIH U19 NS107616

Title: Neural circuit mechanisms of infant neglect and attention

Authors: *C. J. BAIR MARSHALL[1], A. A. AGHA[2], R. C. FROEMKE[3];
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Abstract: Infants in distress evoke strong emotional responses in adults which help to elicit caretaking behaviors from parents to ensure infant needs are met. However, neonatal care can also be challenging, and interactions with infants can lead to stress and negative affect, even in

potential caregivers. Child neglect and maltreatment rates in human populations make it important to understand the neural mechanisms of regulating negative emotions and stress in the parental brain. Here we show how rapid plasticity in female mouse central amygdala (CeA) transforms infant aversion into attentiveness after initial pup experience. Projections from CeA to locus coeruleus (CeA - LC) were strongly activated upon initial pup contact leading to pup aversion. CeA - LC pup responses were reduced with parental experience and down-regulating CeA - LC activity led to less aversion. Oxytocin signaling in central amygdala was required to switch pup aversion to attention, inducing rapid long-term depression of excitatory inputs onto projection neurons. CeA - LC projectors released the stress hormone corticotropin-releasing factor onto LC neurons, modulating phasic firing to regulate attention. This circuit organization enables local CeA computations of pup valence to be broadcast throughout the brain by the LC central arousal system, leading to appropriate pup-directed behaviors depending on adult state.

Disclosures: C.J. Bair Marshall: None. **A.A. Agha:** None. **R.C. Froemke:** None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.01/CC15

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

Support: MSIT of Korea, No. RS-2023-00213187

Title: Dynamics of brain-wide patterns of resting-state fMRI traveling waves is related to arousal levels

Authors: *D. SIHN[1], S.-P. KIM[2];
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Abstract: Brain waves propagate as traveling waves, reflecting the brain's functional organization and information transmission. Macroscale traveling waves observed in blood-oxygen-level-dependent (BOLD) signals offer insights into large-scale neural coordination. Since multiple brain-wide traveling wave patterns can exist, understanding their temporal dynamics may illuminate how neural information processing unfolds. As infra-slow BOLD activity (<0.1 Hz) is known to correlate with arousal, we hypothesized that temporal dynamics of brain-wide traveling wave patterns in this band are modulated by arousal levels. We analyzed a publicly available resting-state functional MRI (rsfMRI) dataset (N = 27) to examine the relationship between arousal and brain-wide traveling wave patterns. Infra-slow BOLD traveling waves were quantified using the 3-D local phase gradient (LPG) method. Wave patterns were identified by clustering LPG directions via k-means clustering, with the optimal number of clusters (k = 2) determined using the silhouette method. We then examined temporal interactions between these clusters and arousal levels, defined using pupillometry data as the lowest and highest 20 percentiles. The two clusters showed distinct characteristics. Cluster 1, compared to

Cluster 2, included more sustained and prominent traveling waves, particularly in the salience ventral attention and frontoparietal control networks. Cluster 1 occurred more frequently during low-arousal periods, whereas Cluster 2 appeared more during high-arousal periods. Moreover, Cluster 2 persisted longer during high- than low-arousal states. These findings suggest that Cluster 1 corresponds to low-arousal dynamics and Cluster 2 to high-arousal dynamics. Low-arousal states were associated with more stable and sustained traveling waves, while high-arousal states involved more transient and variable patterns. Traveling directions differed by network, indicating spatial heterogeneity within each cluster. While prior studies proposed simple top-down vs. bottom-up traveling directions for different arousal levels, our results reveal more complex, brain-wide dynamics tied to arousal, suggesting a richer framework for understanding large-scale neural coordination.

Disclosures: D. Sihn: None. **S. Kim:** None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.02/DD1

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

Support: CONACYT Grant CF-2019-6390
DGAPA-PAPIIT-UNAM IN208622
DGAPA-PAPIIT-UNAM IN212624

Title: The topology of the brain functional connectome and its association with cognitive performance

Authors: *I. ESPINOSA MÉNDEZ[1], D. RAMÍREZ GONZÁLEZ[1], J. DIAZ-PATINO[2], G. ROBLES RODRÍGUEZ[1], T. V. ROMAN-LOPEZ[1], E. PASAYE[1], I. ARELIO[2], A. SOLARI[3], E. HERRERA MEZA[1], A. HERNÁNDEZ MONÁRREZ[1], A. PIÑA HERNÁNDEZ[1], F. LÓPEZ ARGUELLES[1], A. MEDINA-RIVERA[3], A. E. RUIZ-CONTRERAS[4], M. E. RENTERÍA[5], S. ALCAUTER[1];
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Abstract: Associations between intelligence and brain phenotypes have been widely studied. However, findings from resting-state functional connectivity analyses using network analysis approaches remain inconclusive. Some studies report positive associations between intelligence and global efficiency (e.g., van den Heuvel et al., 2009), while others find no significant effects (Pamplona et al., 2015; Kruschwitz et al., 2021). To help clarify these inconsistencies, we analyzed a novel sample of Mexican twins using the area under the Betti-0 curve (AUC), a

topological data analysis metric previously found to be heritable and sensitive to clinical conditions (Gracia-Tabuenca et al., 2022).*Data were acquired at the National Laboratory for MRI (LANIREM) using a 10-minute T2*-weighted EPI sequence (TR = 2 s, voxel size = 3.2 mm^3), with structural T1 images (1 mm^3) for coregistration. Preprocessing was performed with fMRIPrep 2023.0.1, and connectivity matrices were generated via XCP-D using three parcellations: Schaefer, Glasser, and Gordon. Cognitive performance was measured on the same day using the Shipley-2 Brief Intelligence Test and the Creyos Cambridge Brain Sciences battery. Pearson correlations were computed between Betti-0 AUC and two cognitive scores: Shipley-2 composite and the first principal component (PC1) from the 12 Creyos subtests. No significant associations were found between AUC and Shipley-2 scores. However, significant negative correlations emerged with Creyos PC1 across all atlases: Glasser ($r = -0.28$, $p < 0.001$), Gordon ($r = -0.22$, $p = 0.003$), and Schaefer ($r = -0.17$, $p = 0.021$). Since a smaller AUC indicates stronger connectivity (i.e., integration at lower filtration thresholds), this suggests that greater global functional integration may relate to better cognitive performance. Although Shipley-2 and Creyos PC1 were correlated ($r = 0.51$, $p < 0.001$), only the latter showed significant associations with AUC, possibly due to broader domain coverage and greater sensitivity to fluid intelligence. In contrast, the Shipley-2 emphasizes crystallized abilities (e.g., vocabulary and abstract reasoning). Our findings support the relevance of topological metrics like Betti-0 AUC in brain-cognition research and highlight the need for replication and more robust modeling in diverse populations.

Disclosures: I. Espinosa Méndez: None. **D. Ramírez González:** None. **J. Diaz-Patino:** None. **G. Robles Rodríguez:** None. **T.V. Roman-Lopez:** None. **E. Pasaye:** None. **I. Arelio:** None. **A. Solari:** None. **E. Herrera Meza:** None. **A. Hernández Monárrez:** None. **A. Piña Hernández:** None. **F. López Arguelles:** None. **A. Medina-Rivera:** None. **A.E. Ruiz-Contreras:** None. **M.E. Rentería:** None. **S. Alcauter:** None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.03/DD2

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

Title: A Transformer framework for Functional Connectivity Inference in the Brain

Authors: *R. BOSE-ROY;
Yale Univ., New York, NY

Abstract: Modeling the complex spatial and temporal dynamics of the brain is a challenging task. Conventional correlation-based functional connectivity can fail to capture directed, nonlinear, and temporal dependencies between brain regions. This study introduces a transformer-based framework for inferring causal functional connectivity using perturbation experiments. We analyzed resting-state fMRI data from 34 healthy controls and 36 epilepsy

patients using the Yale Brain Atlas (696 parcels), employing encoder-decoder and encoder-only transformers with Hopfield and Vanilla attention mechanisms.Transformers were trained to predict future BOLD activities across all parcels. After model training, the change in prediction after setting an input parcel to 0 was calculated for each parcel to determine pairwise influences between regions. These generated perturbation-based functional connectivity matrices (pFC) were compared against conventional correlation-based connectivity (cFC) and encoder attention weights (eFC).Hopfield attention transformers achieved superior forecasting accuracy compared to Vanilla attention models. pFC matrices exhibited remarkable correspondence with anatomical brain organization, with K-means clustering consistently segmenting networks into 34 clusters matching anatomical regions—a property not observed in cFC or eFC matrices. Connection weights in pFC matrices followed log-normal distributions, consistent with synaptic strength distributions in cortical neurons. Structure-function correspondence revealed minimal global correlation but stronger local correspondence along sensory-fugal gradients.Graph-theoretic analyses successfully differentiated epilepsy patients from controls using entropy (92% accuracy), maximum flow (83% accuracy), and eigenvector centrality (73% accuracy). Epilepsy patients showed significantly different regional network properties, particularly in left inferior temporal-occipital region, temporal pole, and temporal body. The framework also demonstrated potential for identifying seizure onset regions.This transformer-based perturbation approach offers a novel methodology for inferring causal relationships in functional brain networks that captures anatomical organization and pathological alterations, with significant potential for advancing brain connectivity understanding and developing clinical biomarkers.

Disclosures: R. Bose-Roy: None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.04/DD3

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

Support: NIH Grant R01EB031080
NIH Grant R01DC019405

Title: Pushing the limits of Arterial Spin Labeling MRI: a versatile and robust alternative to BOLD functional imaging for regions with significant signal dropout

Authors: *L. S. ZHAO[1], M. TASO[4], D. TISDALL[2], J. A. GOTTFRIED[3], J. A. DETRE[3]; [1]Dept. of Bioengineering, [2]Dept. of Radiology, [3]Dept. of Neurol., Univ. of Pennsylvania, Philadelphia, PA; [4]Siemens Med. Solutions USA Inc, Malvern, PA

Abstract: Functional magnetic resonance imaging (fMRI) has become a primary tool for investigating human brain function, providing critical insights into sensory and cognitive processes. Among fMRI techniques, Blood-Oxygen-Level-Dependent (BOLD) imaging with

gradient-echo echo-planar imaging (GE-EPI) remains the most widely used approach due to its high sensitivity and temporal resolution. However, GE-EPI BOLD fMRI is extremely prone to susceptibility artifacts, manifested as signal dropout, in high susceptibility regions such as the orbitofrontal cortex (OFC), entorhinal cortex, and hippocampus - areas essential for understanding higher-order cognition and predictive processing. Although recent advances (e.g., multi-echo EPI, NORDIC denoising) have mitigated some of these limitations, they remain inadequate for recovery of signal in these regions.
Arterial Spin Labeling (ASL) provides a noninvasive means to quantify cerebral perfusion and enables direct assessment of neurovascular coupling, offering an alternative contrast mechanism that is much less affected by susceptibility artifacts. However, ASL is inherently limited by low signal-to-noise ratio (SNR), leading to a trade-off between spatial and temporal resolution in functional imaging applications.
In this study, we developed a highly accelerated 3D ASL acquisition and reconstruction pipeline with whole-brain coverage using compressed sensing to measure cerebral perfusion, which can be then used to detect brain function. Our protocol substantially improves both spatial and temporal resolution compared to previous implementations and achieves robust temporal SNR across the entire brain, including regions typically inaccessible with conventional BOLD EPI, such as the medial OFC and olfactory bulbs. Across five participants, the cerebral perfusion in these regions was reliably detected. Furthermore, we demonstrated the ability to identify the default mode network using seed-based connectivity analysis.
These results establish the feasibility and reliability of ASL for functional imaging, particularly in high-susceptibility regions that remain challenging for conventional BOLD fMRI. Our findings support ASL as a powerful, versatile and robust alternative for probing human neural dynamics.

Disclosures: L.S. Zhao: None. **M. Taso:** A. Employment/Salary (full or part-time): Siemens Medical Solutions USA Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Siemens Medical Solutions USA Inc. **D. Tisdall:** None. **J.A. Gottfried:** None. **J.A. Detre:** None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.05/DD4

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

Support: NIH Intramural Research Program ZIAMH002783
NIH Intramural Research Program ZICMH002884

Title: Characterizing CSF volume change as a function of brain activation and alertness at 7T

Authors: *S. SWEGLE[1], R. HUBER[1], R. STIRNBERG[2], J. GONZALEZ-CASTILLO[1], P. J. MOLFESE[1], L. LI[1], C. WALSH[1], T. MORGAN[1], P. BANDETTINI[1];
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Abstract: Cerebrospinal fluid, CSF, has the ability to remove waste from the brain and may connect to a variety of diseases and disorders. Therefore, it is important that we are able to effectively image CSF in the human brain. Current research focuses on studying CSF flow, but CSF volume may be more straightforwardly measured. Here, we aim to develop, implement, and validate a new imaging approach to quantify functional changes of CSF volume across the human brain. CSF volume changes can be a contributor and contaminant in Vascular Space Occupancy (VASO) (Donahue, 2006; Scouten, 2008). We propose a VASO-like inversion recovery 7T 3D-EPI protocol that uses CSF's specific relaxation fingerprint to capture CSF volume changes independent of dynamic changes in CBV and BOLD.
We collected images with three echoes and three inversion times at 7T (N=12 sessions (Siemens, Germany) with 8Tx/32Rx head coil (Nova, USA)) using a 3D-EPI with Skipped-CAIPI framework (Stirnberg, 2021). We used a 12-14 minute block designed (30sec blocks) flickering checkerboards. In-scanner eye tracking (EyeLink-1000Plus, SR-Research) and physiological monitoring (BioPack) were done during fMRI resting state scans. Images were processed using AFNI_24.2.01, LayNii_v2.7.0, SPM12, and FSL 1.12.4. We use an additive multi-compartment model to estimate functional contributions of CSF volume, CBV, and BOLD. Parameters: https://github.com/nimh-sfim/mapping_CSF_volume
Using Bloch equations, we predict which volume compartment of CSF and CBV we are most sensitive to at each inversion and echo time combination. Our empirical results roughly match these predictions in how the tissue contrasts evolve.
We see a negative response during the task period in the first inversion time during the checkerboard task (at both high resolution and whole brain). This cannot be explained by BOLD alone, and suggests that we might be seeing CSF volume change in this first inversion.
Layer analysis shows that CSF is where we would expect to see it, above the cortex. We see indications of a small CSF volume reduction in voxels above the cortical ribbon, consistent with previous work (Jin, 2010). The greatest CBV change is where we would expect it as well, in the cortex. BOLD shows an increase towards the cortical surface, as expected from draining vein effects.
Our results show that as eyes get drowsy, CSF volume increases. As eyes are more alert, CSF volume decreases and CBV increases.
In conclusion, our novel sequence allows us to see indications of CSF volume change during functional activation and during changes in drowsiness. Future work will include further validations of the Bloch model with ground truth CSF modulation tasks.

Disclosures: S. Swegle: None. **R. Huber:** None. **R. Stirnberg:** None. **J. Gonzalez-Castillo:** None. **P.J. Molfese:** None. **L. Li:** None. **C. Walsh:** None. **T. Morgan:** None. **P. Bandettini:** None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.06/DD5

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

Support: 23K24748
24KJ2216

Title: Coupling Between Cerebrospinal Fluid and Global Brain Signals in Endurance Athletes: A Resting-State Functional MRI Study

Authors: *D. HOSHI[1], F. MARINA[3], R. ASAHARA[2], K. OHYAMA-BYUN[4], S. MAEDA[5], J. SUGAWARA[3], T. TARUMI[6];
[1]Natl. Inst. of Advanced Industrial Sci. & Technol. (AIST), Tsukuba, Japan; [2]Natl. Inst. of Advanced Industrial Sci. & Technol. (AIST), Takamatsu, Japan; [3]Natl. Inst. of Advanced Industrial Sci. & Technol., Tsukuba, Japan; [4]Univ. of Tsukuba, Ibaraki, Japan; [5]Waseda Univ., Tokyo, Japan; [6]Natl. Inst. of Advanced Industrial Sci. and Technol. (AIST), Tsukuba, Japan

Abstract: Cerebrospinal fluid (CSF) contributes to the brain waste clearance through its exchange with interstitial fluid, a mechanism known as the glymphatic system. This system is activated during states of heightened parasympathetic activity, such as sleep, during which CSF flow is coupled with cerebral hemodynamics. Endurance athletes who engage in high-intensity endurance training exhibit elevated parasympathetic activity at rest. This suggests that athletes may have more efficient clearance of brain waste products in the awake resting state than physically inactive individuals. Therefore, this study aimed to compare the brain blood-CSF coupling between endurance athletes and sedentary individuals. Fifteen male endurance athletes (20 ± 1 yr) and sixteen male sedentary individuals (21 ± 2 yr) participated in this study. Athletes had significantly lower heart rate than sedentary participants (48 ± 5 vs. 57 ± 10 bpm, P = 0.003). Using resting-state fMRI data, we extracted CSF inflow signal at the inferior cerebellum and gray matter BOLD signal (gBOLD) for offline analysis. For the gBOLD signals, time-derivative data were also generated (-d/dt gBOLD). Using time-series data of the gBOLD and CSF signals, we performed cross-correlation analysis (CCA) to calculate the minimal and maximal correlation coefficients (i.e., gBOLD-CSF coupling and -d/dt gBOLD-CSF coupling, respectively). Additionally, power spectral densities (PSDs) of gBOLD and CSF signals were calculated to quantify the variability of each signal. Furthermore, transfer function analysis (TFA) was used to calculate coherence between gBOLD and CSF signals over the frequency range of 0.01 to 0.1 Hz. The gBOLD-CSF coupling exhibited the minimal correlation coefficient at a 10-second lag in both groups with no significant differences between groups (athlete: −0.30 ± 0.26 vs. sedentary: −0.33 ± 0.22, P = 0.753). Similarly, no significant differences were found in the -d/dt gBOLD-CSF coupling at 0 lag (athlete: 0.46 ± 0.24 vs. sedentary: 0.45 ± 0.19, P = 0.853). PSDs of gBOLD (athlete: 0.49 ± 0.30 z^2/Hz vs. sedentary: 0.48 ± 0.20 z^2/Hz, P = 0.916) and CSF (athlete: 2.39 ± 1.38 z^2/Hz vs. sedentary: 1.89 ± 0.91 z^2/Hz, P = 0.245) showed no significant differences, nor did their coherence (athlete: 0.38 ± 0.13 vs. sedentary: 0.43 ± 0.14, P = 0.268). The gBOLD-CSF coupling derived from CCA was significantly correlated or tended to correlate with PSDs of gBOLD (r = -0.522, P = 0.003) and CSF (r = -0.308, P = 0.094), and coherence (r = -0.662, P < 0.001). These findings suggest that resting brain waste clearance may be similar in athletes and sedentary individuals, and that CCA and TFA results are interrelated.

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Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.07/DD6

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

Support: NIMH Intramural Research Program

Title: Replicable brain-behavior associations in fMRI with surprisingly small sample sizes

Authors: *S. J. GOTTS[1], A. W. GILMORE[2], A. MARTIN[3];
[1]Lab. of Brain and Cognition, NIMH/NIH, Bethesda, MD; [2]Psychological and Brain Sci., Univ. of Delaware, Newark, DE; [3]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Understanding brain-behavior relationships is the core goal of cognitive neuroscience. However, these relationships - especially those related to complex cognitive and psychopathological behaviors - have recently been shown to suffer from very small effect sizes (Cohen's *d* of 0.1 or less), requiring potentially thousands of participants to yield robust findings. Here, we focus on a much more optimistic case utilizing task-based fMRI and a multi-echo acquisition with trial-level brain-behavior associations measured within-participant. In a visual object identification task for which the behavioral measure is response time (RT), we show that while trial-level associations between BOLD fMRI and RT can similarly suffer from weak effect sizes, converting these associations to their corresponding group-level effects can yield robust peak effect sizes (Cohen's *d* of 1.0 or larger). Multi-echo denoising (Multi-Echo ICA or ME-ICA) yields larger effects than optimally combined multi-echo with no denoising, which is in turn an improvement over standard single-echo acquisition. While estimating these brain-behavior relationships benefits from the inclusion of a large number of trials per participant, even a modest number of trials (20-30 or more) yields robust group-level effect sizes, with replicable effects obtainable with relatively standard sample sizes for fMRI studies in individual labs (N = 20-30 participants per sample). This approach represents a substantial cost savings in both time and money relative to large research consortia and should be considered a viable tool in data-driven studies of brain-behavior relationships.

Disclosures: S.J. Gotts: None. **A.W. Gilmore:** None. **A. Martin:** None.

Poster

PSTR460: Functional Imaging of the Brain

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Program #/Poster #: PSTR460.08/DD7

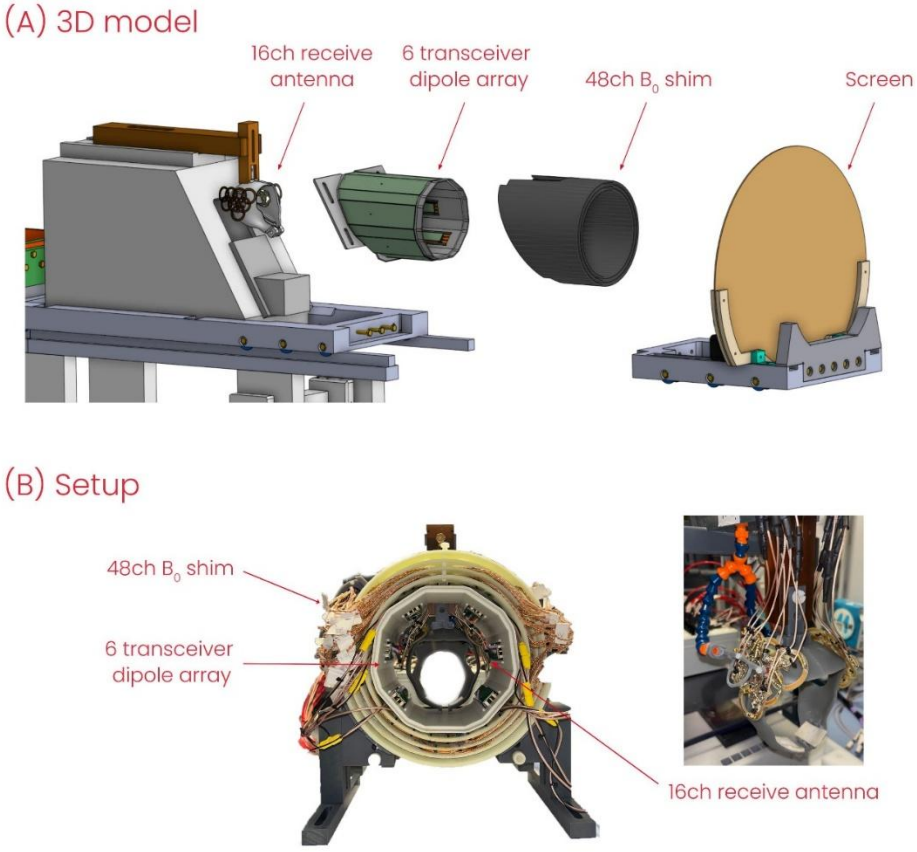
Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: French national research agency (ANR) under the reference ANR-20-CE37-0005
Exploratory program of CEA, the French Alternative Energies and Atomic Energy Commission

Title: Integrated 48-channel B_0 shim, 6-dipole tranceive, and 16-loop receive system for high quality NHP brain imaging at 7 tesla

Authors: *E. DJABALLAH[1,2], E. GIACOMINI[3], P.-F. GAPAIS[3], A. AMADON[3], Q. ZHU[1]; [1]Cognitive Neuroimaging Unit, INSERM, CEA, Univ. Paris-Saclay, GIF-SUR-YVETTE, France; [2]BAOBAB, Univ. Paris-Saclay, CEA/Joliot/NeuroSpin, Gif-sur-yvette, France; [3]BAOBAB, Univ. Paris-Saclay, CEA/Joliot/NeuroSpin, GIF-SUR-YVETTE, France

Abstract: Ultra-high field (UHF) MRI offers superior spatial resolution and SNR but faces unique technical challenges, particularly in non-human primates (NHP) neuroimaging. At 7T, exacerbated $B1^+$ and B0 field inhomogeneities, coupled with SNR demands to achieve high-resolution, necessitate advanced imaging systems. We developed and validated an integrated system combining a 48-channel multi-coil B0 shim array (MCA), a 6-channel preamplifier-decoupled dipole transceive array, and a 16-channel loop receive array, tailored for whole-brain NHP imaging at 7T, compatible with visual stimulus presentation. The B0 shim MCA was designed using 13 B0 field maps from 11 NHPs using the SCOTCH approach (Pinho Meneses B et al, 2022). The final design consisted of a 3-layer, 48-channel B0 shim MCA integrated with an RF system incorporating 6 short (11 cm) transceive dipoles-preamplifier-decoupled during reception-and two sets of 8-loop receive arrays. Electromagnetic simulations informed dipole design and decoupling to minimize mutual interference. Experimental measurements confirmed high B1+ efficiency with excellent homogeneity, aligning with electromagnetic simulation predictions. In vivo imaging showed elevated SNR (with significant contribution from the dipoles), enabling robust parallel imaging acceleration and comprehensive brain coverage. ΔB0 field maps revealed up to a 45% improvement in B0 homogeneity vs. standard scanner shim. High-resolution anatomical scans exhibited strong contrast and uniformity. Submillimeter fMRI (0.75 mm isotropic) showed high SNR/tSNR and reduced B0-induced distortion artefacts. Resting-state functional connectivity (n=2, ~1h data; 30 min/subject), seeded at the posterior cingulate cortex, revealed bilateral connectivity patterns across the macaque prefrontal, temporal and parietal cortices—consistent with the canonical default mode network architecture. These results validate the system's capacity for high quality imaging and its ability to resolve distributed functional networks at submillimeter resolution.



Disclosures: E. Djaballah: None. **E. Giacomini:** None. **P. Gapais:** None. **A. Amadon:** None. **Q. Zhu:** None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.09/DD8

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

Support: F31NS134314-01
T32EB025816-06
1R01NS111470
1R01NS078095
1R01EB029857

Title: Mapping of spontaneous band-limited cortical network activity to hemodynamics

Authors: *L. MEYER-BAESE[1], D. JAEGER[2], S. D. KEILHOLZ[3];
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Abstract: Functional magnetic resonance imaging (fMRI) is a non-invasive tool for studying spontaneous brain activity, relying on <1Hz fluctuations in hemodynamics as a proxy for neuronal activity. Neuronal activity fluctuates across brain regions from 0.05 to 500 Hz. Here we used wide-field optical imaging of the dorsal cortex in awake head-fixed Emx1-Cre mice (4 female, 1 male) to investigate what neural activity aspects are captured by the slower hemodynamic signal in resting-state networks. We included key default mode network (DMN) areas along the midline, such as the retrosplenial cortex and secondary motor cortex, as well as the somatomotor (SoMo) network areas including the primary sensory and motor cortex. Group data comprises 289 resting state trials (40.96s each, 6 sessions per mouse). These mice co-express the fast voltage-sensitive fluorescent protein JEDI-1P-Kv in excitatory cells and hSyn-mCherry. The <1Hz global signal regressed mCherry signal serves as our hemodynamics proxy. The resting-state relationship between the bandpass filtered JEDI voltage signal (0.05-60Hz) and the slow (< 1 Hz) mCherry hemodynamic signal in the barrel cortex shows expected time-lagged correlation, peaking at 0.1 at t = 1.5 sec for 0.05-12 Hz. JEDI functional connectivity (FC) was determined by calculating correlation between 32 ROIs (16 symmetrical pairs for left and right hemispheres) evenly spaced across the dorsal cortex. Intra- and inter-hemispheric connectivity was assessed by calculating correlations within and between hemispheres for all ROI combinations. A general trend shows a drop in FC with increasing frequency for all ROIs. However, intrahemispheric connectivity remains significantly higher ($p < 0.05$, Mann-Whitney U test, FDR correction) than interhemispheric connectivity for fast frequency bands alpha - gamma. Despite a net decrease in correlation for higher frequencies, the FC structure in the dorsal cortex was consistent across all frequency bands (two-sided t-test on z-transformed bandlimited FC matrices). Infraslow JEDI-1P (0.05-0.1Hz) FC resembled mCherry FC the most (two-sample t-test on z-transformed bandlimited FC matrices). On average, mCherry FC matrices exhibit higher connectivity in the SoMo network than any JEDI matrices. However, JEDI signals show significantly stronger correlations with the DMN and DMN pixels from other networks compared to mCherry FC. These findings indicate that the connection between neural networks and hemodynamic responses is frequency-dependent and temporally offset. Variations in spatial FC patterns suggest distinct mechanisms affecting voltage and hemodynamic representations of brain dynamics.

Disclosures: L. Meyer-Baese: None. **D. Jaeger:** None. **S.D. Keilholz:** None.

Poster

PSTR460: Functional Imaging of the Brain

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Program #/Poster #: PSTR460.10/DD9

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

Support: NIH R01NS085200

Title: Chemogenetic manipulations of hippocampus show individual variabilities in behavioral effects related to neuronal network differences

Authors: *Z. YAN[1], L. N. BELOATE[3], N. ZHANG[2];
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Abstract: Chemogenetics, a rapidly advancing neuromodulation technique, has great potential to be applied in animal models of mental disorders, as it enables long-term, region-specific, and reversible manipulations of neuronal activity. While many studies have modeled mental disorders with acute chemogenetic applications, people have begun to explore the potential of chronic chemogenetic manipulation as a method for modeling human mental disorders and developing innovative therapeutic strategies. In the current study, we use chemogenetics to manipulate specific brain regions in adult male rats, and examine its effect variabilities across individuals using resting-state functional magnetic resonance imaging (rsfMRI) and histological quantifications. More specifically, We target the excitatory neurons in the dorsal hippocampus (dHC) through the viral vector expression of inhibitory Designer Receptors Activated Only by Designer Drugs (DREADD), hM4Di, which is, in turn, activated by a microdose of clozapine administrated acutely (i,p, injection) or chronically (drinking water). Following the acute or chronic dHC inhibition, spatial memory is evaluated using a 2-trail Y-maze test and novel object location test. We measure the whole-brain blood-oxygen-level dependent (BOLD) activity and compute brain resting state functional connectivity (RSFC) at different time points alongside clozapine administrations and behavior tests using rsfMRI, to explore the differences and the alterations of neuronal networks. We also perform histology to quantify the DREADD expression and spread in related brain regions using fluorescence microscopy. With both acute and chronic clozapine administrations, there is high individual variability of spatial memory behaviors in rats expressing hM4Di. This variability is either related to the variation of DREADD expression level and spreads, or the differences in brain networks and functional connectivity, indicating the underlying neuronal networks may be associated with the outcomes of chemogenetic interventions. These suggest that the results of chemogentic interventions could be highly influenced by their effects on individual neurons and neuronal networks and that those effects, along with others, should be considered when analyzing and drawing conclusions from studies using chemogenetics for neuronal modulations. This study could, furthermore, inform upon the transitional potential of chemogenetics in modeling and clinical settings.

Disclosures: Z. Yan: None. **L.N. Beloate:** None. **N. Zhang:** None.

Poster

PSTR460: Functional Imaging of the Brain

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.11/DD10

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

Title: Spatiotemporal mapping of ketamine-induced polypopulation spikes using electrophysiology and functional ultrasound imaging

Authors: *W. CHOI[1], W. JIANG[4], M. BERGOSH[5], K. WU[2], M. MCHUGH[1], D. J. LEE[3], C. LIU[3], V. N. CHRISTOPOULOS[1], D. SONG[1,3];
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Abstract: Ketamine, an NMDA receptor antagonist, has dose-dependent neural effects, but its impact at non-therapeutic doses is poorly understood. Given the rise in recreational use, it is critical to characterize ketamine's effects beyond clinical settings. Our previous work showed that supra-anesthetic doses induce polypopulation spikes (PPS)—a highly regular (4-5 Hz), paroxysmal pattern of synchronized activity resembling interictal spikes. However, prior studies were limited to local field potential (LFP) recordings in the sensorimotor cortex, leaving the spatial distribution of PPS unclear. Here, we combined electrophysiology with functional ultrasound imaging (fUSI) to map the spatiotemporal dynamics of PPS. Six female Sprague Dawley rats (10-14 weeks, 200-300 g) were anesthetized with ketamine (75 mg/kg) and xylazine (10 mg/kg). A bipolar electrode was implanted in the right primary somatosensory cortex (S1), and an fUSI probe was placed over cortical and subcortical areas. Recordings began post-implantation, with additional ketamine (36 mg/kg) administered at 2 and 12 minutes. As before, PPS persisted for >20 minutes following supra-anesthetic dosing. A time-varying impulse response model mapped PPS events to fUSI responses. Voxel-wise maps of significant fUSI responses ($p < 0.05$, F-test) revealed PPS localization in the thalamocortical network. Temporal analysis suggested PPS may initiate in the thalamus, with growing synchrony across thalamic and cortical regions. These findings suggest that high-dose ketamine induces a dissociative network state characterized by PPS, potentially serving as a biomarker of altered consciousness. This work also highlights the utility of combining electrophysiology and fUSI to map drug-induced neural dynamics across brain regions.

Disclosures: W. Choi: None. **W. Jiang:** None. **M. Bergosh:** None. **K. Wu:** None. **M. McHugh:** None. **D.J. Lee:** None. **C. Liu:** None. **V.N. Christopoulos:** None. **D. Song:** None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.12/DD11

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

Title: Volumetric time-lagged functional ultrasound for hemodynamic imaging of the healthy and diseased mouse brain

Authors: *A. ZHOU[1,2], M. G. SIMKULET[1,2], A. C. HOWARD[1,2], J. X. JIANG[2], D. A. BOAS[1,2], X. CHENG[1,2];
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Abstract: Quantifying blood flow in the brain is key to studying various pathologies, and by way of neurovascular coupling, neural activity. Functional ultrasound (fUS) has recently emerged as a promising label-free technology for monitoring cerebral blood flow (CBF) and cerebral blood volume (CBV) with high spatiotemporal resolution (~100 μm, ~10 ms) and penetration depth (~10 cm), while maintaining a portable form factor. fUS studies typically utilize linear phased array probes and the Power Doppler and Color Doppler techniques to measure a signal related to CBV and the axial component of CBF speed, respectively, within a 2D plane over time. However, these methods can be susceptible to noise, do not capture the full flow velocity, and are usually limited to a planar field of view. Here, we implement a speckle decorrelation-based time lagged functional ultrasound (tl-fUS) method in 4D (3D space + time) with a 2D row-column array probe (RCA), and demonstrate its ability to robustly measure CBV and CBF in C57BL/6 mice with cranial windows. In healthy mice, we show the efficacy of the tl-fUS in quantifying relative changes in CBV and CBF during air puff whisker stimulation experiments, and using these results, we plan to present 3D maps revealing regions with significant functional activation. Furthermore, we will utilize our tl-fUS method to compare these functional effects in healthy mice to those evoked in stroked and hypercapnic mice during additional air puff whisker stimulation measurements. Our results show improved sensitivity to changes in CBV and CBF compared to conventional Power Doppler and Color Doppler, and characterize in 3D the roles of arterioles and venules in supporting neural activation across healthy and diseased mice.

Disclosures: A. Zhou: None. **M.G. Simkulet:** None. **A.C. Howard:** None. **J.X. Jiang:** None. **D.A. Boas:** None. **X. Cheng:** None.

Poster

PSTR460: Functional Imaging of the Brain

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Program #/Poster #: PSTR460.13/DD12

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

Support: Army Research Laboratory Cooperative Agreement No W911NF2120186
Army Research Office W911NF-21- 1-0094
the Keck School of Medicine Dean's Pilot Funding Program (DL- PI)
NIMH: 1K08MH121757-01A1

Title: Machine Learning Enhanced Functional Ultrasound Imaging for predicting drug-induced brain activity changes

Authors: *S. ZHONG[1], J. DEIGHTON[4], K. A. AGYEMAN[2], W. CHOI[1], C. LIU[1], D. J. LEE[1], V. MAROULAS[5], V. N. CHRISTOPOULOS[3];
[1]USC, Los Angeles, CA; [2]Biomed. Engin., USC, Sherman Oaks, CA; [3]Bioengineering, USC, Los Angeles, CA; [4]The Univ. of Tennessee, Baltimore, MD; [5]Univ. of Tennessee, Knoxville, Knoxville, TN

Abstract: Functional ultrasound imaging (fUSI) measures cerebral blood volume (CBV) changes by detecting backscattered echoes from red blood cells, offering high spatiotemporal resolution for visualizing brain hemodynamics. While fUSI has been utilized in neuropharmacological studies, most rely on predetermined regions of interest (ROIs), potentially overlooking drug effects in other brain areas. To address this limitation, we compared three machine learning approaches—convolutional neural network (CNN), support vector machine (SVM), and vision transformer (ViT)—combined with fUSI to analyze the pharmacodynamics of Dizocilpine (MK-801), a potent NMDA receptor antagonist, thereby eliminating ROI selection bias by processing the entire brain image directly. We performed fUSI recordings in mice (n=23) receiving either MK-801 (n=10) or saline (n=13) for 5 minutes pre-injection and 55 minutes post-injection. After non-rigid image registration, data were analyzed using optimized CNN, SVM, and ViT architectures evaluated through 10-fold cross-validation. XGrad-CAM identified pixels contributing to CNN classification decisions, while attention rollout served this purpose for ViT. We evaluated model performance through classification accuracy and examined the functional significance of model-identified regions by comparing CBV responses between these regions and non-identified regions. All models successfully distinguished MK-801-injected animals from saline-injected animals, with CNN and ViT achieving peak accuracies of approximately 79%, and SVM reaching 74%. All methods identified regions showing progressive CBV decrease in MK-801 animals, but with varying anatomical specificity: CNN activation maps revealed localized patterns in cortical regions and hippocampus—areas with high NMDA receptor density—while SVM's feature weights were diffuse and ViT's attention maps extended beyond brain boundaries, compromising anatomical precision. Ultimately, the combination of fUSI with machine learning techniques creates a powerful analytical framework for examining pharmacological mechanisms without relying on predefined ROIs, as this data-driven approach enables analysis of drug effects based on functional responses instead of anatomical assumptions. This methodological innovation can potentially reveal previously overlooked drug effects, accelerating drug development and enabling more comprehensive characterization of therapeutic compounds across both preclinical and clinical settings.

Disclosures: S. Zhong: None. **J. Deighton:** None. **K.A. Agyeman:** None. **W. Choi:** None. **C. Liu:** None. **D.J. Lee:** None. **V. Maroulas:** None. **V.N. Christopoulos:** None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

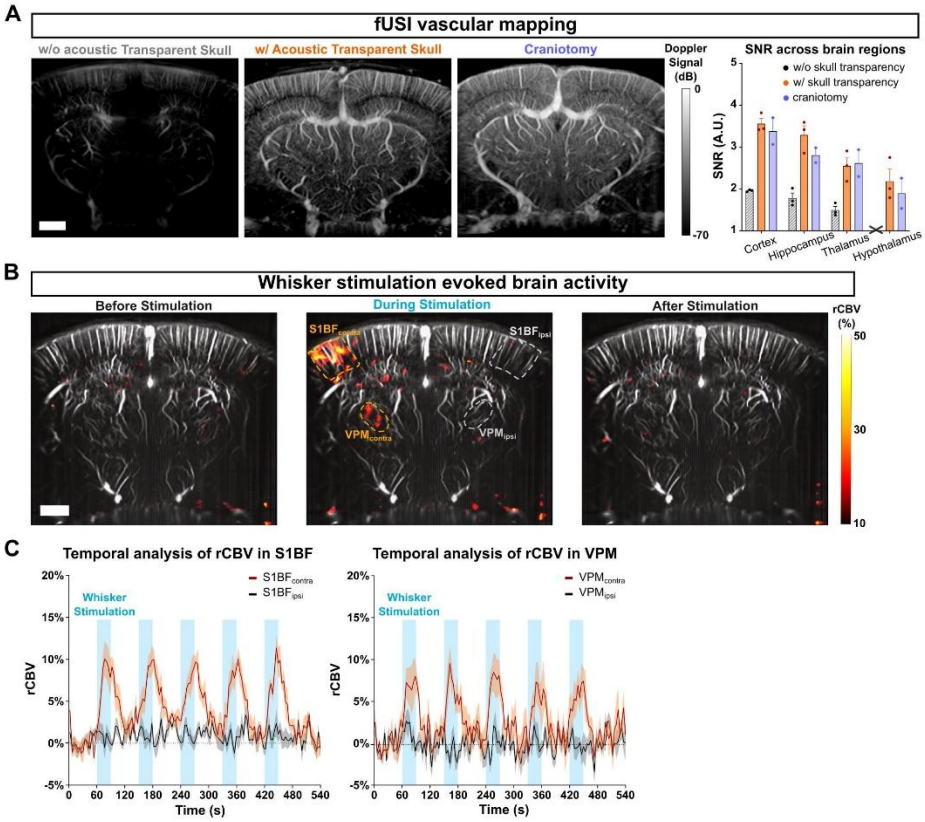
Program #/Poster #: PSTR460.14/DD13

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

Title: Transcranial high-resolution functional ultrasound imaging enabled by skull acoustic transparency

Authors: *Z. WANG, Y. YANG;
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Abstract: High-resolution, whole-brain imaging is essential for neuroscience and clinical diagnostics, yet remains unmet by existing techniques. Functional ultrasound imaging (fUSI) offers a promising alternative, combining micrometer-scale spatial resolution with high sensitivity to neuron-evoked cerebral blood flow. However, this technology is limited by the skull, which attenuates most of the ultrasound energy and distorts focality, thus compromising sensitivity and spatial resolution. Despite efforts such as frequency reduction, phase correction, and microbubble administration, achieving high-resolution transcranial fUSI is still challenging. To address this limitation, we developed a novel skull acoustic transparency technique to enable non-invasive, high-resolution transcranial fUSI by matching the acoustic impedance of the skull to that of brain tissue, thereby minimizing attenuation and focal distortion. We first constructed a three-dimensional (3D) fUSI imaging system integrated with null subtraction imaging algorithm, and validated the efficacy of skull acoustic transparency technique by comparing image intensity and spatial resolution without skull transparency. Our results reveal that this technique enables whole-brain 3D vascular mapping with high signal-to-noise ratio and spatial resolution, comparable to those of craniotomy across imaging depths. Next, we assessed the feasibility and sensitivity of skull acoustic transparency technique for behaviorally evoked brain activity using whisker stimulation. Our findings demonstrate the capability of our technique to detect whisker-evoked brain activity with single trial sensitivity, specifically in the barrel cortex (S1BF) and the ventral posteromedial nucleus of the thalamus (VPM). This study introduces a skull-transparent fUSI technique that unlocks unprecedented capabilities for non-invasive assessment of brain activity with micrometer resolution and single-trial sensitivity, providing a transformative platform for uncovering brain functions and diagnosing brain diseases.



(A) Representative 2D images of whole-brain fUSI vascular mapping. Left: fUSI w/o skull acoustic transparency; middle left: fUSI w/ skull acoustic transparency; middle right: fUSI with craniotomy; right: signal-to-noise ratio across brain regions at various imaging depths. No blood vessel signal observed in hypothalamus of the w/o skull acoustic transparency group. Scale bar, 1 mm. **(B)** Representative 2D activation map of whisker-evoked brain activity, left: before whisker stimulation; middle: during whisker stimulation; right: after stimulation. Scale bar, 1mm. **(C)** Relative cerebral brain volume change (rCBV) for 5-trials of whisker stimulation - 30 sec on followed by 60 sec off - in the region of interest: contralateral barrel cortex (S1BF, left) and contralateral ventral posteromedial nucleus of thalamus (VPM, right). No whisker-evoked brain activity was detected in the ipsilateral part of S1BF and VPM.

Disclosures: Z. Wang: None. **Y. Yang:** None.

Poster

PSTR460: Functional Imaging of the Brain

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Program #/Poster #: PSTR460.15/DD14

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

Title: Multimodal Imaging of the Glymphatic System in Rats

Authors: *F. CHEATAINI[1], M. VALDEBENITO[2], C. BOUILLOT[2], L. ZIMMER[2], B. VIDAL[1];
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Abstract: The glymphatic system has recently been identified as a cerebral clearance pathway. This system also plays a crucial role in the cerebral biodistribution of intrathecally administered drugs. While there is increasing evidence that cardiac and respiratory-induced cerebrovascular pulsatility are important drivers of this system, the influence of hemodynamic changes remains poorly understood at the macroscopic level. In particular, the complex spatiotemporal properties of these changes induced by vasomotion, i.e., oscillations at ~0.1 Hz that can propagate as long-range traveling waves, might play an important mechanical role in facilitating glymphatic flow at such scale. Our goal was to use multimodal neuroimaging tools, including positron emission tomography (PET) and functional ultrasound imaging (fUS), to study the interaction between cerebral vasomotion and glymphatic function. We exposed rats to various states of wakefulness or anesthesia, which are known to be associated with different glymphatic rates, as well as sensory stimulation. We investigated the link between hemodynamic changes across various frequencies, by fUS, and the functionality of the glymphatic system, as assessed by intracisternal [18F]FDG biodistribution. As expected, fUS analysis revealed distinct hemodynamic signatures across anesthesia and awake states, particularly in the vasomotion frequency bands. Preliminary findings showed a significant correlation between the amplitude of frequency fluctuations of the hemodynamic signal around 0.1 Hz and glymphatic function across varying experimental conditions. Furthermore, glymphatic function was also correlated with the propagation of oscillations as traveling waves. Further analysis will explicitly focus on the influence of the trajectories of these waves on the system. Our work aims to provide a novel understanding of the coupling between cerebrovascular function and glymphatic dynamics, in order to advance our knowledge of brain clearance mechanisms and how they are modulated in physiological and pharmacological contexts.

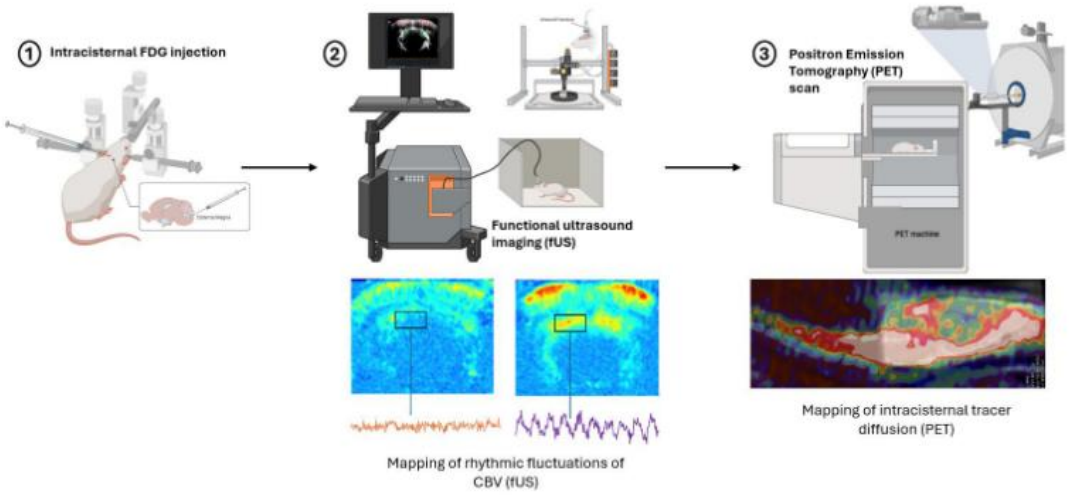


Figure 1. Experimental protocol for multimodal Imaging designed to investigate glymphatic flow and cerebrovascular dynamics in rats.

Disclosures: F. Cheataini: None. **M. Valdebenito:** None. **C. Bouillot:** None. **L. Zimmer:** None. **B. Vidal:** None.

Poster

PSTR460: Functional Imaging of the Brain

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Program #/Poster #: PSTR460.16/DD15

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

Title: In Vivo Imaging of Local Brain Temperature Dynamics Using Thermosensitive Quantum Dots and Two-Photon Microscopy

Authors: *M. HANDA[1], S. TAKEMOTO[1], S. WAKITA[1], T. TORIMOTO[2], H. YUKAWA[1], H. TAKUWA[1];
[1]QST, Inage-ku,Chiba-shi,Chiba, Japan; [2]Nagoya Univ., Aichi, Japan

Abstract: Neuronal activity in the brain is accompanied by increased energy metabolism, leading to substantial heat production. To maintain homeostasis, heat must be efficiently dissipated, a process considered to be primarily mediated by the cerebral vasculature. However, detailed mechanisms underlying the neurovascular coupling in thermal regulation remain poorly understood.In this study, we developed an in vivo temperature imaging system by combining

thermosensitive quantum dots with two-photon excitation laser microscopy to enable the high-resolution visualization of microregional brain temperature dynamics. A cranial window was implanted over the somatosensory cortex of wild-type (C57BL/6J) mice, and quantum dots were locally injected using a fine glass micropipette. Two-photon imaging was performed under wakeful conditions. To induce localized metabolic heating, we activated the somatosensory cortex by applying air-puff stimulation to the whiskers. Increased neuronal activity was confirmed by calcium imaging using GCaMP6s, and stimulus-evoked vasodilation was verified by labeling blood vessels with Sulforhodamine 101. Quantum dot-based thermometry revealed a rapid temperature increase following stimulation, peaking approximately 20-30 s after onset, with an average increase of approximately 1% (~0.5 ℃). This elevation is considered to reflect the enhanced metabolic activity associated with neuronal activation.These findings demonstrate that two-photon imaging with fluorescent nanoparticles is a powerful approach for capturing fine-scale temperature dynamics in the living brain. This technique offers a novel platform for visualizing the relationship between neuronal activity and heat production, and holds promise for elucidating thermoregulatory mechanisms in neurological disorders such as stroke, dementia, and Parkinson's disease.

Disclosures: M. Handa: None. **S. Takemoto:** None. **S. wakita:** None. **T. Torimoto:** None. **H. Yukawa:** None. **H. Takuwa:** None.

Poster

PSTR460: Functional Imaging of the Brain

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Program #/Poster #: PSTR460.17/DD16

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

Support: Janelia, HHMI
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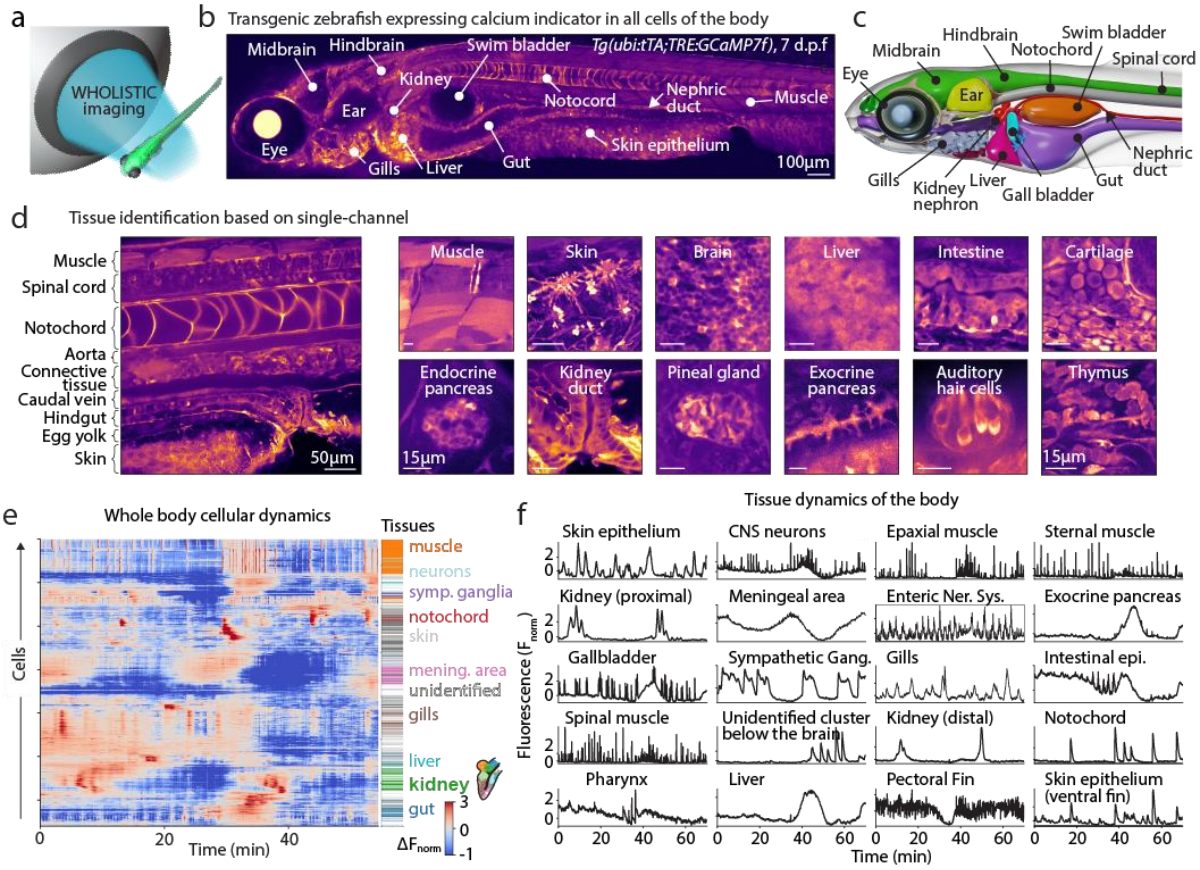
Title: Whole-body imaging of cellular activity: a new paradigm for studying organism-wide communication networks

Authors: *V. RUETTEN[1], W. ZHENG[3], I. SIWANOWICZ[4], B. MENSH[2], A. M. LEMIRE[4], G. IHRKE[4], F. ENGERT[5], Y. WAN[6], M. C. FISHMAN[7], M. RUBINOV[8], C. M. SATOU[4], B. JUDKEWITZ[9], P. TILLBERG[1], M. SAHANI[10], M. B. AHRENS[11];
[1]Janelia Res. Campus, Ashburn, VA; [2]Janelia Res. Campus, San Rafael, CA; [3]Virginia Tech., Falls Church, VA; [4]Janelia Res. Campus, HHMI, Ashburn, VA; [5]MCB, Harvard Univ., Cambridge, MA; [6]HHMI Janelia Res. Campus, Ashburn, VA; [7]Mass Gen. Hosp. - East, Charlestown, MA; [8]Biomed. Engin., Vanderbilt Univ., Nashville, TN; [9]Einstein Ctr. for Neurosci., Charite Berlin / Humboldt Univ., Berlin, Germany; [10]Gatsby Computat. Neurosci. Unit, Univ. Col. London, London, United Kingdom; [11]Janelia Res. Campus / HHMI, Ashburn, VA

Abstract: All cells in an animal collectively ensure, moment-to-moment, the survival of the organism as a whole. Adaptive decision making needs to take into account this collective state. The study of embodied mechanistic cognition seeks to elucidate the network of interactions that sustain life and drive behavior, often spanning multiple organs, cell types, and timescales. However, a major challenge lies in simultaneously recording cellular activity throughout the entire brain and body.

To address this, we developed WHOLISTIC (WHole Organism Live Imaging System for recording Tissue and IntraCellular activity), a method to image second-timescale intracellular dynamics across cell-types of the vertebrate body. By integrating and advancing volumetric fluorescence microscopy, machine learning, and pancellular expression of calcium sensors in transparent young zebrafish and adult Danionella, this method enables real-time recording of organism-wide cellular dynamics. Calcium is a universal intracellular messenger involved in numerous processes, making it an ideal proxy for cellular activity.

Using WHOLISTIC, we discovered unexpected cell-type responses: meningeal cells responding to ketamine, state-dependent oscillatory ependymal-cell dynamics during sleep-like states, and pulsating waves along kidney nephrons. Multi-organ analyses revealed muscle synergies, independencies, and muscle-organ coupling. Integration with optogenetics allowed all-optical determination of brain-body causal interactions. At the whole-organism level, we captured rapid brainstem-controlled blood flow redistribution during hypoxia, followed by decreased enteric activity, suggesting a novel mechanism of cellular activity regulation via controlled oxygenation. Finally, we advanced Whole-Body Expansion Microscopy to add ultrastructural context to recordings, clarifying observed activity patterns. These advances establish a new paradigm for systems biology, bridging cellular and organismal physiology, with broad implications for fundamental research and drug discovery.



Disclosures: V. Ruetten: None. **W. Zheng:** None. **I. siwanowicz:** None. **B. Mensh:** None. **A.M. Lemire:** None. **G. Ihrke:** None. **F. Engert:** None. **Y. Wan:** None. **M.C. Fishman:** None. **M. Rubinov:** None. **C.M. Satou:** None. **B. Judkewitz:** None. **P. Tillberg:** None. **M. Sahani:** None. **M.B. Ahrens:** None.

Poster

PSTR460: Functional Imaging of the Brain

Location: SDCC Halls B-H

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Program #/Poster #: PSTR460.18/EE1

Topic: H.05. Mood Disorders

Support: ONR 00014-19-1-2149
The Pritzker Neuropsychiatric Disorders Research Consortium Fund, LLC
The Hope for Depression Research Foundation

Title: Understanding the interplay between mood, acute social stress and cognitive performance in college freshmen

Authors: *H. KHALIL[1], C. A. TURNER[2], V. MURPHY-WEINBERG[1], A. ONICA[1], F. LI[1], B. DAI[1], C. STACK[1], S. L. LEAL[4], J. MILLER[5], W.-L. CHANG[6], R. HEN[5], J. F. LOPEZ[7], S. J. WATSON[8], H. AKIL[3];
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Abstract: Adaptive coping to ongoing stress at the biological and psychological levels (stress fitness) is an important part of life. To characterize stress fitness in a laboratory setting, we recruited a sample of University of Michigan freshmen (82 female, 49 male) at the start of the 2023 and 2024 academic years. The freshmen were genotyped and characterized using a battery of psychiatric survey instruments at the start of their freshmen year. They were also sampled quarterly on clinical rating scales (the PHQ-9 for depression and GAD-7 for anxiety). Approximately half the subjects (stratified by sex and baseline PHQ-9 scores) were administered an acute social stressor, the Trier Social Stress Test (TSST), prior to the cognitive tests and their heart rate, blood cortisol and ACTH levels were captured before, during and after the test. The cognitive tests included the Deary-Liewald test (a reaction time task), the single N-back (a test of working memory) and a pattern separation task (for emotional episodic memory). We characterized stress fitness by assessing the neuroendocrine profile of subjects in response to the TSST and their cognitive performance in the face of this stressor. Given the sample population (relatively healthy young adults) and the nature of the cognitive tests, we found that greatest differences in performance between TSST-exposed and TSST-unexposed individuals was in the emotional pattern separation task. After an acute stressor, the ability of subjects to discriminate positive valence stimuli was significantly lower. The effect was similar but not as strong for negative stimuli. Those with a higher score on the rejection sensitivity questionnaire were better at discriminating both negative and positive stimuli and this effect was stronger in females. Female subjects with higher PHQ-9 scores were better at discriminating negative stimuli but there was no relationship for male subjects. Overall, we saw an increase in variance in the pattern separation results of subjects undergoing the acute social stressor; any significant correlation between psychiatric state and trait scores and pattern separation was lower or no longer significant for the TSST subjects compared to controls. We are currently examining the relationship between the subjects' neuroendocrine profile and cognitive performance.

Disclosures: H. Khalil: None. **C.A. Turner:** None. **V. Murphy-Weinberg:** None. **A. Onica:** None. **F. Li:** None. **B. Dai:** None. **C. Stack:** None. **S.L. Leal:** None. **J. Miller:** None. **W. Chang:** None. **R. Hen:** None. **J.F. Lopez:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.01/EE2

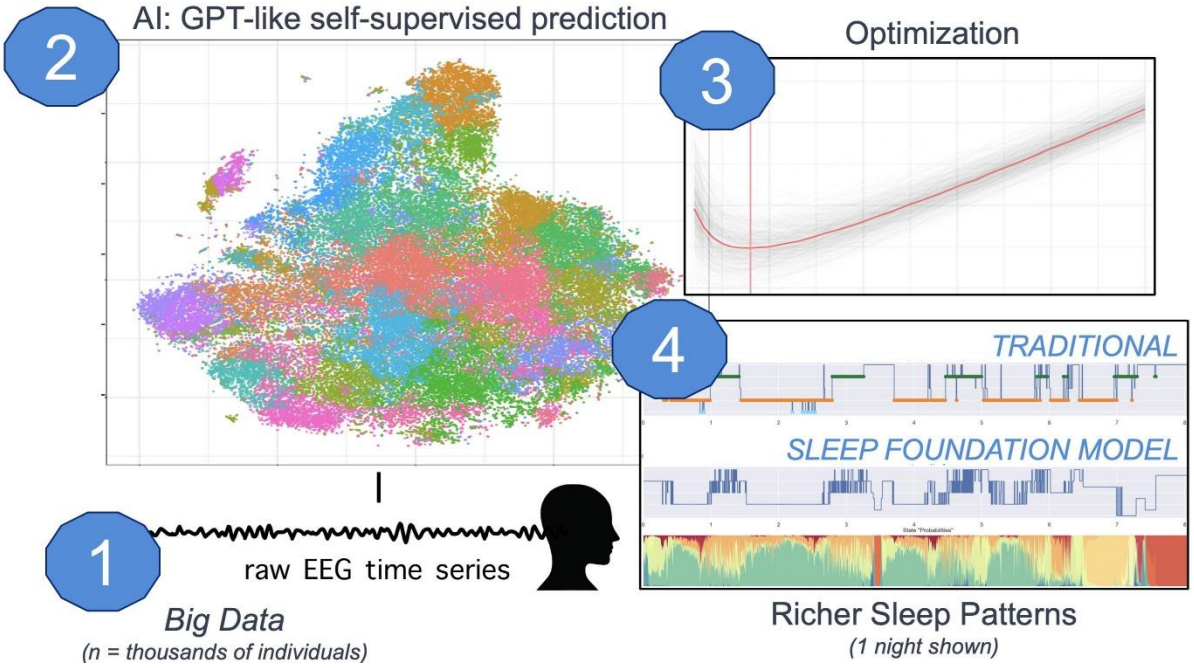
Topic: G.07. Biological Rhythms and Sleep

Support: Johns Hopkins University Applied Physics Laboratory Internal Research & Development Grant

Title: Foundation Models Reveal Untapped Health Information in Human Polysomnographic Sleep Data

Authors: *W. G. COON, M. OGG;
Intelligent Systems Ctr., Johns Hopkins Univ. Applied Physics Lab., Laurel, MD

Abstract: Traditional polysomnographic (PSG) sleep scoring guidelines established by Rechtschaffen and Kales and refined by the American Academy of Sleep Medicine (AASM) have standardized sleep assessment, but their reliance on visual judgment and rigid criteria inherently limit sensitivity to nuanced physiological signals. We applied self-supervised learning (SSL), specifically to train a foundation model (FM) on large-scale PSG datasets (11,000+ records) that autonomously identifies latent structural patterns in sleep data without relying on predefined sleep stage labels. These SSL-derived representations uncovered extensive, previously untapped health-related information beyond traditional five-stage sleep scoring, including enhanced predictive accuracy for cognitive performance, mood disorders, age, and body mass index (BMI). Crucially, SSL-derived representations significantly outperformed supervised methods specifically trained on traditional sleep staging or those initialized from scratch, demonstrating that predictive improvements arose from the latent physiological structure identified through SSL rather than merely from neural network architecture. Additionally, SSL models efficiently learned canonical sleep tasks, such as apnea-hypopnea index (AHI) prediction, from minimal labeled data, highlighting their clinical potential in resource-limited settings. Finally, SSL-based analyses revealed complex sleep-state substructures and transitional states, expanding beyond traditional five-stage sleep categorization. Our findings underscore the potential of SSL foundation models to deeply enrich sleep physiology understanding, improve health outcome predictions, and transform sleep diagnostics and clinical care.



Disclosures: W.G. Coon: None. **M. Ogg:** None.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.02/EE3

Topic: G.07. Biological Rhythms and Sleep

Support: Intramural Research Program of the NIH, NINDS

Title: Enhanced functional connectome fingerprinting during sleep: insights from a whole-night fMRI-EEG study

Authors: N. YANG[1], *D. PICCHIONI[3], J. A. DE ZWART[2], P. VAN GELDEREN[1], J. H. DUYN[4];
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Abstract: Humans exhibit individualized patterns of spontaneous thought, which are believed to be reflected in unique fMRI functional connectomes (FCs), often referred to as FC fingerprints. However, it remains unclear whether these fingerprints persist across varying levels of consciousness. Sleep provides a valuable framework to investigate this question, as consciousness progressively diminishes from light (N1, N2) to deep (N3) sleep and partially re-emerges during rapid eye movement (REM) sleep. We analyzed a dataset of whole-night concurrent EEG-fMRI recordings from 12 participants who slept inside an MRI scanner for two consecutive nights (Figure 1). For each participant, dynamic functional connectivity (window: 30 TRs/90 s; step: 10 TRs) across the whole brain was computed from fMRI during continuous sleep episodes lasting at least three consecutive sleep epochs (90s) within the same stage. Models were built on functional connectivity from each sleep stage separately and tested across all other stages. Our findings revealed a paradox: although inter-individual similarity measured by correlations increased during deep sleep, individuals became more distinguishable based on their FC patterns. Moreover, models built on stable sleep stages, i.e., N2/N3/REM, outperformed those trained on Wake/N1, suggesting the level of consciousness plays a limited role in FC fingerprinting. The networks contributing to individual uniqueness varied by stage—cortical networks, i.e. association networks, dominated during Wake, whereas subcortical hippocampal regions were more prominent during N3. These findings were further supported by a nonlinear machine learning approach using a multi-layer perceptron (MLP), which showed that models trained on N3 or REM generalized well to all other stages, including Wake. Collectively, these results suggest that individual-specific features of brain connectivity are different across sleep stages and may be amplified during deep or REM sleep. Nonlinear models trained on deep or REM sleep provide a robust framework for FC-based fingerprinting.

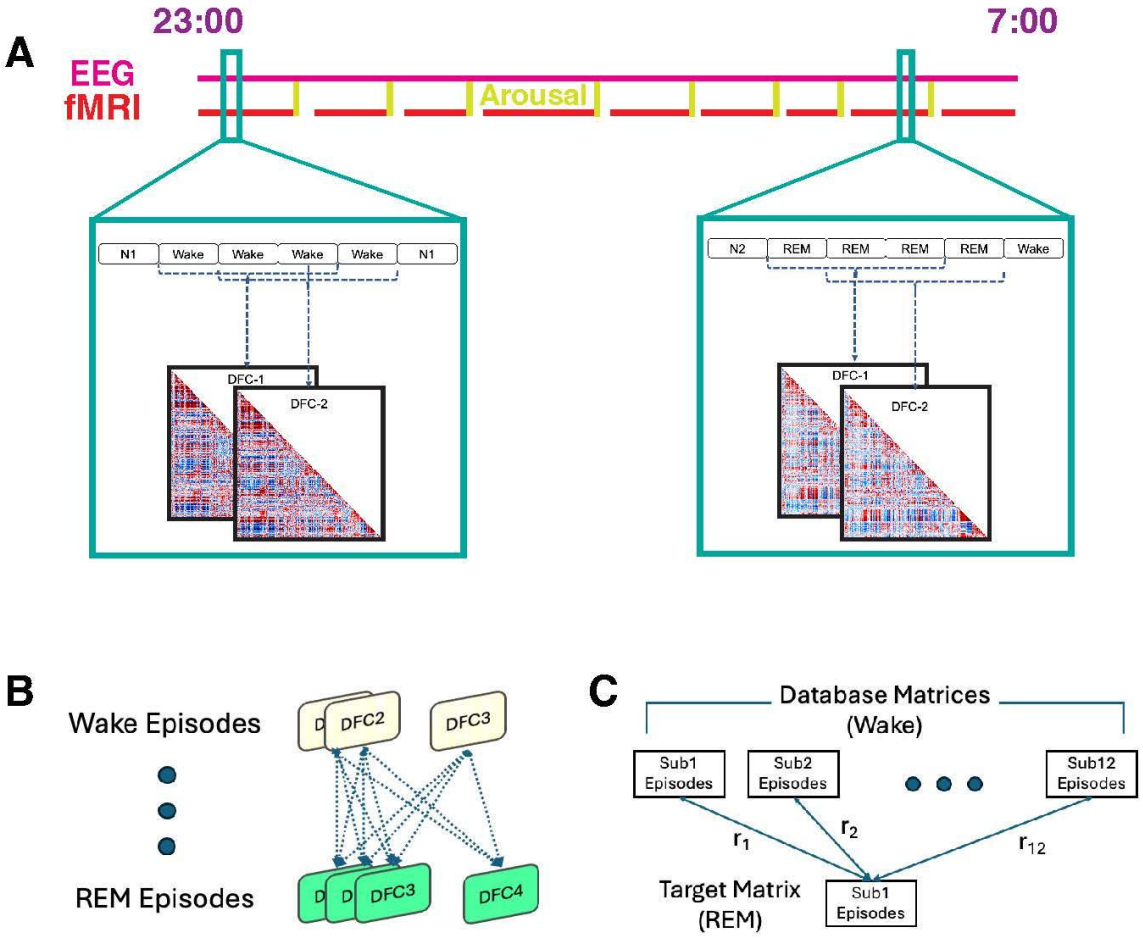


Figure 1. Schematic illustrations of the study design and methods.
A. Participants' sleep were randomly disrupted by acoustic arousals.
B. Average correlation (r) between episodes of two sleep stages was calculated.
C. Identification was determined by the highest correlation coefficient r among participants.

Disclosures: N. Yang: None. **D. Picchioni:** None. **J.A. de Zwart:** None. **P. van Gelderen:** None. **J.H. Duyn:** None.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.03/EE4

Topic: G.07. Biological Rhythms and Sleep

Support: NIH RO1AG072513
NIH T32NS115667

Title: Noninvasive Sleep Characterization from Longitudinal Murine Continuous Video Actigraphy

Authors: *C. J. BOUCHER[1,2,3,4], K. K. NAYLOR[1,2,3], T. M. RIVERA[1,2,3,4], Z. CHEHAB[1,3], B. J. GLUCKMAN[1,2,3,4,5];
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[5]Neurosurg., Pennsylvania State Univ. Col. of Med., Hershey, PA

Abstract: Baseline sleep architecture and quality change across the lifespan, even during healthy aging. Disruptions to sleep and sleep architecture have been shown to be comorbid with various neurological diseases. Exercise is thought to modulate sleep architecture in a way that improves sleep quality and may ameliorate symptoms associated with neurological disease. However, the timing and mechanisms underlying the bidirectional relationship between sleep and exercise remains poorly understood. Established protocols for high-resolution sleep state classification rely on invasive methods - such as intracranial EEG (iEEG) - and/or require the removal of the animals from their home-cage environments, limiting the feasibility of continuous, longitudinal studies without altering natural behavior. To overcome these limitations, we developed a robust, noninvasive video-based system for continuous, long-term home-cage monitoring of behavior and activity in freely behaving mice with access to either a functional or locked running wheel. Home-cages are equipped with both video-based and electrophysiological recording capabilities. In a subset of animals implanted with iEEG, we compared behavioral state classifications derived from video metrics to states of vigilance (SOV) determined by electrophysiology (the golden standard for sleep classification). Here, we present data characterizing our video-based sleep scoring approach against EEG-based SOV. Behavior is detected and quantified based on real-time changes in the pixel intensity across consecutive video frames. This can be used to determine sleep states based on rhythmic oscillations detected during periods in which overall animal movement is minimal. This platform provides a scalable, robust system which can be used to compare patterns across age, sex, and between free wheel and locked wheel groups.

Disclosures: C.J. Boucher: None. **K.K. Naylor:** None. **T.M. Rivera:** None. **Z. Chehab:** None. **B.J. Gluckman:** None.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

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Program #/Poster #: PSTR461.04/EE5

Topic: G.07. Biological Rhythms and Sleep

Support: FOREST JPMJFR2047
JSPS KAKENHI 23K27262

Title: Temporal coupling of rapid eye movements and P-waves during REM sleep in mice: A video oculography study

Authors: *M. KAWATA, T. TSUNEMATSU, H. KAWAGUCHI;
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Abstract: Sleep is a physiological phenomenon conserved across diverse species, comprising two major states: rapid eye movement (REM) sleep and non-REM (NREM) sleep. During REM sleep, characteristic brain waves called P-waves are observed. Although P-waves were first described in cats in the 1950s, their existence in mice remained unverified for over 60 years. In 2020, our group achieved the first successful recording of P-waves in mice. Furthermore, rapid eye movements (EMs), the defining characteristic of REM sleep, are consistently observed during this state. Previous studies in cats and rats have reported that P-waves are likely to occur in synchrony with EMs, as measured by electrooculography (EOG). However, this relationship remains unclear in mice. Therefore, in this study, we aimed to determine whether P-waves and EMs occur synchronously in mice. We employed video-oculography (VOG) to monitor eye movements. First, we assessed the capability of VOG to detect EMs in mice (n=10 recordings from six animals). To monitor eye movements continuously, mice were recorded in a head-fixed condition. Electroencephalograms and electromyograms were also recorded simultaneously to determine the sleep/wakefulness state. Using DeepLabCut, a toolbox for state-of-the-art markerless pose estimation of animals performing various behaviors with deep learning, the changes in pupil position were analyzed. The frequency of changes in pupil positions, i.e., EMs, was significantly increased during REM sleep compared to during NREM sleep, indicating that VOG was capable of detecting EMs. The results also showed that the frequency of EMs dramatically increased approximately 20 seconds after the onset of REM sleep. Furthermore, the frequency of EMs was positively correlated with the duration of REM sleep episodes. This is consistent with the characteristics of the P-wave in previous reports (Tsunematsu et al., 2020) that it occurs more frequently during longer REM sleep. Next, P-waves and VOG were simultaneously recorded in mice that had been implanted with bipolar electrodes in the brainstem, especially the medial parabrachial nucleus, for P-wave detection. A sharp increase in the number of EM occurrences was observed at the onset of the P-wave, indicating that EMs and P-waves are temporally coupled. These findings suggest that EMs may serve as a marker of P-wave occurrences.

Disclosures: M. Kawata: None. **T. Tsunematsu:** None. **H. Kawaguchi:** None.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

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Program #/Poster #: PSTR461.05/EE6

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01AG072513
NIH T32NS115667

Title: Elucidating Sleep and Running Dynamics from Continuous, Longitudinal Video Actigraphy in Freely Behaving Mice

Authors: *K. K. NAYLOR[1,2,3], C. J. BOUCHER[1,2,3,4], T. M. RIVERA[1,2,3,4], Z. CHEHAB[1,3], B. J. GLUCKMAN[1,2,3,4,5];
[1]Ctr. for Neural Engin., [2]Cross Disciplinary Neural Engin., [3]Engin. Sci. and Mechanics, [4]Grad. Program in Neurosci., Pennsylvania State Univ., University Park, PA; [5]Neurosurg., Pennsylvania State Univ. Col. of Med., Hershey, PA

Abstract: Sleep patterns naturally evolve over the lifespan of an animal. Disruption of sleep - regardless of cause - has been identified as a risk factor for neurological diseases and is potentially implicated in mechanisms underlying disease progression. Prospective observational studies have shown that physical inactivity is one of the most prevalent and modifiable risk factors for neurodegenerative disease. While exercise is broadly recognized to benefit sleep-wake regulation, less is known about how factors such as age, sex, activity levels, and sleep quality interact to modulate this complex system. Sleep and exercise interact through a series of complex, bidirectionally linked processes that affect multiple downstream physiologic pathways. To investigate these interactions, we continuously monitor freely behaving mice across their lifespan using a custom-designed home-cage unit and acquisition system. Mice, with or without access to a functional, self-propelled running wheel, are continuously monitored via video and/or EEG in their home environment. This platform enables quantification of sleep architecture (e.g., number of bouts, percentage of time asleep, and bout duration) alongside measures of voluntary activity (e.g., running distance, number of running bouts, and bout duration). These metrics are analyzed longitudinally to examine how sleep and exercise patterns fluctuate throughout the day and evolve over the course of aging. For this work, seventy-two mice were included in this study, with equal distributions by sex (Male/Female) and wheel condition (Free/Locked). Half of the cohort (n = 36) was monitored (video only) longitudinally from 2-18 months of age without interruption. The remaining half underwent surgical implantation of intracranial EEG (iEEG) electrodes between 11-15 months of age, enabling electrophysiological recordings through 18 months of age. Using this data, we show quantified metrics of sleep architecture and activity including duration, temporal distribution, and how these metrics co-evolve over aging.

Disclosures: K.K. Naylor: None. **C.J. Boucher:** None. **T.M. Rivera:** None. **Z. Chehab:** None. **B.J. Gluckman:** None.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

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Program #/Poster #: PSTR461.06/EE7

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01 AG083268

Title: New tool leveraging multi-tapered spectrograms and Artificial Neural Networks to simplify EEG scoring and streamline sleep analysis

Authors: *B. FREIGASSNER[1], R. A. MILSTEAD[2], C. BORSKI[1], S. ZOU[1], J. JACKSON[3], P. CAIN[1], C. HOEFFER, Jr.[4];
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Abstract: Since its invention in the early 20th century, electroencephalography (EEG) has been established as a powerful tool for studying sleep and remains the gold standard for sleep analysis. However, both training and practice to reliably interpret EEG data, as well as the actual scoring itself, require a substantial time investment. By transforming EEG data into spectrograms, that time investment can be reduced substantially.In a further step, we utilized the power of machine learning and the extensive database of the Institute for Behavioral Genetics at the University of Colorado to train an artificial neural network. We implemented an automated scoring process that performs with competitive accuracy while keeping runtimes to a fraction of manual scoring methods:Here, we investigate how the traditional EEG scoring method compares to multi-taper spectral analysis when scoring EEG sleep data of mice. First, we determined the scoring accuracies and time investments of five operators, ranging from beginner to veteran. By comparing scoring performances of multiple rounds, we assessed intra-rater reliability (within one human) as well as inter-rater reliability (human to human).Revealing a significant time advantage for the multi-taper spectral analysis by shortening the required training period from weeks to hours and cutting down the average manual scoring time by almost half while only suffering a slight reduction in accuracy.In the second step, we compared the performance of human operators to that of the automated scoring tool (inter-rater reliability - human to machine).For now, traditional EEG scoring may still produce the highest accuracy; however, in terms of time investment, we can demonstrate the advantages of utilizing multi-taper spectrograms and the potential of computer-aided scoring methods, which allow for reduced scoring times of a 24-hour recording to less than a minute.

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Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.07/EE8

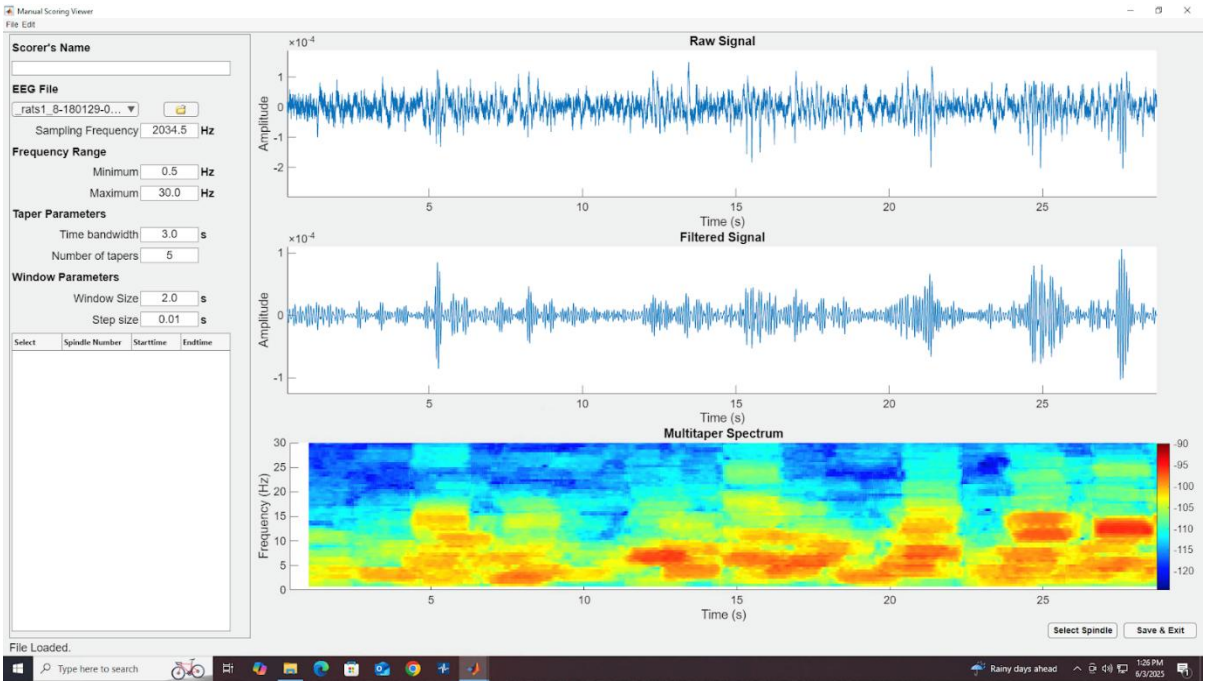
Topic: G.07. Biological Rhythms and Sleep

Support: Rhodes Eminent Scholar Chair, Louisiana Board of Regents (to TAM)
US National Science Foundation, OIA 2217824 (to TAM LLP

Title: Improving time efficiency in manual rodent sleep spindle annotation using a MATLAB application

Authors: P. DHUNGEL[1], K. S. HOLLY[2], S. VILLARRUBIA HEARN[1], A. S. KEMP[3], L. J. LARSON-PRIOR[4], *T. A. MURRAY[1];
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[3]Departments of Psychiatry and Biomed. Informatics, [4]Departments of Psychiatry and Neurosci., Univ. of Arkansas For Med. Sci., Little Rock, AR

Abstract: Sleep spindles—transient oscillations in non-REM sleep—support memory consolidation and sleep stability. Their disruption is linked to neuropsychiatric conditions, making accurate identification vital for both basic and translational sleep research. Rodent models are widely used due to their experimental flexibility, yet spindle scoring in these models remains manual, time-consuming, and prone to interrater variability. To address this, we developed the Manual Sleep Spindle Scorer (MSSS), a MATLAB-based application that streamlines spindle annotation. MSSS supports EDF-format EEG files and simultaneously displays raw, bandpass-filtered, and spectrogram views. Users can visually mark spindles using an intuitive interface, with time-stamped outputs automatically recorded and exportable in CSV format.
Two trained raters scored spindles in ten 10-second epochs of rat intracranial EEG using MSSS and external tools. MSSS significantly reduced annotation time and improved signal clarity and usability. Compared to EDFbrowser and LabChart, MSSS yielded a significant gain in efficiency (130.05 ± 70.20 vs. 227.60 ± 93.04 sec), $t(19) = -4.87$, $p = 0.0001$, 95% CI [-139.45, -55.65]. We invite collaborators to help establish a database of manually scored rodent EEG for sleep spindles to serve as ground truth for future research.



Disclosures: P. Dhungel: None. **K.S. Holly:** None. **S. Villarrubia Hearn:** None. **A.S. Kemp:** None. **L.J. Larson-Prior:** None. **T.A. Murray:** None.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.08/FF1

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01AG072513
NIH T32NS115667

Title: Robust automated algorithms for sleep state classification across mice and aging

Authors: *T. M. RIVERA[1,2,3,4], K. NAYLOR[1,2,3], C. J. BOUCHER[1,2,3,4], Z. CHEHAB[1,3], B. J. GLUCKMAN[1,2,3,4,5];
[1]Ctr. for Neural Engin., [2]Cross Disciplinary Neural Engin. Training Program, [3]Engin. Sci. and Mechanics, [4]Grad. Program in Neurosci., Pennsylvania State Univ., University Park, PA; [5]Neurosurg., Pennsylvania State Univ., Hershey, PA

Abstract: Electrophysiological recordings provide a high-resolution window into neural activity and are essential for characterizing dynamic brain states. Precise identification of these states is critical for understanding sleep architecture and its electrophysiological features - particularly how these evolve over the lifespan. Using intracranial EEG, we can accurately track sleep-wake transitions and states of vigilance, offering insight into age-related changes in brain function. In our study, over two hundred mice at a time are individually housed in custom-designed home-cages that support continuous, real-time monitoring. A subset of animals is implanted with low-impedance intracortical electrodes and tethered to an integrated, eight-channel EEG acquisition system. Animals have access to a running wheel - either freely moving or locked - to assess the influence of voluntary activity on sleep dynamics. Using our custom EEG acquisition system, we are actively developing and refining advanced automated algorithms for sleep state classification. Our objective is to achieve robust and scalable classification that (1) enables accurate scoring for individual mice, (2) generalizes effectively across different animals, and (3) accounts for longitudinal changes in recordings to maintain consistent detection of sleep-wake transitions and states of vigilance throughout development and aging. Here we report comparisons between different machine learning based algorithms (eg. LDA, DNN) across these three metrics. This approach aims to develop high-throughput, automated scoring algorithms for large-scale longitudinal datasets, capable of capturing dynamic shifts in sleep architecture despite variability in signal quality or recording conditions. Our ongoing work demonstrates the potential of these scalable automated methods for comprehensive, long-term sleep analysis in freely behaving mice.

Disclosures: T.M. Rivera: None. **K. Naylor:** None. **C.J. Boucher:** None. **Z. Chehab:** None. **B.J. Gluckman:** None.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

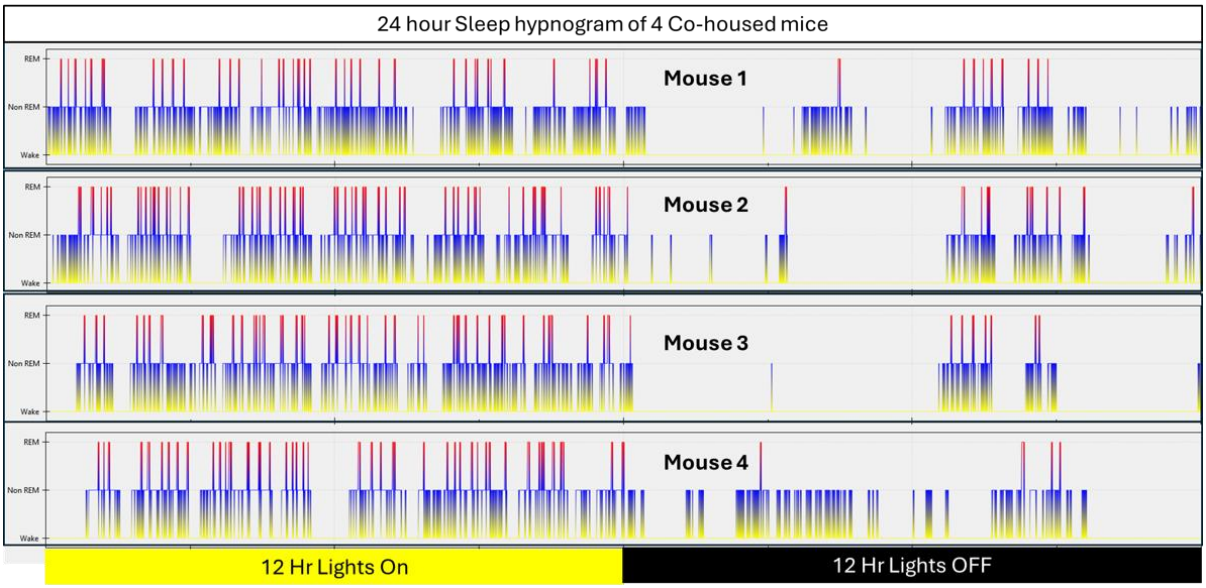
Program #/Poster #: PSTR461.09/FF2

Topic: G.07. Biological Rhythms and Sleep

Title: Wireless EEG/EMG for monitoring sleep in a group housed, social environment

Authors: D. V. AILLON, S. KAPLAN, S. GROTH, S. GABBERT, M. MEIER, M. ZARRAR, ***S. A. LATIF**, D. A. JOHNSON;
Pinnacle Technol. DE, LLC, Lawrence, KS

Abstract: Monitoring rodent sleep in a social environment has traditionally been limited by the constraints of available EEG/EMG technology. Recent advances in wireless systems have significantly improved the feasibility of long-term sleep studies in socially housed animals. In this study, four male C57BL/6J mice were implanted with cranial EEG and nuchal EMG electrodes. Animals were maintained as a social group both before and after implantation surgery.
Each mouse was fitted with a wireless EEG/EMG recording device (Model 8274-HR) for continuous monitoring of vigilance state. Continuous recordings were collected over approximately 96 hours at a 512hz sampling rate.
In subsequent experiments, the social group was divided, and two animals were housed individually to compare EEG/EMG patterns in isolated versus social conditions. Sleep data were scored in 10-second epochs as Wake, NREM, or REM. Mice housed in the social environment exhibited a high degree of sleep state synchronization, with two or more animals asleep simultaneously across 87.5% of a representative 12-hour lights-on period. Both animals that underwent monitoring in individual cages displayed a longer average wake bout length in a solo vs group housed setting. Average duration of wake bouts for the two solo housed animals were 416% and 168% longer than in a group housed setting (12 hours, lights on).





Disclosures: D.V. Aillon: A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **S. Kaplan:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **S. Groth:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **S. Gabbert:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **M. Meier:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **M. Zarrar:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **S.A. Latif:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **D.A. Johnson:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.10/FF3

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01HL059658

Title: Novel Tools to Study Sleep-Active Cortical Neurons

Authors: *S. M. LEE[1], C. YIN[2], G. TERRAL[4], B. TASIC[6], J. T. TING[7], R. BATISTA-BRITO[5], T. S. KILDUFF[3];
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Abstract: While most cortical neurons exhibit reduced firing activities during slow wave sleep (SWS), a rare population of cortical interneurons are active during sleep evidenced in three different species. This subpopulation of GABAergic interneurons, or SNTC cells, co-express somatostatin (*Sst*), neuronal nitric oxide synthase (*Nos1*), the Neurokinin-1 receptor (*Tacr1*) and chondrolectin (*Chodl*), and correspond to Type 1 nNOS neurons that have long range intracortical projections in mammals. Cortical SNTC neurons express c-Fos during SWS proportional to the homeostatic sleep drive from the preceding period of wakefulness. Furthermore, scRNA-seq studies identified these cells as transcriptionally distinct from other classes of *Sst* neurons. However, their specific roles in sleep regulation are yet unknown. Here, we utilized Chodl-P2A-Cre;Sst-IRES-FlpO mice, Tacr1-T2A-Cre;Sst-IRES-FlpO mice and a novel enhancer virus (AiP12689) as tools to further investigate the role of cortical nNOS neurons in sleep/wake regulation.
Chodl-P2A-Cre;Sst-FlpO and Tacr1-T2A-Cre;Sst-FlpO mice were bred with Ai65 for endogenous labeling of nNOS neurons and, in C57BL6/J mice, the AiP12689 enhancer virus was injected retro-orbitally to label the same population. Responses of labeled cells to Substance P (200 nM) were measured by slice electrophysiology. Substance P activated 73%, 78%, and 67% of labeled cortical neurons, respectively, in the three strains. In sleep deprivation (SD) studies, one group of mice underwent 6 h of SD and another group was allowed 2 h of recovery sleep (RS) following SD. Consistent with our previous studies, labeled nNOS neurons from all three strains expressed c-Fos during RS but not during SD ($p<0.0001$, unpaired t-test). To systematically investigate c-Fos activation after RS, whole brain light sheet imaging was performed using mice injected with the enhancer virus. A comparison of cortical subregions and subcortical regions showed increased c-Fos activation throughout the cortex as well as in striatum and amygdala. For chemogenetic activation of nNOS cells, AAV8.nEF.Con/Fon.DREADD(Gq)-mCherry.WPRE.hGH was injected at 16 sites in the cerebral cortex across both hemispheres in Tacr1-Cre;Sst-FlpO mice of both sexes (n=7).

Deschloroclozapine (DCZ, 0.3mg/kg) injection at ZT18 increased NREM sleep compared to saline injection control (p=0.0041).
Our findings indicate that cortical nNOS neurons are active during sleep and that activation of these cells can drive NREM sleep. These results are consistent with our previous results and show that these novel tools can be used to further characterize the role of nNOS neurons in sleep/wake control.

Disclosures: S.M. Lee: None. **C. Yin:** None. **G. Terral:** None. **B. Tasic:** None. **J.T. Ting:** None. **R. Batista-Brito:** None. **T.S. Kilduff:** None.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.11/FF4

Topic: G.07. Biological Rhythms and Sleep

Title: An EEG-Based Platform to finely score vigilance states in a preclinical context

Authors: *C. HABERMACHER, C. ALLIOUX, B. CARABALLO, M. VILLALBA, C. DUMONT, E. GRONLIER, D. DARANKOUM, J. VOLLE;
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Abstract: Wake-promoting agents were primarily reserved for the treatment of syndromes characterized by impaired alertness, however their use is becoming more widespread in neuropsychiatric disorders with sleep-wake disturbances. A fine characterization to distinguish the effects on substates of wakefulness is now crucial in the preclinical field, in order to evaluate potential adverse outcomes.
Behavioral states range from highly active to deep sleep stages. Sleep itself is a complex phenomenon comprising two major states in mice: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. During wakefulness, periods of activity alternate with wakeful quiescence.
Wakefulness and sleep substates are complex brain states that emerge from the interaction of brain structures and can be identified by their specific electroencephalographic (EEG) and electromyographic (EMG) signatures. However, the awake substates (quiet and active) have not been as thoroughly characterized as sleep states, with defining criteria often laboratory specific. In this project, we developed an optimized EEG recording and analysis pipeline to study in details modulations of vigilance states following the administration of drugs. We combined EEG and EMG recordings to piezoelectric sensors to collect data on wild-type C57/Bl6 males during pharmacological challenge. Recordings are first scored semi-automatically with a supervised machine learning approach in 4-second epochs to identify sleep stages. In parallel, piezoelectric data are used to discriminate obvious awake substates. Advanced analysis is applied to each epoch to extract a set of EEG features, including Fourier transform, power spectral density, entropy, coherence,), and aperiodic components. Subsequently, wake epochs are labeled based

on their predicted probability using a pre-trained decision tree model.
In this study, we investigated the relevance and effectiveness of this approach in preclinical drug development. We tested the effects of a wake-promoting agent, caffeine, on substates of wakefulness in a cohort of 16 mice, using a cross-over design to precisely characterize its impact on EEG activity. As expected, caffein (10 $mg \cdot kg^{-1}$, IP) promotes active wake and increases sleep onset latency. This compound specifically modifies the EEG profile during quiet wake epochs, particularly in the high-frequency range, and tends to mitigate discrepancies between wake substates.
This project lays the foundation for the development of a drug screening process focused on fine sleep/wake architecture analysis to objectively assess the specific profile of compounds in development for various indications.

Disclosures: **C. Habermacher:** A. Employment/Salary (full or part-time): SynapCell. **C. Allioux:** A. Employment/Salary (full or part-time): SynapCell. **B. Caraballo:** A. Employment/Salary (full or part-time): SynapCell. **M. Villalba:** A. Employment/Salary (full or part-time): SynapCell. **C. Dumont:** A. Employment/Salary (full or part-time): SynapCell. **E. Gronlier:** A. Employment/Salary (full or part-time): SynapCell. **D. Darankoum:** A. Employment/Salary (full or part-time): SynapCell. **J. Volle:** A. Employment/Salary (full or part-time): SynapCell.

Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.12/FF5

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01AG072513
NIH T32NS115667

Title: Continuous, Multimodal Neural and Behavioral Monitoring in Freely Behaving Mice Using a Custom Platform

Authors: *Z. CHEHAB[1,2], K. NAYLOR[1,3,2], C. J. BOUCHER[1,3,2,4], T. M. RIVERA[1,3,2,4], B. J. GLUCKMAN[1,3,2,4,5];
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[5]Neurosurg., Pennsylvania State Col. of Med., Hershey, PA

Abstract: Understanding how sleep, activity, and environmental variables contribute to aging and neurodegenerative disease requires continuous, multimodal monitoring in freely behaving animals. To meet this need, a custom system was developed to enable chronic, synchronized acquisition of electrophysiological and behavioral data from mice. Each individually housed mouse is continuously monitored via two single-board computers (SBCs) - one dedicated to real-

time video acquisition and processing (vSBC) and the other to EEG recording from surgically implanted depth electrodes (eSBC). Implanted mice are connected to a low-noise amplifier, which interfaces directly with the eSBC to allow tethered, long-term neural recordings. Each SBC is equipped with custom hardware designed for autonomous control and efficient communication with automated processes. These interfaces include physical buttons to initiate or terminate recordings, RGB LEDs to indicate system status, and onboard accelerometers to detect handling events such as cage lid openings. GPIO-based communication links between the SBCs. Mice are housed with or without access to a functional running wheel to assess the modulatory effects of exercise on both sleeping and waking behavior. This system supports longitudinal, large-scale studies - comprised of hundreds of cages - that a small team of researchers can manage. It is currently being used to investigate the interplay between sleep architecture and exercise dynamics and how those relationships shift with aging in a home-cage setting. By providing a comprehensive, integrated, and scalable acquisition platform, we can elucidate aspects of behavior and electrophysiological signatures that may play a role in both natural and neurodegenerative disease progression over aging.

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Poster

PSTR461: Novel Approaches to Monitoring and Quantifying Sleep

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.13/FF6

Topic: G.07. Biological Rhythms and Sleep

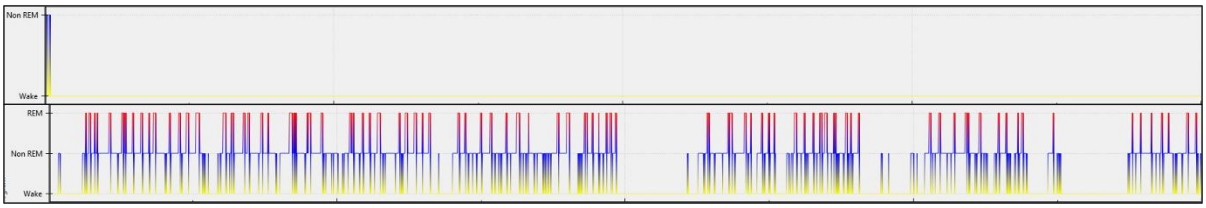
Title: Automated sleep deprivation: Full-time stimulus versus state-dependent feedback control

Authors: *D. AILLON, S. GABBERT, S. GROTH, M. MEIER, M. ZARRAR, S. KAPLAN, D. A. JOHNSON;
Pinnacle Technol. DE, LLC, Lawrence, KS

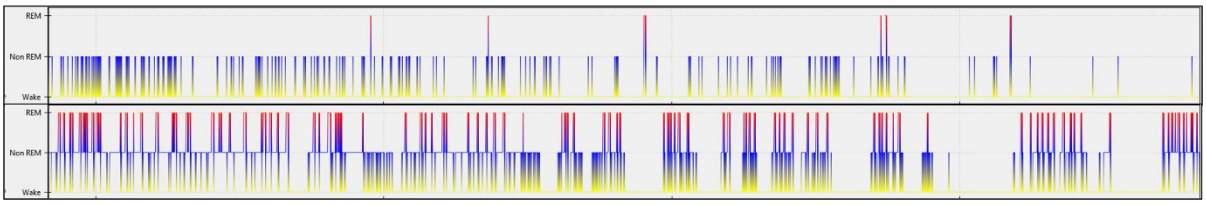
Abstract: Automated sleep deprivation (SD) can be performed on a fixed schedule or based on real-time EEG and EMG feedback. In Feedback mode, the deprivation stimulus activates only when the animal enters a sleep state. We compared full-time application (FTA) versus state-dependent feedback (SDF) control of the deprivation stimulus (bar rotation). A male Sprague Dawley rat was implanted with EEG and EMG electrodes and underwent two 24-hour SD sessions, spaced three weeks apart. Each session included three 24-hour phases: baseline, SD, and recovery. During FTA, the bar rotated continuously throughout the SD period. In SDF, the bar was triggered when high EEG delta power and low EMG activity were detected, and paused when EMG activity increased. Data were scored in 10-second epochs as Wake, NREM, or REM. Both methods effectively disrupted sleep. FTA eliminated 100% of sleep during the SD period, while SDF reduced scored sleep by over 90% compared to baseline. Recovery sleep during the 12-hour lights-on period immediately following SD was similar between methods: FTA resulted

in 105.7 minutes of REM and 460.3 minutes of NREM sleep; SDF resulted in 98.2 minutes of REM and 476.3 minutes of NREM sleep. Although SDF allowed brief sleep episodes before interruption, it substantially minimized total sleep without continuous stimulation. Video analysis revealed that during FTA, the rat traveled over twice the distance compared to SDF-controlled SD.

24 hour FTA Sleep Deprivation Period (top) and Recovery Period (bottom)



24 hour SDF Sleep Deprivation Period (top) and Recovery Period (bottom)



Disclosures: D. Aillon: A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **S. Gabbert:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **S. Groth:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **M. Meier:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **M. Zarrar:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **S. Kaplan:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC. **D.A. Johnson:** A. Employment/Salary (full or part-time): Pinnacle Technology DE, LLC.

Poster

PSTR462: Dopamine Waves and Their Effects

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.01/FF7

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Somatic Origins of Dopamine Wave Motifs for Credit Assignment in Striatum

Authors: *H. ZHANG, D. FLINK, A. HAMID;
Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Synchronous spiking of midbrain dopamine (DA) neurons and their widespread projections informed the classical view of a globally uniform DA decision signal for reinforcement learning. However, emerging evidence reveals that DA release across the striatum

is heterogeneous, varying by region and task epoch. We recently demonstrated that DA release in the dorsal striatum exhibits coordinated spatiotemporal structure governed by distinct initiation and propagation rules on sub-second timescales—challenging the broadcast model. These structured dynamics enable optimal credit assignment and policy arbitration across cortico-striatal channels.
This shift in the computational framing of forebrain DA calls for a deeper investigation into the circuit mechanisms that generate heterogeneous DA signals. While slice studies implicate striatal interneurons in shaping local release, the contribution of sequentially recruited, projection-defined midbrain somata to wave-like DA dynamics remains underexplored. To quantify somatic influence on terminal release patterns, we performed simultaneous calcium imaging of midbrain DA neurons and widefield DA imaging in the dorsal striatum of DAT-Cre mice. Somatic activity was deconvolved and compared to terminal dynamics extracted through dimensionality reduction and hidden Markov modeling. We mapped somatic population trajectories into the latent space of release motifs using linear discriminant analysis, then assessed directional influence via multivariate transfer entropy, phase-slope index, and Granger causality. These analyses reveal how temporally structured somatic firing contributes to spatially heterogeneous DA release, offering a new framework for understanding how global and local mechanisms jointly sculpt DA's circuit-level function.

Disclosures: H. Zhang: None. **D. Flink:** None. **A. Hamid:** None.

Poster

PSTR462: Dopamine Waves and Their Effects

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.02/FF8

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Valuation Mechanisms that Shape the Interaction of Phasic and Tonic Dopamine

Authors: *A. GOTTSCHALK[1], A. HAMID[2];
[1]Univ. of Minnesota Twin Cities, Minneapolis, MN; [2]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Reward learning and motivation are supported by fluctuations in striatal dopamine (DA) across multiple timescales. Phasic DA transients encode reward prediction errors critical for learning, while tonic DA levels regulate motivational arousal. Yet, how these timescales interact to mediate the relationship between learning and motivation—and support flexible motivational engagement—remains unresolved. Although several computational models propose algorithms linking tonic and phasic DA, empirical tests of these competing accounts have been limited by the inability to measure broadband DA dynamics across behaviorally relevant timescales. We addressed this gap by developing a technique that enables calibrated measurement of absolute DA levels in awake, behaving mice across sub-second to hour-long intervals. By modifying standard fast-scan cyclic voltammetry (FSCV), we engineered the scan

sequence to modulate electrode sensitivity and applied ratiometric principles to eliminate artifacts unrelated to DA, enabling wideband DA quantification. We leverage this method in tasks specifically designed to isolate valuation processes that govern reward expectation and motivational engagement, dependent or independent of recent reward surprise. This approach allowed us to test a critical assumption of prevailing theoretical frameworks: that tonic DA reflects an accumulation of recent phasic signals. More broadly, this platform enables empirical dissection of how tonic-phasic DA interactions are shaped by task structure and provides a novel window into the mechanistic and algorithmic basis of multi-timescale DA signaling in adaptive behavior.

Disclosures: A. Gottschalk: None. **A. Hamid:** None.

Poster

PSTR462: Dopamine Waves and Their Effects

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.03/FF9

Topic: H.02. Reward and Appetitive Learning and Memory

Support: HHMI Hanna Gray Fellowship

Title: Spatiotemporal Circuit Constraints on Striatal Dopamine Waves

Authors: D. FLINK, A. GAMAM, H. ZHANG, ***A. A. HAMID**;
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Abstract: Midbrain dopamine (DA) neurons are classically understood to encode reward prediction errors (RPEs) and broadcast them uniformly across the striatum. However, recent evidence challenges this notion; our group discovered wave-like structured DA dynamics that are lawfully modulated by ongoing task demands. These waves deliver precisely timed DA decision signals to local striatal experts, indicating that they represent a mechanism for implementing a regional vector-weighting of RPEs. Here, we sought to study circuit and spatiotemporal mechanisms that organize DA dynamics. Building on previous studies of striatal microcircuits, we hypothesize that the complexity of DA waves emerges from the interplay between global control via midbrain soma spiking and local modulation via striatal axo-axonal interactions with interneurons. Using various tools with high spatial and temporal precision, we dissect the relative contributions of midbrain and striatal mechanisms to DA wave motif assembly. We further test whether a competitive exchange between these local-global control systems governs motif transitions leveraged during reward learning. Ultimately, our results reveal fundamental and dissociable building blocks of DA recruitment that are essential for reinforcement learning and may represent vulnerable nodes in psychopathology.

Disclosures: D. Flink: None. **A. Gamam:** None. **H. Zhang:** None. **A.A. Hamid:** None.

Poster

PSTR462: Dopamine Waves and Their Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR462.04/FF10

Topic: H.02. Reward and Appetitive Learning and Memory

Support: DA045913
P50DA046346
R01AA028215

Title: Contrasting roles of central and basolateral amygdala activity and dopamine release during goal-directed versus habit-like behaviors

Authors: *M. HAFENBREIDEL[1], E. HERRING[2], N. MILLER[1], S. E. MORRISON[2], M. M. TORREGROSSA[1];
[1]Psychiatry, [2]Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Substance use disorders (SUDs) are characterized by compulsive drug seeking and taking despite negative consequences. It is thought that casual drug use transitions to SUD over time as the behavior becomes more ingrained and habit-like. Activity and dopamine signaling in the dorsal medial striatum (DMS) are associated with early goal-directed behaviors; however, as the behavior becomes more habit-like, related activity increasingly shifts to the dorsal lateral striatum (DLS). Studies have demonstrated a direct pathway from the basolateral amygdala (BLA) to the DMS that mediates goal-directed behaviors, and recent evidence suggests that a pathway from the central amygdala (CeA) to the DLS is necessary for habit-like behaviors. However, the precise amygdala signaling and neurochemical mechanisms underlying the shift from goal-directed to habit-like behavior remain unclear. Therefore, we examined this transition using *in vivo* electrophysiology and fiber photometry to measure activity and dopamine release in the BLA and CeA during two different behavioral paradigms. First, we employed a Pavlovian reward conditioning paradigm that promotes sign-tracking behavior (i.e., approach and interaction with a reward cue). Sign tracking can be thought of as a habit-like behavior because it is resistant to devaluation and extinction. Second, we used a cocaine self-administration paradigm that promotes the development of habit-like drug-seeking behavior. Surprisingly, in the CeA, there was little change in cue- or reward-evoked excitatory neuronal activity in early compared to late Pavlovian conditioning. However, overtraining neurons with cue-evoked inhibitions had enhanced cue-evoked responses, while reward-evoked responses switched from inhibitory to excitatory. Similarly, during drug-seeking, there was an increase in CeA inhibitory signaling as behavior transitioned from goal-directed to habit-like. Finally, we observed contrasting patterns of dopamine release related to goal-directed versus habit-like behaviors in both paradigms, along with differences in CeA versus BLA dopamine release. These results begin to elucidate the mechanisms underlying the transition from goal-directed to habit-like reward-seeking and could ultimately provide insights into different treatment options for SUDs.

Disclosures: M. Hafenbreidel: None. **E. Herring:** None. **N. Miller:** None. **S.E. Morrison:** None. **M.M. Torregrossa:** None.

Poster

PSTR462: Dopamine Waves and Their Effects

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.05/FF11

Topic: H.02. Reward and Appetitive Learning and Memory

Support: MRC Project Grant MR/X022080/1

Title: Heterogeneous influence of dopamine on striatal neuronal activity in freely moving rats

Authors: *C. TOSCHI[1], A. VERGHESE[2], B. PERRY[1], L. M. BURGENO[3], M. E. WALTON[3], A. SHAROTT[4];
[2]Brain Network Dynamics Unit, [3]Exptl. Psychology, [1]Univ. of Oxford, Oxford, United Kingdom; [4]Brain Network Dynamics Unit, Oxford, United Kingdom

Abstract: Dopamine (DA) signaling in the striatum has been extensively studied for its role in reinforcement learning and value-based cue processing. However, the extent to which DA release directly shapes the activity of post-synaptic striatal neurons remains unclear. While some evidence suggests that DA is essential for enabling synaptic plasticity at cortico-striatal synapses, recent in vivo studies -simultaneously monitoring DA release and neuronal activity- have reported minimal influence of DA on striatal firing patterns. To address this controversy, we recorded sub-second DA release and spiking activity of striatal units simultaneously in the same region of freely moving rats. Our results reveal a striking heterogeneity: some neurons display strong correlations with DA transients, while others show no apparent modulation. These findings suggest a more nuanced and cell-specific role for DA in shaping striatal output than previously appreciated, with implications for our understanding of basal ganglia function and dopaminergic modulation.

Disclosures: C. Toschi: None. **A. Verghese:** None. **B. Perry:** None. **L.M. Burgeno:** None. **M.E. Walton:** None. **A. Sharott:** None.

Poster

PSTR462: Dopamine Waves and Their Effects

Location: SDCC Halls B-H

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Program #/Poster #: PSTR462.06/FF12

Topic: H.02. Reward and Appetitive Learning and Memory

Support: R01-NH126178

Title: Differential serotonin release across striatal subregions during reward

Authors: *M. G. SPRING, A. LYNDAKER, K. M. NAUTIYAL;
Dartmouth Col., Hanover, NH

Abstract: Serotonin in the central nervous system is implicated in numerous disparate processes, ranging from homeostatic thermoregulation to emotional dysregulation in psychiatric conditions. However, the mechanisms behind its diverse actions remain unclear. These two facts may both be credited to the enormous anatomical and physiological heterogeneity of serotonin neurons arising in the dorsal raphe nucleus (DRN), which provides the majority of serotonergic innervation in the forebrain. By focusing on serotonin release in discrete forebrain regions targeted by the DRN, we are able to reduce some of this complexity and develop clearer—and simpler—models of serotonin function within these brain regions. Previous work from our lab, using a genetically encoded fluorescent biosensor for serotonin (GRAB-5-HT), found that serotonin release in the dorsomedial striatum (DMS) of mice corresponded to reward consumption, external reward value, and internal satiety state. We have extended these findings to recordings of serotonin release in the ventral striatum, specifically targeting the medial nucleus accumbens (mNAc), in a similar battery of reward tasks in a capacitance based gustometer. Interestingly, in contrast to the DMS, serotonin levels in the mNAc (after a small initial increase) *decrease* during consumption of palatable evaporated milk. The initial increase in signal persists for 1-2 seconds around the onset of consumption and its magnitude does not vary with milk concentration. The decrease below baseline, however, lasts for the remainder of the consummatory window and is graded by reward concentration, with a sharp offset at termination of consumption. Finally, we found the consummatory decrease was sensitive to reward devaluation in a satiety devaluation design. In total, serotonin release in the mNAc displays sensitivity to similar features of reward as release in the DMS, however in the opposite direction. Interestingly, preliminary tracing studies of DRN projections to both striatal subregions suggest a significant overlap between the two populations, raising the possibility that the differential release patterns observed in the mNAc and DMS are due to terminal regulation of serotonin release. We are currently working to confirm the findings of these tracing studies. Ongoing work in the lab is using pharmacological and optogenetic tools to manipulate serotonin release in both regions to identify the mechanisms underlying these release patterns and their role in motivated behavior. Finally, we are also extending our characterization of striatal serotonin release to aversive stimuli in both the DMS and mNAc.

Disclosures: M.G. Spring: None. **A. Lyndaker:** None. **K.M. Nautiyal:** None.

Poster

PSTR462: Dopamine Waves and Their Effects

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.07/GG1

Topic: H.02. Reward and Appetitive Learning and Memory

Support: R37DA032750
R21DA050868
P30DA048736
NSF DMS-2322920
N000142312589
K99DA059612
F32DA054719

Title: Dopamine signals across the anterior-posterior axis of the striatum represent unique components of consummatory behavior

Authors: *A. G. GORDON-FENNELL[1], B. M. BENOWITZ[1], I. MONTEQUIN[1], H. STEVENSON[1], P.-Y. LU[1], E. ANCELL[1], M. HJORT[1], D. WITTEN[1], G. D. STUBER[2]; [2]Anesthesiol. and Pain Med., [1]Univ. of Washington, Seattle, WA

Abstract: Objective & Rationale: Dopamine (DA) release in anatomically distinct striatal subregions modulates specific behavioral components, yet how those signals coordinate during ongoing consumption of appetitive and aversive solutions remains unclear. We combined multi-site fiber photometry with a head-fixed brief-access taste task to generate a spatiotemporal map of striatal DA dynamics during consumption. In this exploratory study, our goal was to determine how multiple facets of consumption contribute to DA dynamics across different subregions of the striatum. **Methods:** C57BL/6J mice (n = 6-22 per region; >8 wk; roughly equal males and females) performed a head-fixed brief-access taste task where they were allowed to consume a range of rewarding and aversive solutions. We recorded GRAB-DA2m fluorescence in 131 fiber locations, with two to six sites recorded simultaneously per mouse.Peri-event time-histogram analysis, generalized linear modelling (GLM), and principal-component analysis (PCA) were employed to characterize DA dynamics during consumption. Fiber placements were determined post-hoc and aligned to a common atlas to assess the relation between position in the striatum and DA dynamics. **Results:** *Consumption*: DA scaled with solution value across all time windows, but encoding shifted along the anterior-posterior axis. Posterior subregions displayed rapid DA rises preceding licking onset, whereas anterior/ventral regions showed larger value-dependent plateaus during licking and sustained post-consumption signals (ANOVA). GLMs revealed gradients of contributions of different task components (time in trial, licking, solution concentration, and solution history) along the anterior-posterior axis of the striatum (ANOVA conducted on delta ΔR^2). Specifically, a greater representation of value and solution history was observed in more rostral striatal subregions. PCA trajectories diverged by solution concentration even when lick counts were matched, indicating value coding independent of motor output. **Conclusions & Significance:** Striatal DA release is neither globally homogeneous nor purely motor-linked during consumption; instead, it exhibits a coordinated gradient wherein posterior regions rapidly signal trial initiation while anterior/ventral regions preferentially encode integrated value. These findings provide the first striatum-wide, spatiotemporal map of DA dynamics during adaptive consummatory behavior, advancing our understanding of how distributed DA signals represent multiple facets of consumption behavior.

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Poster

PSTR462: Dopamine Waves and Their Effects

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.08/GG2

Topic: H.04. Emotion

Support: Bourse de recrutement de la Fondation du CHU Sainte-Justine

Title: Anatomical characterization of VGLUT3-positive projections from the raphe nuclei to the lateral septum

Authors: *L. I. ELVERS[1,2], S. VAN DER VELDT[2], G. DUCHARME[2], B. AMILHON[1,2]; [1]Univ. de Montréal, Montreal, QC, Canada; [2]Ctr. de recherche Azrieli, CHU Sainte-Justine, Montréal, QC, Canada

Abstract: The lateral septum integrates diverse afferents from multiple brain regions, including the raphe nuclei (RN). The topography of LS inputs participates in region-specific functions: spatial coding in the dorsal LS and emotional regulation in the ventral LS. RN-LS inputs comprise glutamatergic axons, characterized by the vesicular glutamate transporter type 3 (VGLUT3). In many LS subregions, these projections form pericellular baskets, densely surrounding local LS neurons. This project aims to provide a comprehensive overview of VGLUT3-positive RN inputs to the LS, with focus on sex differences. Our aims are to 1- characterize the expression pattern and density of VGLUT3+ terminals in the entire LS, 2- quantify the degree of colocalization with serotonin (5-HT), which partially overlaps with VGLUT3 in the RN and 3- map the origins of VGLUT3+ inputs within the different raphe sub-regions. Using immunohistochemistry, we quantified the distribution of VGLUT3+ axons across the entire rostro-caudal axis of the LS and the extent of colocalization with 5-HT. Heat maps show that vLS has the highest density of VGLUT3+ axons while highest levels of co-expression with 5-HT are found in the dLS. Our results also suggest that density of VGLUT3+ terminals and colocalization with 5-HT are modulated by sex. Using retrograde tracing in VGLUT3-Cre mice, we identified VGLUT3+ inputs to the LS originating from several raphe subregions, including the median raphe. In addition, we uncover a subpopulation of VGLUT3 neurons ventral to the median raphe. Previous studies from our laboratory have identified VGLUT3 neurons in the median raphe that send inputs to the ventral hippocampus (vHP). We therefore used 2-color retrograde tracing to identify putative LS-vHP co-projecting glutamatergic neurons and found low levels of overlap between both populations. In addition, vHP- and LS-projecting populations are spatially segregated within the raphe. Retrograde tracing also revealed VGLUT3+ inputs to the LS originating from the bed nucleus of stria terminalis (BNST), paraventricular thalamus nucleus, anterior part (PVA) and nucleus incertus (NI). Anterograde tracing revealed that RN, BNST, PVA and NI inputs tile specific sub-regions of the LS. Our findings highlight multiple sources of VGLUT3+ inputs to the LS, including but not limited to the RN. In addition, we reveal sex differences in VGLUT3-5-HT colocalization levels. Our results suggest that VGLUT3+ circuits contribute uniquely to affective behaviors such as anxiety

and motivation, potentially offering new insights into the cellular basis of emotional brain function.

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Poster

PSTR462: Dopamine Waves and Their Effects

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.09/GG3

Topic: I.03. Decision Making

Support: JSPS KAKENHI 23K27985
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Naito Foundation
Joint research and education project between Princeton University and the University of Tokyo
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Title: A coherent explanation of various dopamine patterns by online reinforcement learning of recurrent network and readout with random feedback and potential value-decay

Authors: *K. MORITA[1], A. KATO[2];
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Abstract: It has been posited that, once Pavlovian conditioning has been completed, dopamine (DA) in nucleus accumbens (NAc) exhibits a phasic response to the reward-predicting cue, resembling the temporal-difference-reward-prediction-error (TD-RPE) in the reinforcement learning (RL) theory. However, recent studies revealed heterogeneous DA responses. One study (Floeder et al. *eLife* 2024) has shown that NAc DA exhibits a ramping pattern when the inter-trial-interval (ITI) is short and the cue is dynamic (changing tone) but not when the ITI is long or the cue is fixed (fixed tone). Another study (Garr et al., 2024 *Sci Adv*) has shown that DA cue response becomes reduced if the cue-reward contingency becomes degraded, i.e., the reward is also delivered during ITIs. These studies argued that their DA responses are hard to explain by TD-RPE but can be explained if DA represents 'adjusted net contingency for causal relations (ANCCR)' (Jeong et al., 2022 *Science*). By contrast, yet another study (Qian et al., 2025 *Nat Neurosci*), using a similar but modified contingency-degradation paradigm, has shown that if reward is given after a different cue rather than during ITIs, DA response to the original cue declines to a lesser degree. They argued that it can be explained not by ANCCR but by TD-RPE with particular state representations, which can be learnt through training of recurrent neural network using TD-RPE. However, this latter model, called value-recurrent-neural-network (VRNN) (Hennig et al., 2023 *PLoS Comput Biol*), assumed symmetric feedback ('transported

weight') and offline updating ('backpropagation-through-time (BPTT)'), which are biologically not plausible, and also would not be able to explain DA ramping. We show that the abovementioned diverse DA patterns in the previous experiments could be coherently explained by biologically plausible VRNN, which (1) learns online, (2) uses random feedback instead of symmetric weights, and (3) potentially includes a slight decay of learned values (value-decay) (Tsurumi et al., 2025 *eLife* in revision; Kato & Morita, 2024/5 *bioRxiv*). Specifically, the biological VRNN could reproduce the different degrees of reduction of DA cue response in the two conditions of contingency-degradation paradigm similarly to the original VRNN with BPTT. Moreover, value-decay causes ramp-like TD-PRE in a manner depending on state representation formed by the biological VRNN, explaining the ITI- and cue-type dependent DA patterns. Notably, value-decay could enable flexible value learning, and also could promote 'feedback alignment' (Lillicrap et al., 2016 *Nat Commun*), thereby potentially making random feedback more useful for learning.

Disclosures: K. Morita: None. **A. Kato:** None.

Poster

PSTR462: Dopamine Waves and Their Effects

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Program #/Poster #: PSTR462.10/GG4

Topic: I.03. Decision Making

Support: DFG Grant PE1627/5-1

Title: Dopamine Effects on Explore-Exploit Behavior and the Role of Interindividual Differences

Authors: *E. SMITH[1], T. VAN EIMEREN[2,3], K. KNAUTH[1], D. TUZSUS[1], D. MATHAR[1], J. PETERS[1];
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Abstract: Dopamine (DA) regulates key aspects of decision-making, such as explore-exploit behavior, i.e., choosing between novel options and known, rewarding ones. Imbalances in this trade-off may underlie maladaptive decision-making in psychiatric disorders linked to DA dysfunction, e.g., substance use disorders and schizophrenia. While pharmacological studies implicate DA in explore-exploit decisions, mixed findings suggest effects may depend on interindividual differences related to baseline DA function. To address this, we examined how increased DA neurotransmission affects explore-exploit behavior in reinforcement learning. In a randomized, double-blind, placebo-controlled preregistered study (https://osf.io/a4k9j/), we collected an original dataset by administering the DA precursor L-DOPA to N = 75 healthy

participants (32 female) performing a restless four-armed bandit task. We further pooled our data with Chakroun et al. (2020) for a total N = 106 to reassess reported effects of L-DOPA on uncertainty-based exploration in a large sample. Using a model-based approach, we compared Delta rule and Bayesian learner models and tested whether interindividual differences in putative markers of baseline DA, including spontaneous eye blink rate, working memory capacity, and impulsivity, modulated drug effects. In our original dataset, accounting for higher-order perseveration and total uncertainty improved model fit. However, we found no overall drug effects in our original dataset. Exploratory analyses suggested L-DOPA increased random exploration in females, pointing to potential subgroup-specific effects that warrant further investigation. In the pooled sample, we confirmed that L-DOPA vs. placebo reduced uncertainty-based exploration and further found that L-DOPA increased random exploration. Working memory capacity modulated L-DOPA's effect on random exploration, while no other interindividual differences modulated drug effects. Our study highlights the importance of modeling multiple explore-exploit mechanisms jointly to capture multifaceted choice strategies. Further work is needed to clarify DA's nuanced effects on specific explore-exploit processes and interindividual factors influencing these.

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Poster

PSTR462: Dopamine Waves and Their Effects

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Program #/Poster #: PSTR462.11/GG5

Topic: H.04. Emotion

Support: NIH RNS131987A
Stanford Bio-X Graduate Fellowship

Title: The Architecture of Serotonergic Projections in the Mouse Brain

Authors: *J. SONG[1], D. FRIEDMANN[4], Y. WU[5], A. M. MOSES[2], Q. WANG[6], X. CHEN[3], L. LUO[1];
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Abstract: Serotonin neurons exhibit considerable heterogeneity and project axons across nearly the entire mouse brain. However, the logic underlying their axon collateralization remains unclear. Here we use viral-genetic tracing, whole-brain imaging, and statistical analyses to reveal that dorsal and median raphe serotonin neurons can be organized into five projectomic groups that preferentially innervate the hippocampus, basal ganglia, cortex, medial interbrain, and brainstem/lateral thalamus, respectively. Notably, basal ganglia- and cortex-projecting groups exhibit discrete and continuous innervation subpatterns, respectively. Although spatially

intermingled in the raphe, these projectomic groups exhibit characteristic cell body distributions. Spatial transcriptomic analysis suggested mixed yet distinct molecular identities of the projection-specific serotonin neurons. Taken together, our study offers insight into brain organization from the perspective of serotonergic co-innervation and provides an anatomical resource for functional dissection of serotonin modulation of diverse physiology and behavior, as well as tools for revealing architectures of complex circuits.

Disclosures: J. Song: None. **D. Friedmann:** None. **Y. Wu:** None. **A.M. Moses:** None. **Q. Wang:** None. **X. Chen:** None. **L. Luo:** None.

Poster

PSTR462: Dopamine Waves and Their Effects

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Program #/Poster #: PSTR462.12/GG6

Topic: H.04. Emotion

Support: UK Research and Innovation [MC_UP_1201/22]
Human Frontier Science Program [LT0065/2022-L]

Title: Decoding serotonergic wiring specificity using multiregional brain organoid

Authors: *Z.-K. CHAN, C. QI, J. REN;
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Abstract: The forebrain-projecting serotonergic neurons modulate diverse functions and brain states and have been linked to mental disorders such as depression and anxiety. Recently, we have shown that these serotonergic neurons are highly heterogeneous and form subsystems defined by their projection targets (Ren *et al., 2018* Cell). There are at least two molecularly distinct subtypes with differential projections to cortical and subcortical regions (Ren *et al., 2019* eLife). However, the molecular mechanisms underlying their region-specific targeting remain unclear, largely due to the lack of suitable experimental models. Here, we established an *in vitro* assembloid system combining brainstem, hypothalamic, and cortical organoids to model the connectivity formation of forebrain-projecting serotonergic neurons. This platform allowed us to investigate the role of membrane proteins identified by proximity labelling in guiding serotonergic projections to the hypothalamus and frontal cortex. We successfully generated the self-organized brainstem organoids containing serotonergic neurons and demonstrated that they mimicked the in vivo heterogeneity of the serotonergic neurons by immunostaining, smFISH, and single-cell RNA sequencing. Further single-cell RNA sequencing analysis showed that brainstem serotonergic neurons in the assembloid strongly correlated with their corresponding developmental stages in vivo (unpublished data), confirming that the assembloid modelled the developmental trajectory of serotonergic neurons. Using viral-genetic strategies, we demonstrated that two molecularly distinct serotonergic subtypes send biased yet complementary projections to hypothalamic and cortical organoids. These findings indicate that the brainstem-

hypothalamic-cortical assembloid recapitulates key features of serotonergic innervation of cortical and subcortical targets. To profile the molecular determinants of projection specificity, we performed horseradish peroxidase (HRP)-based proximity labelling coupled with mass spectrometry to identify the membrane proteins enriched in serotonergic terminals within the hypothalamus and frontal cortex. We further employed serotonergic neuron-specific CRISPR/Cas9-mediated loss-of-function approaches to investigate the roles of candidate membrane proteins in projection targeting within the assembloid. Collectively, our work establishes a novel platform for studying the mechanisms underlying region-specific serotonergic projections and identifies potential molecules that guide serotonergic wiring specificity.

Disclosures: Z. Chan: None. **C. Qi:** None. **J. Ren:** None.

Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Program #/Poster #: PSTR463.01/GG7

Topic: H.03. Motivation

Support: NIH Grant MH132822
HHMI Gilliam Fellows Program

Title: Hippocampal oxytocin signaling controls social instability stress

Authors: *D. L. TAYLOR, M. A. CONOSCENTI, M. ZELIKOWSKY;
Dept. of Neurobio., Univ. of Utah, Salt Lake City, UT

Abstract: Disruptions to one's social stability, such as divorce, housing instability, or entrance into the foster care system represent a profound source of chronic stress. This diverse set of experiences, known as social instability, result in a number of negative outcomes, such as increases in recidivism and mood disorders as well as a lower overall socioeconomic status. The internal state produced by chronic social instability (SIN) has also been shown to generate a host of deleterious effects on socioemotional behaviors, yet the neurobiology underlying this state remain largely unknown. While oxytocin (OT) is known for its role in maternity, bonding, and social behavior, how this positive valence, "social" neuropeptidergic signaling system responds to negative, chronic social stress has yet to be determined, revealing a critical gap in our understanding of OT's neurobiological function. The Cornu Ammonis 2 region of the dorsal hippocampus (dCA2) has well established roles in social behavior and memory and has been shown to express high levels of oxytocin receptor (OxtR), highlighting the potential sensitivity of this region to changes in OT signaling. Using in-depth behavioral assessment, cFos mapping approaches, cell-type specific chemogenetic silencing, and machine learning, we discovered that SIN promotes a unique set of impacts on subsequent social behavior, including an increase in social indifference. Disrupting OT signaling during the SIN period reversed the effects of SIN to promote social indifference, suggesting that OT signaling plays a key role in the establishment

and expression of the SIN state. We further identified a necessary role for OxtR+ dCA2 neurons in SIN-induced social indifference behaviors. This work reveals how the brain encodes internal states produced by chronic social instability stress to impact future behavior, and questions the canonical role for oxytocin in regulating positive prosocial behaviors.

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Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Program #/Poster #: PSTR463.02/GG8

Topic: H.03. Motivation

Support: 1F31MH13159
MH132822

Title: Co-release of opposing signaling molecules from cortical neurons controls the escalation and release of aggression

Authors: *R. GATLIN[1], S. PARK[2], H. WALKER[3], L. KRONHEIM[3], N. A. FROST[4], M. ZELIKOWSKY[3];
[1]Dept. of Neurobio., Univ. of Utah, SALT LAKE CITY, UT; [2]Dept. of Neurobio., Univ. of Utah, Salt lake city, UT; [3]Dept. of Neurobio., [4]Dept. of Neurol., Univ. of Utah, Salt Lake City, UT

Abstract: Prolonged social isolation induces a distinct state characterized by numerous impacts on behavior, including increased aggression and altered social behaviors, but the contributions of cortical circuits to these behaviors are poorly understood. Here, we find that social isolation promotes aggression and increases investigatory behaviors leading up to aggression in both male and female mice. Genetic characterization of the neuropeptidergic population of Tachykinin-2 expressing ($Tac2^+$) neurons in the medial prefrontal cortex (mPFC) reveals a population of predominately early-layer GABAergic neurons that are activated by aggressive encounters in isolated mice. *In vivo* recording of $Tac2^+$ neurons during social investigation and aggression indicates tuning to both investigation behaviors that precede aggression and aggression itself. Loss of function perturbations targeting the co-release of Neurokinin B (NkB), the stimulatory peptide encoded by the gene *Tac2*, and the inhibitory neurotransmitter GABA from mPFC $Tac2^+$ neurons, reveals dissociable functions for each signaling molecule in the distinct behaviors that tile an aggressive encounter. Specifically, GABA transmission from $Tac2^+$ neurons controls the release of aggression, whereas *Tac2*/NkB signaling controls the investigatory behaviors escalating to aggression. These findings reveal dissociable roles for opposing signaling molecules released from the same neuron in the control over aggression, suggesting a neurochemical mechanism by which internal states may exert coordinated, sequential effects on temporally sequential, coordinated behaviors.

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Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

Location: SDCC Halls B-H

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Program #/Poster #: PSTR463.03/GG9

Topic: H.03. Motivation

Support: University of Utah Seed Grant # 51900675

Title: Hypothalamic control of social state transfer

Authors: *S. PARK[1], C. KERN[2], A. DRYER[2], M. ZELIKOWSKY[1];
[1]Dept. of Neurobio., Univ. of Utah, Salt Lake City, UT; [2]Univ. of Utah, Salt Lake City, UT.

Abstract: Social isolation induces widespread, negative impacts on mental health, including increases in depression, anxiety, aggression, and social dysfunction. Importantly, these effects can extend beyond the isolated individual - impacting the health and well-being of those around them. Despite this, the biobehavioral mechanisms underlying this social transmission of stress remain poorly understood. To test this, we developed a model of social state transmission, where target male mice were socially isolated (SI) for an extended period of time, followed by co-housing with a female partner mouse. Following co-housing, the degree to which the social state of the male "transferred" onto the partner female was assessed using behavioral testing combined with computational analyses. Females co-housed with SI males exhibited increased aggression, reduced prosocial behaviors, and altered social investigation patterns when compared to control co-housing conditions. Using miniature microendoscopic imaging and loss-of-function perturbations in the partner female brain, we identified a role for hypothalamic neural ensembles in the encoding and control of partner social state identification and transfer. Together, these findings suggest that hypothalamic neurons in the brain of a female represent a key node in the social transmission of the stress states of others and may contribute to how female states are influenced by the condition of partner conspecifics.

Disclosures: S. Park: None. **M. Zelikowsky:** None.

Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR463.04/GG10

Topic: H.03. Motivation

Title: Extended amygdala circuit control of social defense

Authors: *M. A. CONOSCENTI, L. MALADY, C. REYNOSO FERNANDEZ, M. ALLEN, M. ZELIKOWSKY;
Dept. of Neurobio., Univ. of Utah, Salt Lake City, UT

Abstract: The circuits underlying adaptive territorial aggression and social avoidance have been well characterized, but little work has examined how the brain controls the distinct phases of defensive social behavior. Using deep behavioral analyses combined with computational approaches, we have identified that social defense behaviors lie along a continuum, with animals flexibly moving through different defensive nodes on the continuum depending on the temporal and spatial proximity of a social threat, the valence of that threat, and an animal's own internal state as shaped by past experience. To identify the neurobiological locus that exerts control over this continuum, we targeted the dorsal aspect of the bed nucleus of the stria terminalis (dBNST), which has known roles in stress, anxiety, and social behavior. Importantly, the dBNST is heavily populated by neuropeptidergic cell types, including those that express the stress-sensitive neuropeptides tachykinin 2 (Tac2) and corticotropin-releasing hormone (CRH), further supporting the idea that this region could serve as an integrator of stress and social information to guide adaptive behavior. Here, we test the hypothesis that the dBNST plays a central role in the orchestration of social defensive behavior via unique, genetically-defined, neuropeptide-releasing cellular ensembles. Using optogenetics targeted to Tac2+, CRH+ or Tac2+CRH+ cells, *in situ hybridization*, and *in vivo* calcium imaging, we discovered that each of these neuropeptide+ dBNST cell populations control dissociable aspects of defensive social behaviors. Critically, we found that these dBNST subclasses project to the ventromedial hypothalamus to control social defensive behaviors including aggression, identifying a functional circuit by which neuropeptide+ cells in the dBNST exert their influence. Collectively, our findings illustrate a critical role for dBNST neurons in defensive social behavior.

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Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Program #/Poster #: PSTR463.05/GG11

Topic: H.03. Motivation

Support: NIMH R01 MH132822
NSF GFRP
University of Utah Graduate Research Fellowship

Title: Nac-projecting neurons in the dbnst control social anxiety

Authors: *A. GRAMMER[1], M. ZELIKOWSKY[2];
[2]Dept. of Neurobio., [1]Univ. of Utah, Salt Lake City, UT

Abstract: Prolonged social isolation has been shown to promote a host of deleterious effects on behavior including increased social anxiety; however, the neural circuits underlying this effect are poorly understood. To address this challenge, we developed a novel behavioral task, Selective Access to Unrestricted Social Interaction (SAUSI), which measures social motivation, hesitancy, and free social interaction in mice. Using SAUSI, we discovered that prolonged social isolation produces a significant increase in social aversion. To determine the neural circuit mechanisms driving isolation-induced social aversion, we targeted a largely unknown population of neurons in the dorsal Bed Nucleus of the Stria Terminalis (dBNST) which are anatomically characterized by their projection to the Nucleus Accumbens (NAc), as we hypothesized that this projection represents a critical link between brain regions which encode the social state of the animal as well as the valence of a social conspecific, respectively. Using circuit mapping, genetic labeling, and projection-specific perturbations, we found that this circuit bi-directionally controls social aversion after isolation. Collectively, these findings support the hypothesis that this pathway lies at the intersection between social motivation and anxiety. Our project defines a mouse model of social aversion using a novel social choice assay that allows for motivated *and* free interaction, unveils isolation induced changes in neural activity in a critical social reward and aversion circuit, and explores a novel role for this circuit in isolation-induced social anxiety-like behavior.

Disclosures: A. Grammer: None. **M. Zelikowsky:** None.

Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Program #/Poster #: PSTR463.06/GG12

Topic: H.03. Motivation

Support: R00 MH117264

Title: Experience-dependent modulation of aggression is revealed by behavioral modeling

Authors: *S. MALAGON PEREZ[1], M. A. CONOSCENTI[2], M. ZELIKOWSKY[2], A. KENNEDY[3];
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Abstract: Intermale aggression evolves over multiple timescales, and the dynamics of this aggression are strongly influenced by an animal's prior experiences. However, the degree to which distinct experiences have dissociable impacts on the generation and execution of aggression remain largely unexplored. In particular, while mated male mice typically exhibit persistent aggression towards a novel intruder in their homecage, stress-exposed mice (e.g., those

that are chronically socially isolated or foot-shocked) display sporadic and transient attacks in the same setting. This raises a central question: is the underlying motivation to fight the same regardless of the experience that induces it? To address this question, we developed a mathematical model to capture animals' decisions to initiate attacks in a standard resident intruder assay. The model predicts attack behavior using a linear combination of three components: a linear filter on self and partner posture and movement features that captures the moment-to-moment sensorimotor transformations leading to attack initiation, a leaky integrator that serves as a memory trace of aggressive motivation, and a bias term that reflects an animal's overall propensity to initiate an attack. We fit this model to a large dataset of videos of mated, chronically isolated, or foot-shocked animals engaged in the resident intruder assay, where the postures of resident and intruder mice were tracked using markerless pose estimation. We found that we can fit a single linear filter across all tested animals, fine-tuning only the persistence and bias of the model to match individual animals' levels of aggression. Analysis of fit models reveals that the bias term is highly correlated with the total time animals spend fighting, whereas the time constant of the leaky integrator distinguishes different motivational regimes: mated mice exhibit longer integration time constants, whereas both foot-shocked and socially isolated mice show shorter time constants, regardless of their overall aggressiveness. Our modeling approach provides quantitative insights into how the dynamics of aggression vary across individuals, suggesting potential neural mechanisms for regulation of aggressive behavior. For example, the dual contributions of the bias and integration terms to model fit suggest that there could exist distinct neural elements regulating the overall likelihood of attack initiation vs the degree of persistence of aggressive motivation. Integration of this model with neural imaging studies could help elucidate the anatomical substrates of these two components of aggressive regulation.

Disclosures: S. Malagon Perez: None. **M.A. Conoscenti:** None. **M. Zelikowsky:** None. **A. Kennedy:** None.

Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Topic: H.03. Motivation

Support: R01MH132822
R25NS130964

Title: Defensive Social Behaviors are Organized Along a Threat Imminence Continuum

Authors: *C. P. REYNOSO FERNANDEZ[1], M. A. CONOSCENTI[2], M. ALLEN[3], L. MALADY[4], M. ZELIKOWSKY[2];
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Abstract: Defensive behaviors are a fundamental part of mammalian survival. Responses to predatory threats vary with a threat's proximity; distal threat provokes behaviors aimed at avoiding detection, while proximal threat leads to behaviors aimed at avoiding contact. The Predatory Imminence Continuum framework organizes these behaviors into 3 distinct stages: pre-encounter (vigilance and anxiety-like behaviors), post-encounter (freezing or avoidance), and circa-strike (escape or aggression). Mammalian species, such as mice, also exhibit defensive behaviors during social encounters with conspecifics. However, the topographic organization of these behaviors remain largely understudied. To determine whether social defense follows a hierarchical structure based on threat imminence, similar to antipredator behavior, we examined defensive social behaviors in mice during the resident intruder (RI) assay. Behaviors were assessed across three categories: prosocial behavior, social avoidance, and aggression, to determine how resident defensive responses shifted over time as well as in response to intruder proximity. In addition, we tested the effect of changing the state of the resident mouse (e.g. via footstress exposure) or changing the state of the intruder (e.g. via mouse strain). We found that prior stress exposure shifts the timing and structure of social defense. Stressed mice showed a faster decline in prosocial behavior, accompanied by earlier onset of both aggressive and avoidant behaviors compared to non-shocked controls. These effects were more pronounced in encounters with CD-1 (aggressive) intruders compared to BALB/c intruders. Additionally, we found that greater distances between mice were associated with increased avoidance and decreased prosocial behavior, while closer proximity led to more aggressive behaviors. These findings support the idea that defensive social behaviors shift over time according to threat imminence and that this progression is affected by stress and the threatening nature of a social conspecific. This research offers insight into how stress shapes social threat perception and defensive decision-making, with relevance to social anxiety and stress-related disorders

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Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Topic: H.03. Motivation

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Title: Social isolation reshapes courtship behavior and social vocalization

Authors: *E. CARROLL[1,2], A. COVINGTON[2], M. A. CONOSCENTI[2], R. HANSON[3], A. KENNEDY[4], M. ZELIKOWSKY[2];

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Abstract: Social communication is a vital component of courtship behavior across species. Prolonged periods of social isolation have been shown to negatively impact relationship quality, sexual behavior, and fertility. However, the impact of extended social isolation to alter mouse courtship-related ultrasonic vocalizations (USVs) and behavior has been relatively unexplored. Using a deep behavior approach, acoustic recordings, computational modeling, *in vivo* imaging, and neural perturbations, we tested whether prolonged isolation alters mating behavior, vocalizations and neural activity in group-housed (GH) and socially-isolated (SI) mice. We discovered that long-term social isolation increases mounting behavior, while disrupting Markovian behavior chains, and decreases the complexity and frequency range of USVs. To further analyze vocalizations, we used DeepSqueak to extract a set of features from each syllable and used k-means clustering to group the syllables into five classes for subsequent analysis. Strikingly, we found that SI mice, but not GH mice, alter the spectral properties of their calls in a behavior-dependent manner, producing longer, lower-frequency calls ("class 5") during mating but not during investigation or periods of no interaction. Next, we tested whether social isolation reshapes the neuronal population encoding of USVs and behavior in the hypothalamus. Isolated males with altered USVs showed increased cfos expression in the lateral preoptic nucleus (LPO), a region previously implicated in mouse USVs more generally. To further probe the role of the LPO in courtship-related vocalizations and behaviors we chemogenetically inhibited (DREADDS) the LPO of SI males. We found that inhibition of the LPO was sufficient to reverse the effects of isolation on mating and USVs. To further probe the function of the LPO, we assessed the *in vivo* activity of neurons in the LPO during mating behavior and USVs using miniature microendoscopy. We found that modulation of neural activity is correlated with periods of high USV production. We sorted neurons by the identity of the behavior or USV associated with highest mean GCaMP activity and found that isolated mice rearranged their tuning of behavioral responses with a greater focus on chasing. Finally, analysis of female behavior and responses to both GH and SI male mice in the courtship assay indicated the negative effects of isolation on successful courtship. Collectively, our findings indicate that SI negatively modulates mouse courtship behaviors and song, and that this modulation is encoded by unique ensembles of neurons in the LPO.

Disclosures: E. Carroll: None. **A. Covington:** None. **M.A. Conoscenti:** None. **R. Hanson:** None. **A. Kennedy:** None. **M. Zelikowsky:** None.

Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR463.09/GG15

Topic: H.03. Motivation

Title: Inhibitory and disinhibitory connections between MeA-GABA neurons and a hypothalamic area for aggression control

Authors: ***N. JANA**[1], A. BALEISYTE[2], R. SCHNEGGENBURGER[1], O. KOCHUBEY[1]; [1]Lab. of Synaptic Mechanisms, EPFL, Brain Mind Inst., Lausanne, Switzerland; [2]Lab. of Mol. Genet., Rockefeller Univ., New York, NY

Abstract: Aggression is a fundamental social behavior displayed by most animals, critical for the success of animal populations. The medial amygdala (MeA) contains both excitatory and inhibitory (GABAergic) long-range projection neurons, and is an important hub for processing social cues. Optogenetic stimulation of MeA^{GABA} neurons has been shown to trigger inter-male aggression (Hong et al. 2014); however, this effect depends on the channelrhodopsin variant employed (Baleisyte et al. 2022). Furthermore, the downstream inhibitory or disinhibitory actions caused by MeA^{GABA} neurons to control aggression, remain elusive. The ventromedial hypothalamus, ventrolateral part (VMHvl), is a central node for the control of aggression (Lee et al., 2014), and it is surrounded by the tuberal area (TU) rich in inhibitory GABA neurons. We analyzed the connectivity from MeA^{GABA} neurons to the $VMHvl^{Esr1}$ and the TU^{GABA} neurons using optogenetically-assisted circuit mapping in $VGAT^{Cre}$ x $Esr1^{Flp}$ mice. This revealed direct inhibitory inputs from MeA^{GABA} to $VMHvl^{Esr1}$ neurons (connectivity, 58%; n = 24 recordings), but also connections from MeA^{GABA} to TU^{GABA} neurons (connectivity 44%; n = 27). The TU^{GABA} neurons, in turn, inhibit $VMHvl^{Esr1}$ neurons with 100% connectivity (n = 21). Thus, a putative inhibitory - as well as an indirect disinhibitory pathway from MeA^{GABA} neurons to the VMHvl likely exist. We performed resident-intruder tests using $VGAT^{Cre}$ x $Esr1^{Flp}$ mice crossed to the CD1 strain, and Balb/c intuders, to ensure reliable baseline aggression. After expression of $ChR2^{H134R}$ in MeA^{GABA} neurons, optogenetic stimulation of MeA^{GABA} axons in the VMHvl robustly triggered aggression (5 ms pulse width, 20 Hz). This effect was also observed with Chrimson, but not with the faster excitatory opsin Chronos. To dissect the role of the VMH^{Esr1} neurons downstream of MeA^{GABA} neurons in aggression control, as well as the role of TU^{GABA} neurons as a putative disinhibitory link, we performed the same experiment under simultaneous chemogenetic inhibition of either VMH^{Esr1} or TU^{GABA} neurons using hM4Di. Preliminary data suggest that chemogenetic inhibition of VMH^{Esr1} neurons caused a decreased 'background' aggression as expected, but in both cases optogenetic stimulation of MeA^{GABA} axons with $ChR2^{H134R}$ continued to stimulate aggression. Further experiments are needed to isolate the possible opposing roles of inhibitory and disinhibitory pathways from the MeA to the VMHvl in aggression control, and to unravel the mechanism(s) underlying the differential efficiency of channelrhodopsin variants in stimulating aggression.

Disclosures: N. Jana: None. **A. Baleisyte:** None. **R. Schneggenburger:** None. **O. Kochubey:** None.

Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Program #/Poster #: PSTR463.10/HH1

Topic: H.03. Motivation

Support: NIH Grant R15HD110925
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Title: Familiarity gates socially transmitted aggression via the medial amygdala

Authors: M. ADJEI[1], ***J. C. NORDMAN**[2];
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Abstract: Aggressive behavior can be acquired through observation, providing adaptive advantages but also posing significant social risks. Individuals repeatedly exposed to aggression are more likely to engage in violent behavior later in life. Yet, the environmental factors and neural mechanisms underlying observationally acquired aggression remain unclear. Here, we propose that social familiarity with an aggressor is critical for activating neural circuits in observers that primes aggression. To investigate this, we established a novel behavioral paradigm termed "socially transmitted aggression (STA)," in which witness mice observed either familiar or unfamiliar demonstrators attacking intruder mice. Remarkably, witnesses displayed increased aggression only after observing familiar demonstrators, with no effect from unfamiliar ones. Given that excitatory neurons in the posterior ventral segment of the medial amygdala (MeApv) have been implicated in aggression priming, we hypothesized these neurons might be involved in STA as well. Supporting this hypothesis, fiber photometry revealed selective activation of excitatory MeApv neurons during familiar, but not unfamiliar, demonstrator attacks. Optogenetically inhibiting these neurons suppressed STA, while activating them during unfamiliar demonstrator attacks promoted aggression. These results establish social familiarity as essential for the observational transmission of aggression and identify excitatory MeApv neurons as critical mediators of this phenomenon, offering potential avenues for clinical intervention.

Disclosures: M. Adjei: None. **J.C. Nordman:** None.

Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

Location: SDCC Halls B-H

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Topic: H.03. Motivation

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JP 22H04922 (AdAMS)

Title: Increased social interaction and anxiety-like behaviors in FLRT2 deficient mice.

Authors: *S. YAMAGISHI[1], F. ETO[2], Y. SHINODA[3], I. YAO[4], K. TAKAO[5], T. MIYAKAWA[6], K. SATO[7];
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Abstract: During cortical development, migrating neurons and pathfinding axons are guided by molecular cues within the extracellular matrix or on the surface of ambient cells. These cues are interpreted as attractive or repulsive, depending on the set of receptors and signal transducers the cell expresses. We previously identified fibronectin leucine-rich transmembrane protein (FLRT) family as a ligand of Unc5 proteins, a well-known Netrin receptors. FLRT2 is expressed in the cortical plate (CP) and inhibited migration of Unc5D+ cells in the subventricular zone (SVZ). The upper layer neurons in FLRT2 mutant mice showed earlier migration to CP, indicating the repulsive function of FLRT2. However, the behavioral phenotype of FLRT2 deficient mutant mice was unclear. Here, we comprehensively analyzed behaviors of Emx1 cre induced- FLRT2 conditional knock-out mice using the test battery, including rotarod, T-maze, Barns maze, fear conditioning, prepulse inhibition, tail suspension, forced swim, object location test, pattern separation test, open-field, light/dark transition, elevated plus maze, hot plate test and social interaction tests. Among these tests, we found that mutant mice showed significant enhancement of anxiety-like behaviors (light/dark transition and elevated maze tests), pain sensitivity (hot plate test) and social behavior (social-interaction test). Furthermore, exploratory locomotor activity was decreased (open-field and Y-maze tests). Next, we analyzed the amino acids contents in the brain by matrix-assisted laser desorption/ionisation (MALDI) based imaging mass spectrometry. We found that serotonin content in the forebrain of FLRT2 cKO is higher than control mice. These results suggest that serotonin of forebrain might affect the behaviors of FLRT2 deficient mice resulting in increased social interaction.

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Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Program #/Poster #: PSTR463.12/HH3

Topic: H.03. Motivation

Support: NIH Grant R01DK136810

Title: A novel homecage operant task reveals dopaminergic modulation of social motivation in mice

Authors: *Y. CHEN, S. E. MALONEY, A. V. KRAVITZ;
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Abstract: Deficits in social motivation are a core feature of many neurodevelopmental disorders, including autism spectrum disorder. While a range of tools exists to assess social behavior in rodents, many current approaches can be limited in throughput, may introduce stress, or lack ecological validity. To address these challenges, we developed a new, automated social operant task that operates continuously within the homecage. In this task, mice learned to nosepoke to open a door to interact with a mouse in a neighboring cage, while proximity sensors tracked the position of each mouse near the door. Our homecage design can run around-the-clock without experimental intervention, reducing handling stress and allowing for monitoring of circadian rhythms. To validate our novel task, we tested C57BL/6J mice (both sexes, around postnatal day 60), individually housed with an empty adjacent cage for five days. A same-sex social partner was then introduced for nine days. Mice nose-poked significantly more when the social partner was present vs. the empty cage (n=9, paired t-test, $p<0.0001$), demonstrating that the task effectively captures socially motivated behavior. Given prior literature, we tested whether this social behavior depended on dopamine function. Blocking dopamine D1 receptors with SCH23390 reduced social seeking (n=14, Wilcoxon signed-rank test, p=0.033, Bonferroni-corrected) without affecting overall activity (p=1.0) or feeding (p=0.78), demonstrating that blocking D1 receptors selectively impaired social motivation. Blocking dopamine D2 receptors with haloperidol reduced social seeking, overall activity, and feeding (n = 14, all $p<0.05$, Bonferroni-corrected), suggesting that blocking D2 receptors causes a general reduction in behavior that was not specific to social seeking. No significant sex differences were found on any measured metric. We also examined circadian rhythms of social behavior. Relative to the circadian rhythm for feeding, social behavior was delayed by 1.80 (± 0.25) hours (n=10, Wilcoxon signed-rank test, p=0.0020). This means that mice first addressed their caloric needs each day, and then focused on socializing. Overall, our homecage-based social motivation task offers a new way for studying social motivation, which may be particularly valuable for studying disorders that involve both social and circadian disruptions.

Disclosures: Y. Chen: None. **S.E. Maloney:** None. **A.V. Kravitz:** None.

Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

Location: SDCC Halls B-H

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Program #/Poster #: PSTR463.13/HH4

Topic: H.03. Motivation

Support: NIMH: 1R15MH118627-01
Vassar College Internal Research Funds

Title: Oxytocin has a bidirectional effect on sociability and VTA activity in social and asocial mice

Authors: *S. SKLAR[1], S. BABITSKY[1], A. BISHOP[1], K. BILLOW[1], N. LAI[1], B. ZUPAN[2]; [2]Psychological Sci., [1]Vassar Col., Poughkeepsie, NY

Abstract: Central oxytocinergic (OTergic) signaling is a critical modulator of social behavior. In rodents, circuit-specific OT effects modulate prosocial, avoidant, and aggressive behaviors. Various studies have shown that activation of OT receptors (OTRs) in brain regions such as the nucleus accumbens (NAc) increases, while activation of OTRs in the bed nucleus of the stria terminalis (BNST) decreases social approach. Furthermore, factors such as cooperative or competitive environments, social dominance, sexual experience, age, and genetic variability modify OT signaling and social behavior, although causal relationships between many of these have yet to be elucidated. Using a single-chamber, indirect-contact sociability assay, we previously found that FVB male mice exhibit bimodally distributed individual differences in sociability, with approximately half of the mice approaching ("social") and half avoiding ("asocial") a novel conspecific. In male mice, a higher social dominance rank is positively correlated with greater social approach behavior and increased OTR expression in the NAc. Additionally, OXTRs in the ventral tegmental area (VTA) directly activate dopamine (DA) neurons, and the activation of the DAergic VTA-NAc pathway increases both investigation of a novel social conspecific and social hierarchy position with cagemates. Here, we asked whether individual variability in FVB mouse social behavior is associated with social rank and VTA activity, and whether activation of OTR via intranasal (IN) oxytocin can modify VTA activity and/or alter individuals' sociability phenotype. Using a tube test to determine social hierarchy followed by our single-chamber sociability assay, we found no association between social dominance and sociability in FVB male mice. However, the bimodal sociability distribution was maintained and associated with altered VTA activation. Specifically, social mice had a greater number of cfos+ cells in the anterior, but not posterior VTA relative to asocial mice, a finding in line with published studies. We administered 0.3IU/2µL/nostril of OT 15 minutes before the start of our assay and found that this increased social approach and anterior VTA cfos+ cell number in asocial, but not social mice. In fact, IN OT administration reduced social approach and increased avoidance of a novel conspecific in social mice, and reduced VTA cfos+ cell number relative to saline-treated controls. This data suggests that OTergic regulation of VTA activity may contribute to individual variability in social behavior independent of social dominance-related mechanisms.

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Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Topic: H.03. Motivation

Support: HKRGC-GRF 14112523
HKRGC-GRF 14113522
HKRGC-CRF C4052-24G
CUHK 7105306

Title: Investigating brain processing of observational reward

Authors: *M. GAO[1,2], R. GOH[1,2], W. ZHIKUN[1], W. YUNG[2], Y. KE[1];
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Abstract: Given the inherently social nature of humans and other social animals, the ability to process rewards in social contexts is essential for fostering cooperation, building relationships, and navigating complex social environments. While much is known about the effects of self-reward, the behavioral and neural mechanisms underlying responses to observing others receiving rewards remain less understood. The anterior cingulate cortex (ACC) is strongly implicated in observational experiences, yet its role in observational reward is not fully understood. Using a rodent model and in vivo electrophysiology, this study investigated behavioral and neural responses in the ACC to observational reward delivery. We observed that mice exhibited heightened investigation of rewards inaccessible to them, especially when those rewards were observed being delivered to others. At the cellular level, we examined responses in ACC neurons and classified them based on the direction and magnitude of their activity during observations. We identified two types of task-related neurons in each condition: investigation-excited neurons, which exhibited increased activity during the investigation event, and investigation-inhibited neurons, which showed decreased activity during the same event. Notably, distinct clusters of ACC neurons demonstrated selective activity patterns for no delivery or observational delivery scenarios, though overlapping representations were also observed. Interestingly, there were fewer event-inhibited cells during observational reward contexts, potentially driving the increased behavioral engagement. These findings highlight the critical role of the ACC in processing rewards within social contexts, integrating information about self and others to guide behavior.

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Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Program #/Poster #: PSTR463.15/HH6

Topic: H.03. Motivation

Support: NIH grant: ZIAMH002784

Title: Modulation of mouse social interactions by prior experience is dependent on adult hippocampal neurogenesis

Authors: M. A. GONZALEZ-PEDRAZA, *M. C. TSUDA, H. A. CAMERON;
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Abstract: In the dentate gyrus of the hippocampus, new neurons are continuously generated throughout adulthood. Functionally, adult neurogenesis plays a role in attention, motivation, and responses to stressors and unpredictability. We recently demonstrated that suppressing neurogenesis in male mice decreases social aggression, implicating adult neurogenesis as an important mediator of social behaviors. Here, we further investigated the role of adult-born neurons in modulating social interaction behaviors. Experiences, whether positive or negative, have the potential to shape subsequent behavior, such as learning and memory tasks and anxiety-related behaviors. However, it is still unclear how these experiences change social behavior and how adult-born neurons are involved in these changes. To suppress adult hippocampal neurogenesis, we treated 8-week-old female and male transgenic mice expressing the herpes simplex virus thymidine kinase (TK) under a GFAP promoter with the anti-viral drug valganciclovir. After 8 weeks of drug treatment, mice with (WT) and without neurogenesis (TK) underwent either positive or negative experiences and their subsequent social behaviors were assessed. In male mice, we investigated how (1) prior positive fighting experience or (2) the negative experience of a frustrative nonreward, i.e., omission of an expected food reward, impacts aggressive behavior. Overall, positive and negative experiences modified aggression levels in male mice, but these changes were dependent on adult neurogenesis. In female mice, we are currently investigating how experience of an acute stressor influences social interaction behaviors toward conspecifics with similar negative experiences. Findings from these studies will not only provide us with an understanding of how prior experiences - whether it be aversive or appetitive- influences social behaviors but the contribution of adult hippocampal neurogenesis in these behavioral changes.

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Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Topic: H.03. Motivation

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Title: Cellular resolution spatio-molecular mapping of the human lateral septum across neuroanatomical axes

Authors: *M. ABRAMSON[1], Y. DU[1], S. V. BACH[1], I. DEL ROSARIO[1], S. E. MAGUIRE[1], H. ALGRAIN[2,1], R. MILLER[1], J. E. KLEINMAN[1,3], T. M. HYDE[1,3,4], S. HICKS[7,5,8,9], K. MARTINOWICH[1,3,6,10], R. A. PHILLIPS, III[1], S. C. PAGE[1,3];

[1]Lieber Inst. for Brain Develop., Baltimore, MD; [2]Univ. of Maryland Baltimore County, Baltimore, MD, ; [3]Dept. of Psychiatry and Behavioral Sci., [4]Dept. of Neurol., [5]Dept. of Biomed. Engin., [6]Dept. of Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD; [7]Dept. of Biostatistics, Johns Hopkins Bloomberg Sch. of Publ. Hlth., Baltimore, MD; [8]Ctr. for Computat. Biol., [9]Malone Ctr. for Engin. in Healthcare, [10]The Kavli Neurosci. Discovery Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Difficulties in social behaviors are a major component of many neurodevelopmental and neuropsychiatric disorders, but a meaningful understanding of their etiology is lacking. The lateral septum (LS), a GABAergic structure in the basal forebrain, is a key modulator of social behavior and motivated processes such as addiction and feeding behavior in non-human animal studies. Rodent literature has identified spatially and functionally distinct cell populations in the LS, which is subdivided into dorsal (LSd), intermediate (LSi), and ventral (LSv) subregions. As a densely interconnected region, the innervation patterns of the LS are topographically organized along the rostral-caudal axis in rodents. While single-nucleus RNA sequencing (snRNA-seq) studies in mice and humans have revealed broad evolutionary conservation of gene expression signatures, the spatial organization of these cell populations has yet to be mapped in human tissue at least in part due to the distortion of septal neuroanatomy during post-mortem brain processing. Additionally, available human brain atlases are cataloged in increments of several millimeters, restricting the anterior-posterior (A-P) resolution needed to perform comparative molecular neuroanatomy. Here we present the first detailed molecular atlas of the human LS with preserved anatomy using spatially resolved transcriptomics (N=3 donors), sampled across the A-P axis while retaining dorsoventral and mediolateral orientation. Using high-resolution spatial technologies and snRNA-seq, we find conservation of the canonical spatial domains of the LSd, LSi, and LSv in humans. We also identify novel marker genes of anatomical regions neighboring the LS with transcriptomic similarities, including the bed nucleus of the stria terminalis (BNST), medial septum, and diagonal band. The data generated here will enable computational inference of cellular identity in samples with suboptimal neuroanatomical presentation, allowing for future investigations of disease-associated gene expression in this region. This study provides the first in-depth neuroanatomical map of the human LS, crucial to translating the molecular foundations of LS-mediated social and motivated behaviors from model species to human.

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Poster

PSTR463: Social Motivation, Aggression, and Defense Across Species

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Program #/Poster #: PSTR463.17/HH8

Topic: H.03. Motivation

Support: NIH R01MH105592
NIM R01DA053581

Title: Spatial molecular profiling of the macaque lateral septum reveals cross-species conserved and divergent neuronal subtypes from rodents and humans

Authors: *Y. DU[1,2], M. ABRAMSON[1], S. V. BACH[1], R. MILLER[1], M. ROMAC[6,8,9], J. E. KLEINMAN[1,10], T. M. HYDE[1,10,11], S. HICKS[14,12,3,4], V. D. COSTA[8,9,7], K. MARTINOWICH[1,10,13,5], R. A. PHILLIPS, III[1], S. C. PAGE[15,10];
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Abstract: The lateral septum (LS) is a subcortical structure located along the medial boundary of the lateral ventricles. The LS regulates social behaviors that are frequently impaired in neurodevelopmental and psychiatric disorders, including schizophrenia and autism spectrum disorder. Rodent studies have identified neuronal subpopulations within the LS that control different facets of affective, motivated, and social behaviors. The rodent LS has been subdivided into dorsal (LSd), intermediate (LSi), and ventral (LSv) subdomains, based on distinct molecular signatures and anatomical connectivity. Transcriptionally distinct neuronal subtypes are distributed across these subdomains, with their spatial allocation varying along the anterior-posterior, dorsoventral, and mediolateral axes. Previously, our lab classified the neuronal subtypes within the human LS; however, the spatial topography of molecularly distinct cell types across anatomical planes has not been characterized. Because it is challenging to obtain anatomically accurate postmortem human LS samples due to its midline location and the collapse of the lateral ventricles during brain processing, we utilized the nonhuman primate (NHP) as a translational bridge between rodent and human work. We generated single-nucleus RNA sequencing data from subdissected regions of the rhesus macaque LSd, LSi, and LSv, medial septum (MS), and the ventral diagonal band (vDB). We examined the conservation of the LS subdivisions in the macaque and defined their associated molecular signatures. Through cross-species analysis of LS neuronal subtypes identified in human, macaque, and rodents, we aim to characterize species-specific gene expression patterns, establish correspondences between homologous cell subtypes across species, and uncover insights into the evolutionary development of septal circuitry. This study advances our understanding of the cytoarchitecture and neuronal heterogeneity of the LS and surrounding regions. Moreover, it lays the groundwork for future functional studies aimed at dissecting the roles of specific human LS cell subtypes in modulating social, affective, and motivated behaviors, and how their dysfunction may contribute to neurodevelopmental and psychiatric disorders.

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Poster

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Program #/Poster #: PSTR463.18/HH9

Topic: H.03. Motivation

Title: Elucidating the role of lateral septum neurotensin expressing neurons in social pursuit

Authors: *T. DALY[1], R. L. FISHER-FOYE[3], R. DURAND-DE CUTTOLI[2], H. OH[4], A. V. AUBRY[5], M. CAROLE[5], L. LI[6], S. J. RUSSO[7];
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Abstract: Social trauma can alter the way in which the brain processes social interaction. As a result, interactions that should be rewarding are interpreted as threatening. Specifically, the activation of the neurotensin positive (NT^+) neurons of the lateral septum are known to induce social avoidance behavior in stress resilient mice. Conversely, the inhibition of the NT^+ neurons of the lateral septum are known to induce social investigation behavior in stress resilient mice. However, the role of the lateral septum NT^+ neurons in the motivation for social reward has yet to be explored. In this study we use chemogenetics in neurotensin Cre-mice to manipulate NT^+ neuron activity within the lateral septum during social self-administration, an operant task where mice lever press for a juvenile social partner. These mice are subjected to chronic social defeat stress (CSDS) where they are subordinated by a CD-1 aggressor for 10 days. Following CSDS, the mice are classified as susceptible or resilient by the time they spend with a novel CD-1 mouse in the social interaction task. These mice are then exposed to novel juvenile mice in the resident intruder task where interaction and avoidance time are quantified. Preliminary results show that resilient mice lever press more than susceptible mice, suggesting that interaction with a juvenile social partner is more rewarding to this group. Additionally, we found that upon administration of CNO to activate NT^+ neurons, there was a decrease in lever pressing. This demonstrates a decrease in desire for social interaction with a juvenile, suggesting it is no longer rewarding. This research will help to further establish the importance of lateral septum NT^+ neurons in social interaction, and potentially social motivation. This work provides valuable insight on the mechanism behind specific social deficits caused by traumatic events.

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Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR464.01/HH10

Topic: H.04. Emotion

Support: Regis University Startup Funds

Title: Cea activation: trait anxiety as a determinant of valence

Authors: *E. YEVARA[1], K. SHIFFER[1], B. PETRIE[1], K. EMERY[2];
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Abstract: The central amygdala (CeA), a component of the extended amygdala, has been associated with anxiety and negative affect, particularly in the context of drug withdrawal (Koob et al., 2017). However, growing evidence indicates that CeA activation facilitates reward-seeking behaviors - even toward harmful stimuli - highlighting its involvement in both aversive and appetitive states (Warlow, 2017). For example, optogenetic activation of CeA can cause rats to exclusively pursue either cocaine or sucrose when given a choice between the two rewards (Warlow et al., 2020). Furthermore, even activation of stress systems within the CeA, specifically CRF neurons, generate positive incentive motivation and enhance both reward pursuit and self-stimulation (Baumgartner et al., 2021). These findings raise the possibility that the affective valence of CeA activation may be dependent on individual differences such as trait anxiety, which has been shown to influence reward seeking (Zalachoras et al., 2022). Specifically, high trait anxiety animals showed decreased breakpoints for palatable food rewards in response to acute stress, while low trait anxiety animals showed increased breakpoints in the same conditions (Zalachoras et al., 2022). Given the CeA's paradoxical role in both aversive and incentive behavior, it is plausible that individual differences such as trait anxiety may bias whether CeA activation generates incentive or aversive motivation. To test this hypothesis, we classified anxiety phenotype through the elevated plus maze (EPM). We then used chemogenetics to selectively activate the CeA in a conditioned place paradigm (CPP), allowing us to determine whether CeA activation is experienced as appetitive or aversive depending on anxiety phenotype. We hypothesize that CeA activation will generate a conditioned place preference in low anxiety rats but result in conditioned place avoidance in high anxiety rats.

Disclosures: E. Yevara: None. **K. Shiffer:** None. **B. Petrie:** None. **K. Emery:** None.

Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

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Program #/Poster #: PSTR464.02/HH11

Topic: H.04. Emotion

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Title: Behavioral and affective transitions across the fear-safety continuum in rodents

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Abstract: The Fear Threshold Model (Bao et al., 2024) posits that as the certainty of threat stimuli diminishes, subjective fear experiences and objective behavioral responses in animals diverge due to distinct underlying thresholds, ultimately leading to fear extinction. However, it remains unclear whether and how animals can recover their original positive behavioral repertoires and affective states in contexts previously associated with fear. To address this critical gap, we integrated the Fear Threshold Model with the Tri-Reference Point Theory (Wang & Johnson, 2012) to construct a behavioral-affective continuum ranging from "highly certain threat" to "absolute safety." Using a rat fear conditioning paradigm, we systematically tracked five key indicators—50kHz ultrasonic vocalizations (USVs), reward-seeking (lever pressing), freezing, defecation, and 22kHz USVs—across graded contexts reflecting transitions from below the minimum requirement reference point (MR), through the status quo (SQ), to the goal (G) and beyond. Our results revealed that during the initial high-threat phase (below MR), rats exhibited robust freezing, 22kHz USVs, and defecation, reflecting maximal defensive and physiological stress. As threat ambiguity increased during generalization testing (MR to SQ), 22kHz USVs declined more rapidly than other negative indicators, supporting the notion of dissociable thresholds for subjective and objective fear. In the extinction and safety acquisition phases (SQ to G), 50kHz USVs—reflecting positive affect—significantly increased, indicating partial affective recovery, whereas lever pressing remained suppressed, suggesting persistent inhibition of reward-seeking motivation. Notably, even in contexts theoretically representing "absolute safety," full recovery of pre-conditioning behavioral patterns was not observed, implying that the original baseline (pre-fear) state may lie beyond the attainable "goal" (G) after fear learning. These findings empirically validate and conceptually refine the Fear Threshold Model, demonstrating that emotional and motivational recovery after fear learning is both multidimensional and incomplete. By integrating graded behavioral measures with the tri-reference-point framework, our study presents a dynamic model of fear-safety transitions, with direct implications for understanding persistent functional impairments following trauma and for developing more effective therapeutic strategies that target both fear extinction and positive affect restoration.

Disclosures: J. Rao: None. **B. Yin:** None.

Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

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Topic: H.04. Emotion

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Title: Comparison of anxiety measures in phenotyping trait anxiety

Authors: C. WARD[1], R. CORDOVA[1], R. HILLS[1], M. JONES[1], G. SCALERCIO[2], *K. EMERY[1];
[1]Psychology and Neurosci., Regis Univ., Denver, CO; [2]Rocky Mountain Sch. of Expeditionary Learning, Denver, CO

Abstract: Trait anxiety is an individual organism's genetic predisposition to experience anxiety, which may alter stress behavior in response to adverse stimuli (Landgraf & Wigger, 2002). Trait anxiety has become increasingly relevant in addiction research where individual differences, particularly in reward seeking, risk taking, and negative affect, are thought to contribute to predisposition for drug seeking (Aydin et al., 2021; Clinton et al., 2008; Homberg et al., 2002). The elevated plus maze (EPM) is a well-established method for measuring and classifying trait anxiety based such that high anxiety phenotypes tend to avoid the open arms and spend more time grooming while rats with low anxiety phenotypes will spend more time in the open arms and less time grooming (Homberg et al., 2002; Landgraf & Wigger, 2002; Ravenelle et al., 2014). However, there is conflicting data as to whether other tests of anxiety, such as the open field test (OFT), can also be used to reliably phenotype trait anxiety as a stable characteristic (Cerqueira et al., 2023; Sudakov et al., 2013). Furthermore, much of the current data focuses on mice and the exploratory behavior of the open arms or center of the open field, but may not thoroughly address differences in grooming behavior (Carola et al., 2002; Cerqueira et al., 2023). Grooming behavior in response to anxiety is particularly interesting as it relies on mesostriatal dopamine pathways that are also critical in studying reward seeking (Spruijt et al., 1986). To address this, we used the EPM and the OFT to characterize trait anxiety and assess the construct validity of these two anxiety measures in rats. Preliminary data seem to suggest that the OFT yields different classifications of trait anxiety than the EPM based on both exploratory and grooming behavior. Exploring the possibility of using the OFT as an alternative to the EPM in classifying trait anxiety may be useful in expanding our understanding of trait anxiety and make this research more feasible for labs with different resource constraints.

Disclosures: C. Ward: None. **R. Cordova:** None. **R. Hills:** None. **M. Jones:** None. **G. Scalercio:** None. **K. Emery:** None.

Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

Location: SDCC Halls B-H

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Topic: H.04. Emotion

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Laureate Institute for Brain Research

Title: Neurocomputational mechanisms of cognitive avoidance during prospective planning: effects of interoceptive anxiety induction in affective disorders

Authors: *M. MEHTA[1], C. LAVALLEY[1], A. CHUNING[3], J. STEWART[1], Q. J. M. HUYS[4], S. S. KHALSA[5], M. P. PAULUS[2], R. SMITH[1];
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Abstract: Background: Aversive pruning (AP) is a computational mechanism that deters consideration of plans with short-term negative outcomes during prospective planning, even if long-term outcomes would be ideal. Thus, it can be seen as a form of cognitive avoidance. Yet, its relation to anxiety remains unknown. This study examined how AP differs in high-anxiety individuals and how it is affected by interoceptive anxiety induction. **Methods:** During functional magnetic resonance imaging (fMRI), individuals with anxious-depression (AD; N = 50) and healthy comparisons (HCs; N = 49) completed a validated planning task under baseline and anxiety induction (via inspiratory breath loading resistance of 40 cmH20/L/sec) conditions. Computational modeling estimated each participant's AP tendencies. Linear mixed effects models tested effects of group, anxiety induction, and self-reported anxiety on AP. AP was also used to predict neural activation on trials with AP responses (relative to correct responses). **Results:** ADs displayed greater AP than HCs at baseline ($F(1,126.28)=4.38$, $p=0.038$, $\eta;p;^2=0.05$). An interaction between anxiety induction and self-reported anxiety indicated a greater increase in AP was associated with higher anxiety post-induction ($F(1,106.19)= 7.63$, $p=0.007$, $\eta;p;^2=0.09$). fMRI analyses revealed that AP was associated with greater activation in the anterior insula (AI; *right***:** x=-37, y=-21, z=-5; *left*; x=39, y=-19, z=1), pre-supplementary motor area (pre-SMA; x=-5, y=-37, z=+43), and right lateral prefrontal cortex (rlPFC; x=-53, y=-15, z=+29). **Conclusion:** These findings suggest a causal link between high anxiety (trait and state) and AP. AP appears to involve affect-driven (AI) discounting processes (rlPFC) during action sequencing (pre-SMA), highlighting a novel mechanism of cognitive avoidance in anxiety that could represent a novel treatment target.

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Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

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Title: Male mice have more Pnoc-expressing neurons in the posterior oval nucleus of the BNST than female mice

Authors: *K. MEHTA[1], A. MAITI[1], M. ORTIZ-JUZA[2], N. MILLER[3], N. C. PEGARD[4], J. RODRIGUEZ-ROMAGUERA[5];
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Abstract: Prepronociceptin-expressing neurons in the bed nucleus of the stria terminalis ($Pnoc^{BNST}$ neurons) of male mice have a role in mediating pupil-linked arousal to motivationally salient stimuli and in signaling escape behavioral responses to predator odor (Rodriguez-Romaguera et al., 2020; Ortiz-Juza et al., 2025). However, the role of $Pnoc^{BNST}$ neurons in female mice has not been studied. In this study, we assessed the anatomical distribution of $Pnoc^{BNST}$ neurons across male and female mice using a transgenic Cre mouse line for Pnoc crossed with a tdTomato reporter mouse line (Pnoc-IRES-Cre x Ai9). We found no difference in the amount of $Pnoc^{BNST}$ neurons across the anterior and posterior BNST. However, when we quantified anterior and posterior sub-compartments, we found that the dorsal-lateral subregions had the highest amount of $Pnoc^{BNST}$ neurons, with the highest amount in the oval nucleus (ovBNST) across both anterior and posterior portions of BNST. Given the known sexual dimorphism in BNST, we next quantified whether these amounts were differentially expressed across sexes. We found that in anterior BNST subregions, the amount of $Pnoc^{BNST}$ neurons was not different across sexes. However, we found that in the posterior BNST, the amount of Pnoc neurons in the ovBNST was higher in males compared to females. These findings expand on previously reported sexual dimorphism of the ovBNST, which has been reported to be involved in regulating anxiety responses differently across males and females. Our future studies will investigate whether having more $Pnoc^{BNST}$ neurons in the posterior ovBNST of males has an impact on regulating arousal-mediated responses.

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Poster

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Program #/Poster #: PSTR464.06/HH15

Topic: H.04. Emotion

Support: University of Richmond School of Arts and Sciences

Title: Chronic anticipation of cued rewards elicits sex-dependent phenotypes that vary with threat and reward imminence.

Authors: *S. C. HARTVIGSEN[1], J. SHATALOV[2], O. HARDING[2], M. H. KENT[4], K. G. LAMBERT[3];
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Abstract: The ability to shift one's behavior to either avoid aversive situations or approach appetitive stimuli is critical for survival and mental well-being. Dysregulated emotional and behavioral responses in the face of threat imminence and reward imminence is seen in various mental health disorders ranging from anxiety to addiction. To examine alternative avenues for improving mental health, our lab is interested in behaviorceuticals, behavior-based interventions to increase resiliency and improve well-being. Using a rodent model of chronic positive event anticipation (Unpredictable Positive Event Response training / "UPER"), we previously found increased anticipation to confer sex-specific cognitive and emotional phenotypes depending on the specific context. In more appetitive contexts, UPER training shifts cognitive bias to be more optimistic in males. Faced with an uncertain threat, such as an open field, UPER training reduces anxiogenic behavior in both males and females. How UPER training shapes behavior when a threat is imminent, however, remains unknown. To investigate this, the current study exposed male and female rats to either four weeks of UPER training, un-cued positive events (enriched controls) or handling (handled controls). Following training, rats underwent an Imminent Challenge task to assess behavior responses in the face of a threat. Rats were individually placed in an arena containing a thick layer of sawdust on the floor and contextual cues on the walls. A physical barrier separated the opposite side where an escape ladder led to a platform with Froot Loops. Rats were allowed to explore the arena and discover they could dig to escape and reach the reward platform. The task was again repeated on Day 2 but with a thicker layer of sawdust. On day 3, the sawdust was removed and the arena was filled with water. Latency to dive, swim under the barrier and reach the Froot Loop platform was recorded. Interestingly, no group differences were found, suggesting that UPER training does not affect behavioral strategies in the presence of an imminent threat. We also recorded ultrasonic vocalizations in anticipation of, and during, positive event training. In both males and females, acquisition of the cue-reward association resulted in an increase of dopamine-modulated (50 kHz) USVs, suggesting the appetitive nature of our UPER training. Additionally, ongoing experiments are currently examining potential neurochemical differences between training groups in brain regions associated with reward and threat processing.

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Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

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Title: Cortico-striatal projections in mice regulate avoidance behavior during social threat

Authors: *S. GRIZZARD[1], N. W. MILLER[2], G. VELAZQUEZ-HERNANDEZ[3], S. M. LOWE[4], S. S. MOY[5], A. S. ZANNAS[4], N. C. PEGARD[6], A. BURGOS-ROBLES[8], J. RODRIGUEZ-ROMAGUERA[7];
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Abstract: Social behavior is critical for survival. This can be observed as motivation to approach social stimuli or as avoidance of social stimuli that represent a potential threat. While the neuronal contributions to social approach behavior have been widely studied, research on social avoidance has been limited. To study the neural circuits activated in response to a social threat, we used an automated social threat conditioning (STC) task in which social interaction leads to an aversive consequence (a mild foot-shock; McTaggart et al., 2024). This results in long-lasting social avoidance, even during other contexts or situations, as seen in the three-chamber sociability test. To identify the potential neurophysiological mechanisms mediating these behavioral effects, we examined brain-wide expression of the immediate early gene cFos (a molecular marker of neuronal activity) in mice that underwent STC, compared to control mice that did not undergo STC. STC was associated with a significant decrease in cFos activity in the infralimbic cortex (IL) and the nucleus accumbens (NAc). Since IL projects to NAc, we then tested whether selective activation of IL neurons that project to the NAc could rescue social behavior in the STC group using an optogenetics approach. Strikingly, photoactivation of IL-NAc neurons was sufficient to rescue social behavior in the three-chamber sociability test. These results indicate that social-related trauma suppresses IL-NAc activity, which seems critical for promoting normal social behavior. These results also suggest that the IL-NAc pathway promotes the signaling of social safety.

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Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

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Title: Interoceptive pathways signaling emotional states in the primate parabrachial nucleus

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Abstract: Interoception, the perception of the internal body, enables self-monitoring, while exteroception allows us to understand the external environment through sensory inputs. Environmental stimuli with affective valence may engage both systems, giving rise to emotional experiences. Elucidating the role of interoception in this process is fundamental to understanding the neuronal mechanisms underlying the generation of emotion within the body-brain axis. The parabrachial nucleus (PBN) in the dorsolateral pons is known to receive diverse bodily signals via the vagus nerve-nucleus of solitary tract pathway and via the spinal cord. The PBN also plays a crucial role in mediating escape and defensive behaviors based on nociceptive learning, suggesting that it functions to convert somatic signals into emotional responses. However, how interoceptive signals are transformed into emotional representations within PBN remains largely unknown. To address this, we identified monkey PBN neurons that receive interoceptive input by orthodromically stimulating the vagus nerve while recording single-unit neuronal activity in PBN. We then aimed to ask whether the PBN neurons that receive interoceptive inputs encode the monkey's emotional states and, if so, to characterize the nature of this representation. Electrical stimulation (0.1 - 2 mA, duration 0.3 ms, repeated 3 times with 4 ms intervals) of the vagus nerve (VNS) was delivered via a cuff-shaped electrode wrapped around the left cervical vagus nerve. To modulate emotional states, the monkey underwent Pavlovian conditioning in which red, gray, and green visual stimuli were associated with an appetitive reward, a neutral sound, and an aversive air puff, respectively. The distinctive emotional states of the monkey were validated by autonomic responses, including changes in heart rate and pupil size. Among the 285 PBN neurons examined, 152 exhibited responses evoked by left VNS and were

distributed bilaterally. Excitatory responses (n=109) were more prevalent than inhibitory responses (n=43). The VNS-excited neurons were located more ventrally and exhibited lower levels of spontaneous activity than VNS-inhibited neurons. Among VNS-responsive neurons tested in Pavlovian conditioning, nearly half of VNS-excited neurons (20/46, 43%) and a smaller proportion of VNS-inhibited neurons (5/14, 36%) showed modulation of activity depending on emotional context during the Pavlovian conditioning. These findings suggest the convergence of interoceptive and emotional signaling within the PBN and functional distinction between the two types of VNS-responsive neurons.

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Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

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Program #/Poster #: PSTR464.09/II3

Topic: H.04. Emotion

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Title: Overactivation of subgenual anterior cingulate cortex induces both negative and positive judgment biases in the common marmoset: a computational analysis

Authors: *A. GARCIA VERGARA, R. N. CARDINAL, K. G. MULVIHILL, A. C. ROBERTS;
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Abstract: Affective biases, whereby negative affective states bias cognition, have been implicated in the etiology of depression. One example is judgment bias, in which depressed individuals interpret ambiguous situations more negatively. The neurobiological underpinnings of such biases remain poorly understood, although clues come from knowledge of the pathophysiology of depression. Of significance is the subgenual region of the anterior cingulate cortex (sgACC) which is hyperactive at rest in depressed subjects, and normalized after successful treatment. Consistent with this, sgACC overactivation in the common marmoset monkey (*Callithrix jacchus)* heightens reactivity to both certain and uncertain threat, and blunts both anticipatory and motivational appetitive behavior (Alexander et al., 2023, *J Physiol*, 601(1):37-50). Marmosets (n=4; 2 female) trained on a touchscreen apparatus using liquid reinforcement performed a judgment bias task. Following pharmacological overactivation of sgACC with the glutamate transporter (GLT-1) inhibitor dihydrokainic acid (DHK), performance was assessed across two task modalities (reward vs punishment, R-P; reward vs high reward, R-HR), which map onto two motivational components: sensitivity to punishment and sensitivity to reward. Preliminary data on the R-P task (n=3), revealed that after sgACC overactivation, the ambiguous cue was treated as if it was the negative cue relative to vehicle (paired t-test, $p<.05$). A similar analysis in the R-HR task (n=4) revealed that the ambiguous cue was treated as if it

was the high reward cue ($p<.05$). Drift diffusion modeling (DDM) applied to the data suggested that the effects in both cases were due to a significant increase in the drift rate parameter (effect credible at the 95% highest density interval level). Together, these results demonstrate a causal role of sgACC in judgment bias in the marmoset. sgACC overactivation induces modality-specific shifts in responses to the ambiguous cue. DDM reveals that, in both modalities, these biases may in fact be attributable to faster accumulation of information, and not reductions in decision threshold, nor starting bias. While effects in the R-P task align with heightened threat reactivity, those in the R-HR task do not align with appetitive blunting. However, they do align with ecological studies in depression, where valuation of rewarding events is heightened despite blunted reward sensitivity in laboratory settings. These unexpected results may reflect a contrast effect: by blunting baseline reward sensitivity, sgACC overactivation may cause the high reward to appear disproportionately valuable. This is currently being tested.

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Poster

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Title: Evaluating The Operant Frustration Effect in Long-Evans rats

Authors: *Y. MARMOL CONTRERAS[1], A. THOMAS[2], D. MUELLER[3], T. A. GREEN[4]; [1]Univ. of Texas Med. Br. (UTMB), Galveston, TX; [2]Univ. of Texas Med. Br., Galveston, TX; [3]Univ. of Texas Med. Br. Galveston, League City, TX, ; [4]UT Med. Br., Galveston, TX

Abstract: Frustration is a fundamental emotion and a strong predictor of neuropsychiatric disorders, yet it remains severely understudied in pre-clinical and clinical settings. A primary challenge has been the lack of robust and reliable measures of frustration-related behavior in animal models that can yield clinically-relevant insights. To address this gap, we recently developed a way to assess frustration-related behavior concurrently with motivation-related behavior by monitoring duration of bar pressing during operant tasks. Previously, we have demonstrated and consistently replicated robust increases in duration of bar pressing during extinction and progressive ratio tasks using Sprague-Dawley rats, which we have termed the "Operant Frustration Effect". In this strain, we have also demonstrated increased force of bar pressing using our novel point-subtraction paradigm. This tool has enabled us to link cellular functions, molecular targets, and psychological factors to reactivity to frustration. For the large-scale dissemination of this tool, it is important to assess the validity of these measures in other

laboratory strains, specially those used to develop neurobiological tools such as transgenic lines. To this end, we characterized the operant frustration effect in Long-Evans rats using between-session extinction with relief, within-session extinction with relief, within-session progressive ratio, and our novel point subtraction task. We find that Long-Evans robustly increase their duration of bar pressing for both extinction sessions and for progressive ratio. In addition, Long-Evans rats exhibit increased force of pressing during our novel point-subtraction task. However, interestingly, we note persistent increased duration of bar pressing during relief periods in Long-Evans rats, which is atypical in Sprague-Dawley rats. Ongoing fiber photometry investigations seek to clarify these phenotypes. Moreover, the full extent of these differences should be investigated both behaviorally and mechanistically.

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Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR464.11/II5

Topic: H.04. Emotion

Support: NIH T32 NS007431
NSF DGE-1650116
HHMI GT15752
NIH R01MH132073
NIH F31MH138104-01

Title: Using Pupil-Light to measure pupil size in freely behaving mice

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Abstract: The dynamic regulation of arousal is critical for both internal emotional states and outward behaviors. Measurement of changes in pupil diameter has long been used to infer an animal's state of arousal to supplement investigation into neural mechanisms of internal and external state changes. Historically, this research has been largely limited to restrained animals due to methodological limitations in capturing pupil size in freely-moving animals. However, animal restraint can be a major stressor, confounding measurements of stress-sensitive physiological signals like pupil size. Existing tools performing these measurements in ambulatory animals are limited by device weight and tether flexibility, posing additional

challenges. To address these limitations, we have developed a lightweight device named Pupil-Light to accurately track fluctuations in pupil diameter in freely-moving mice with minimal impact on naturalistic behavior. This tool has been successfully validated against a head-mounted camera as a ground-truth, showing accurate tracking of pupil diameter in ambulatory mice over time. Pupil-Light has also been employed in a variety of behavioral paradigms to yield insight into the connection between internal bodily cues and outward behaviors. From this work, a variety of pupil-linked arousal changes have been identified in different behavioral states and contexts. Additionally, this device has been used alongside fiber photometry recordings of calcium activity from noradrenergic neurons in the locus coeruleus to investigate coordination in pupil-linked arousal responses and activity of this region during behavioral testing. By measuring pupillary changes alongside behavioral testing with prominent neuroscience tools like fiber photometry, Pupil-Light provides unprecedented access to dissect the relationship between arousal-linked pupillary changes, behavioral output, and neural activity.

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Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

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Topic: H.04. Emotion

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Title: Using mixed effects modeling to isolate interacting variables that influence pupil-linked arousal

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Abstract: Arousal, an evolutionarily conserved state marked by heightened neural and behavioral responsiveness, plays a key role in modulating attention, perception, and reactivity to environmental stimuli. Pupil dynamics (changes in pupil size) is a widely used proxy for arousal, correlating with behaviors like locomotion and exploration as well as neural activity across multiple brain regions that regulate motivational states. Traditional approaches to analyze pupil dynamics often rely on binary comparisons (e.g., moving vs. still or pre vs. post stimulus), which fail to account for multiple interacting variables. To disentangle the overlapping influences of behavioral and environmental variables on pupil size, we developed a multi-level mixed-effects model capable of analyzing multiple contributing factors during a head-fixed paradigm in mice on a running wheel that were presented with freely moving social stimuli. Preliminary results (n = 8) from our model revealed significant effects of several variables on pupil size. For instance, locomotion and stimulus proximity were shown to increase overall pupil size. However, when we used the same model to isolate significant interactions, we found that locomotion reduced pupil size when the social stimulus was in view. Together our data suggests that social context can modulate the direction of movement-related pupil responses and highlight the importance of accounting for context when using pupillometry measurements to infer behavioral states. Ongoing work will extend this model to assess whether pupil dynamics are affected by other contextual variables across multiple behavioral paradigms, as well as its underlying neural circuits.

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Poster

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Title: Non-invasive environmental sensing tracker for continuous monitoring of rodent home cages and experimental setups

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Abstract: Continuous monitoring of environmental elements can aid behavioral researchers in determining if unpredicted external factors influence rodent behavior both during and outside experimental paradigms. To enable this, we developed a Non-invasive Environmental Sensing Tracker (NEST) that continuously records mouse behavior and nearby environmental elements. Our technology is a battery powered wireless device that takes up less than a cubic inch of volume, and can be placed inside mouse home cages, in behavioral arenas, and in vivarium rooms. Our device integrates a thermal imaging camera to track animal displacements as well as 3-axis accelerometers and gyroscopes to monitor cage motion. Environmental elements are recorded with multiple sensors to track air quality, sound level, temperature, humidity, and ambient light. This approach allows us to track the mouse's behavioral activity relative to environmental conditions. An on-board microcontroller logs the data every second on a flash memory card, and a real-time clock (RTC) ensures all data is recorded with an accurate time stamp. Our device is tailored for animal research applications and provides turn-key monitoring capabilities that would otherwise require multiple independent devices that would take up space, potentially disturbing experiments, and require synchronization. We are currently validating the functionality of our device to demonstrate its relevance in animal research measuring mouse behaviors within home cages and a diverse set of experimental setups and tasks. These results will demonstrate that continuous monitoring of animal environments can substantially improve the reliability of experimental results.

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Topic: H.04. Emotion

Support: HHMI Gilliam Grant GT15752
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Title: Pupillary dynamics differentiate same sex versus opposite sex social interactions in mice

Authors: *M. ORTIZ-JUZA[1], J. TORMES-VAQUERANO[2], A. MAITI[1], S. PIRES[1], R. CARPENTER[1], I. CASTRO RIVERA[3], V. K. NAMBOODIRI[4], N. C. PEGARD[5], J. RODRIGUEZ-ROMAGUERA[6];
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Abstract: Changes in physiological arousal—reflected in pupil dynamics—occur in response to salient social stimuli. While such arousal responses are typically adaptive, atypical patterns are linked to social anxiety disorders. However, defining what constitutes a "typical" social arousal response requires a well-controlled behavioral paradigm to establish reliable baseline responses across different types of social stimuli (e.g. same-sex versus opposite-sex, or novel versus familiar conspecifics). In this study, we developed a head-fixed behavioral paradigm that allows for controlled measurement of pupil dynamics in response to freely moving social stimuli. Adult male and female mice (n = 8; 4 per group) were head-fixed on a running wheel and exposed to two types of novel social stimuli, a same-sex or opposite-sex mouse, moving freely within an L-shaped maze positioned in front of the subject. A social interaction window within the maze allows for naturalistic engagement while maintaining experimental control. We were able to define the pupil dynamics of a social interaction between different groups: male to male, male to female, female to female, and female to male. Interestingly, we found that both male and female mice showed a significant decrease in their pupil size in response to opposite-sex compared to same-sex mice. These results demonstrate that pupil dynamics provide a readout of various types of social interaction across male and female mice, and reveal distinct, sex-specific arousal responses. Our next step is to perform in vivo two-photon calcium imaging using this social interaction paradigm to monitor the activity of prepronociceptin-expressing neurons in the bed nucleus of the stria terminalis (*Pnoc*^{BNST} neurons). While these neurons are known to encode arousal responses to motivationally salient odors, their role in social arousal remains unexplored.

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Poster

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Program #/Poster #: PSTR464.15/II9

Topic: H.04. Emotion

Title: Pupil responses to social stimuli are associated with adaptive behaviors across the first 24 months of human life

Authors: *R. S. CARPENTER, III[1], R. GRZADZINSKI[1], M. ORTIZ-JUZA[2], J. ELISON[1], N. C. PEGARD[3], J. RODRIGUEZ-ROMAGUERA[4];
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Abstract: Pupil changes in response to well-controlled stimuli can be used to understand processes that regulate attention, learning, and arousal. This study investigates whether pupil dynamics to social stimuli are associated with concurrent adaptive behavior in typically developing infants. To accomplish this, we developed and assessed pupillary responses to Stimuli for Early Social Arousal and Motivation in Infants (SESAMI). A sample of forty-six typically developing children aged six to twenty-four months were exposed to SESAMI. Infants were presented with either dynamic social faces or non-social stimuli that controlled for luminance, motion, and auditory exposure. A multi-level mixed effects model was used to fit pupillary response functions (PRFs) that measure the change in pupil size over time as the infants fixate on either a socially dynamic face or a non-social control. This model produces separate social and non-social PRFs for both the population and each individual. An average individual deviation score from the population PRF was calculated separately for social and non-social trials yielding the pupil response index (PRI). Vineland Adaptive Behavior Scales (VABS) were regressed on social and non-social individual PRIs while controlling for age and average fixation time. We tested whether the social PRI was a statistically significant predictor of adaptive behavior by comparing the model predicted VABS scores with observed scores. An increase in PRI to social stimuli was significantly associated with better adaptive behaviors in typically developing children between 6 and 24 months of age. SESAMI combined with pupillometry and multi-level mixed effects modeling, provides a novel and scalable framework for quantifying individual differences in pupil changes in response to social stimuli relative to a population-level baseline. By demonstrating that pupil response indices during social fixations predict adaptive behaviors, we lay the foundation to test how these measures may help identify infants with intellectual and developmental disorders.

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Poster

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Location: SDCC Halls B-H

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Program #/Poster #: PSTR464.16/II10

Topic: G.03. Stress and the Brain

Title: Impact of Social Stress Contagion on Socio-Affective Behaviours in Observer Rats (Rattus Norvegicus)

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Abstract: Social contagion of stress refers to the transmission of stress-related emotional and physiological states between individuals through observation and interaction. In this process, a non-stressed subject may begin to exhibit behavioral and physiological responses similar to those of a stressed conspecific. This phenomenon is considered a form of emotional contagion and plays a key role in reinforcing social bonds and promoting adaptive behaviors in highly social species. Understanding how stress spreads through social interaction is particularly relevant in the context of mental health, where indirect exposure to stress may influence vulnerability to anxiety and affective disorders.The present study aims to evaluate the effect of exposure to a social stress contagion protocol on socio-affective behavioral responses in observer rats (Rattus norvegicus). Sixteen female Holtzman rats (8-10 weeks old) were randomly assigned to either a demonstrator (DEM) or an observer (OBS) group. DEM rats were subjected to an acute stress protocol involving exposure to predator odor, while OBS rats were handled without stress induction. During the experimental phase, OBS rats were exposed to DEM rats through a transparent, perforated partition that allowed sensory contact without direct interaction.Behavioral assessments were conducted on OBS rats both before and after exposure using three validated paradigms: the three-chamber social interaction test (to measure sociability and social preference), the open field test (to assess exploratory behavior and anxiety), and the elevated plus maze (to evaluate anxiety-related responses). Behavioral data were video-recorded and are currently being analyzed.Preliminary observations indicate that observer rats exposed to stressed demonstrators exhibit a reduction in social approach behaviors, along with increased signs of anxiety and avoidance. These findings suggest that stress can be transmitted socially in rats and may have a significant influence on emotional regulation and social behavior. This model may contribute to a better understanding of how indirect exposure to stress affects emotional processing and could have implications for the study of stress-related disorders in humans.

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Poster

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Title: Neuron-astrocyte coupling in lateral habenula mediates depressive-like behaviors

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Abstract: The lateral habenula (LHb) neurons and astrocytes have been strongly implicated in depression etiology, but it was not clear how the two dynamically interact during depression onset. Here, using multi-brain-region calcium photometry recording in freely moving mice, we discover that stress induces a most rapid astrocytic calcium rise and a bimodal neuronal response in the LHb. LHb astrocytic calcium requires the α1A-adrenergic receptor and depends on a recurrent neural network between the LHb and locus coeruleus (LC). Through the gliotransmitter glutamate and ATP/adenosine, LHb astrocytes mediate the second-wave LHb neuronal activation and norepinephrine (NE) release. Activation or inhibition of LHb astrocytic calcium signaling facilitates or prevents stress-induced depressive-like behaviors, respectively. These results identify a stress-induced positive feedback loop in the LHb-LC axis, with astrocytes being a critical signaling relay. The identification of this prominent neuron-glia interaction may shed light on stress management and depression prevention.

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Poster

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Title: Neural substrates of prosocial behaviors

Authors: ***F. SUN**[1], K. LIM[1], J. DANG[1], L. I. ZHANG[2], E. WU[1], W. HONG[1];
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Abstract: Prosocial behaviors that assist and benefit other individuals play a pivotal role in fostering social cohesion. These behaviors entail the ability to recognize the needs or negative states of others and the motivation to address them. Allogrooming is a common form of affiliative social touch across many species and can provide a stress-relieving effect. However, the neural circuitry that controls allogrooming is still largely unclear. In this study, we show that the medial preoptic area (MPOA) contains neurons that encode the stressed state of adult conspecifics and that MPOA $Vgat^{+}$ neurons bidirectionally regulate prosocial allogrooming. Moreover, prosocial comforting is associated with dopamine release and is causally regulated by a subpopulation of MPOA $Vgat^{+}$ neurons projecting to the VTA. Collectively, these findings reveal new circuit elements underlying prosocial allogrooming behavior.

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Title: Blunted neural tracking of reward prediction errors confers distinct depressive and anxiety phenotypes

Authors: ***J. BELTRAN**[1], M. MEHTA[3], G. BUTLER[4], J. MURROUGH[4], A. RADULESCU[5], L. MORRIS[2];
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Abstract: Major Depressive Disorder (MDD) is a prevalent, heterogeneous disorder, featuring overlapping symptom profiles including anhedonia and anxiety. Parsing discrete symptom domains is imperative to the development of more targeted, precise interventions. Preclinical research suggests divergence in the neural correlates of anhedonia and anxiety-related phenotypes, predominantly stemming from the ventral tegmental area (VTA). However, these neural pathways are difficult to discern in humans in part due to methodological barriers with 3-Tesla (3T) MRI. To address this, we used a probabilistic instrumental learning task during ultra-high field 7T functional MRI, which we have previously used to demonstrate VTA network changes in MDD that were not detectable at 3T. During the task, N=74 (37 Healthy; 37 MDD)

participants chose between pairs of stimuli to maximize rewards and minimize losses. Behavioral data fitted to a Q-learning algorithm within a hierarchical Bayesian framework was used to explore reward prediction error (RPE) signaling, combined with enhanced precision for examining VTA circuitry via 7T MRI. Analyses revealed a significant reduction in learning rates during reward trials (W=910, p=0.0281), but not loss trials, in MDD participants compared to controls. MDD participants demonstrated reduced neural tracking of RPEs in the nucleus accumbens (W = 882, p= 0.033) which was associated with worse anhedonic symptoms (anticipatory anhedonia: rho=0.260, p=0.0253; consummatory anhedonia: rho=0.257, p=0.0274). Meanwhile, basolateral amygdala responses to unexpected positive outcomes were associated with worse anxiety symptoms (rho=-0.245, p=0.0352). This divergence between VTA pathways replicates preclinical findings and demonstrates a cross-species dissociation of neural circuits associated with distinct symptoms of depression and anxiety.

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Title: Resilient Specific Sex-Conserved Transcriptomic Networks in the Nucleus Accumbensfollowing Chronic Social Defeat Stress in Mice

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Abstract: Major depressive disorder (MDD) is a leading cause of disability and a major contributor to suicideworldwide. Chronic stress is a key risk factor for MDD and is often modeled in rodents using the chronicsocial defeat stress (CSDS) paradigm. This model classifies animals into two groups based on theirresponses to stress: those with depression-like behaviors (susceptible) and those who maintain normalbehavior (resilient). However, the CSDS model has been predominantly studied in male mice, leaving acritical gap in understanding female-specific mechanisms, despite MDD being more prevalent in women.Identifying sex-specific molecular drivers of stress resilience is essential for advancing personalizedtreatments. We adapted the CSDS model for female mice and employed RNA-sequencing to analyzetranscriptional changes associated with susceptibility and resilience across multiple brain regions.Comparative analyses between sexes were conducted on the nucleus accumbens (NAc), a key brainregion involved in stress responses. Weighted Gene Co-Expression Network Analysis (WGCNA)identified gene modules associated with resilience in males and females. Our findings revealed significantsexual dimorphism in molecular responses to stress. However, approximately 40% of genes upregulatedin the NAc of resilient mice overlapped between sexes. WGCNA identified convergent gene moduleswith one pair showing a 25% overlap—the highest across sexes. Within these modules, GPRIN1 andSTX1A emerged as key driver genes positively correlated with resilience. Overexpression of these genesin male mice using viral manipulation induced pro-resilient effects. This study advances ourunderstanding of sex-specific resilience mechanisms, highlighting molecular pathways that could guidetargeted antidepressant development.

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Title: Dissecting VTA circuitry with ultra-high field 7T MRI: Relationships with anhedonia, depression and sex hormones

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Abstract: Anhedonia, a core symptom of major depressive disorder (MDD), includes anticipatory and consummatory subtypes, reflecting reduced motivation for future events and diminished pleasure from current experiences. Its neural basis in dopaminergic system remains unclear, especially within the mesocorticolimbic pathways originating from the ventral tegmental area (VTA) that form the VTA circuitry. Animal studies suggest that hyperconnectivity within the VTA circuitry play a crucial role in MDD and anhedonia, demonstrating impaired reward processing and dopamine-driven motivation. Limited spatial resolution of 3T MRI has hindered full exploration of the VTA circuitry, particularly deep regions, in humans. To improve signal quality and spatial resolution, we combined ultra-high-field 7T MRI with multi-echo ICA. Here, we examined VTA resting-state functional connectivity with selected mesocorticolimbic regions in MDD (n=40) and healthy controls (HC, n=38), further performed a dependency network analysis to investigate the VTA influence on the mesocorticolimbic network, and explored the role of sex hormones in these neural interactions. Anhedonia was assessed with the Temporal Experience of Pleasure Scale, and blood samples were collected to measure testosterone and estradiol levels. Consistent with preclinical models, MDD participants exhibited a pattern of VTA circuitry hyperconnectivity across mesocorticolimbic pathways, particularly pronounced in subgenual anterior cingulate cortex and ventromedial prefrontal cortex before multiple comparison correction, and showed increased network influence of VTA ($\beta_{influencing}$=-0.153, $p_{influencing}$=0.028; $\beta_{influenced}$=-0.201, $p_{influenced}$=0.040). For both anticipatory and consummatory anhedonia, we observed distinct hyperconnectivity patterns and amplified overall impact on the VTA from other regions across the entire network ($\beta_{anticipatory}$=-0.013, $p_{anticipatory}$=0.001, p_{FDR}=0.002; $\beta_{consummatory}$=-0.013, $p_{consummatory}$=0.006, p_{FDR}=0.006). Estradiol levels were associated with both VTA circuitry connectivity and influence within the mesocorticolimbic network, both across all participants ($r_{influencing}$=0.317, $p_{influencing}$=0.034; $r_{influenced}$=0.380, $p_{influenced}$=0.011) and within the MDD group ($r_{influencing}$=0.526, $p_{influencing}$=0.008; $r_{influenced}$=0.556, $p_{influenced}$=0.005). These findings indicated enhanced VTA circuitry connectivity and influence in MDD and anhedonia, reveal selective network dysfunction across anhedonia types, and implicate estradiol as a potential modulator of VTA circuitry involved in reward processing and motivation deficits in MDD.

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Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR464.22/JJ2

Topic: H.04. Emotion

Title: Boldine Attenuates Chronic Unpredictable Stress-Induced Depression-Like Behavior via Modulation of Neuroinflammation and 5-HT_{3A} Receptor in Rats

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Abstract: Abstract Major depressive disorder is a debilitating condition linked to neuroinflammation, oxidative stress, and dysregulated serotonin (5-HT) signalling. Boldine (BDN), a natural aporphine alkaloid with antioxidant and neuroprotective properties, has not been extensively studied for its antidepressant potential via serotonin receptor modulation. This study investigated the effects of BDN on chronic unpredictable stress (CUS)-induced depression-like behaviour in male Wistar rats n=8 per group (200-220 g, 12-14 weeks old), focusing on neuroinflammation, oxidative stress, monoamine levels, and 5-HT3 receptor modulation. Rats were subjected to CUS for 42 days and treated with BDN (20, 40, or 80 mg/kg) or vortioxetine (VORT, 20 mg/kg) from days 22-42. In results CUS significantly altered behavioural functions (###p<0.001 n=8) while BDN (80 mg/kg) significantly alleviated anhedonia, immobility, and anxiety-like behaviours. Two-way repeated measures ANOVA showed significant treatment and time effects on body weight, sucrose preference, and head dipping behaviour (***p < 0.001, **p<0.01). In the forced swim test, one-way ANOVA confirmed a reduction in immobility time with BDN treatment (***p < 0.001 n=8). BDN at 40 and 80 mg/kg produced a dose-dependent improvement in behavioural parameters. One way ANOVA followed by Dunnet post hoc test showed CUS increased serum and hippocampal cortisol, oxidative stress (elevated malondialdehyde, reduced glutathione, superoxide dismutase, catalase), and pro-inflammatory markers NLRP3, IL-1β (###p<0.001 n=4) which BDN 40 and 80 mg/kg effectively normalized (***p<0.001). High-performance liquid chromatography showed that BDN restored hippocampal dopamine, norepinephrine, and serotonin levels (**p<0.01 n=4). RT-PCR analysis demonstrated that BDN 80 downregulated hippocampal *HTR3A* and upregulated *HTR1A* gene expression (*p<0.05), suggesting serotonergic modulation. Histopathological evaluation confirmed BDN's neuroprotective effects, preventing CUS-induced neuronal damage in the CA1 and CA3 hippocampal region. These findings indicate that BDN exerts antidepressant effects by mitigating oxidative stress, suppressing NLRP3 mediated neuroinflammation, normalizing HPA axis hyperactivity, and modulating 5-HT receptor signalling. Thus, BDN represents a promising multi-target therapeutic candidate for stress-related depression. **Keywords:** Boldine, chronic unpredictable stress, depression, NLRP3 inflammasome, 5-HT3 receptor, oxidative stress, neuroinflammation

Disclosures: L. Akotkar: None. **U. Aswar:** None.

Poster

PSTR464: Preclinical Models of Arousal, Anxiety, Depression, Frustration, and Stress

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR464.23/JJ3

Topic: H.04. Emotion

Support: NIH Grant R01MH127820

Title: Investigating the role of the anterior cingulate cortex in stress-driven social impairments

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Abstract: Diminished social interaction is a hallmark behavior in numerous psychiatric diseases, including major depressive disorder, and has been linked to increasing suicide rates in recent years. However, the neurobiological mechanisms underlying altered prosocial behavior remain poorly understood. Utilizing a preclinical model of social trauma, the chronic social defeat stress (CSDS) model, we aim to elucidate the brain-wide neurobiological mechanisms contributing to social deficits. We used clearing and whole brain c-Fos mapping to identify alterations in brain reward circuitry following CSDS, highlighting a potential role for the anterior cingulate cortex (ACC) in regulating social behavior. We seek to delineate the role of ACC in social reinforcement and motivation using an operant social self-administration (SSA) task in conjunction with the resident intruder (RI) task. We will identify specific ACC neuronal cell types associated with stress-induced social deficits using immunohistochemistry and in vivo Ca^{2+} imaging with fiber photometry in both the RI and SSA tasks. We will also explore the causal relationship between ACC neuronal dynamics and social behaviors using chemogenetics or optogenetics in both the RI and SSA tasks. Preliminary data indicates reduced social interaction in RI and SSA acquisition in CSDS-exposed mice, indicating that there are broader deficits beyond classical social avoidance. We hypothesize that CSDS-induced alterations in ACC neuronal activity contribute to reduced social reinforcement and motivation. This research will provide novel insights into the neurobiological substrates of social deficits, a prominent transdiagnostic symptom in psychiatric disorders. By elucidating the role of ACC neuronal dynamics in stress-induced social motivation, this study has the potential to inform the development of targeted interventions for social anhedonia and other related psychiatric symptoms.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.01/JJ4

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Frequency-dependent modulation of neuronal firing by local field potential oscillations

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Abstract: Neuronal coding of behavior has long been interpreted through the lens of firing rates of single neurons. However, emerging evidence emphasizes the role of temporal coding, where the timing of spikes relative to neural oscillations carries meaningful information. A well-known example is phase coding, in which neurons preferentially fire at specific phases of the local field potential (LFP). In addition to phase, the instantaneous frequency of LFPs may provide an underexplored dimension for modulating neural activity.We investigated this using 5-minute resting-state recordings from 19 patients undergoing intracranial monitoring for drug-resistant epilepsy. From hippocampus (Hipp), entorhinal cortex (EC), anterior and posterior cingulate cortex (ACC & PCC), and orbitofrontal cortex (OFC), we isolated 359 single units and used ORCA, an unsupervised algorithm that adaptively identifies frequency bands, to decompose the LFP into instantaneous frequencies and phases below 30 Hz. We then assessed neuronal firing relative to the instantaneous phase or frequency of the LFP.We found that 8% of band-specific responses (27/357) showed significant frequency tuning (binomial test, chance = 0.01, $p < 0.000$), distributed across 13 of 19 patients. Additionally, 15% of neurons (54/357) displayed significant phase tuning ($p < 0.0001$) across 16 of 19 patients. Only 0.1% (3/357) were jointly modulated by frequency and phase, suggesting largely distinct tuning mechanisms.Frequency-modulated neurons were observed in all regions: 5% in Hipp (7/147), 11% in EC (8/70), 7% in ACC (7/100), 17% in PCC (3/17), and 8% in OFC (2/23), but without significant regional differences ($\chi^2(3, N=357) = 3.26$, $p=0.19$). Phase-modulated neurons were similarly widespread: 12% in Hipp, 24% in EC, 14% in ACC, 6% in PCC, and 17% in OFC, without a trend toward regional variation ($\chi^2(3, N=357) = 5.49$, $p=0.06$).Together, our results demonstrate that the instantaneous frequency of neural oscillations modulates neuronal firing, independent of both phase and firing rate. This novel form of frequency tuning may serve as an additional mechanism for information processing in the human brain and has implications for frequency-targeted neural stimulation strategies.**Key words:** human single neuron recordings, frequency-tuning, phase-tuning.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.02/JJ5

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Differences between white and gray matter spectral content in stereo-electroencephalography

Authors: *R. JAFRI[1], Z. JOURAHMAD[2], D. DEVARA[2], L. MATTAR[2], S. CHAMARTHI[2], A. WATROUS[2], S. A. SHETH[2], S. R. HEILBRONNER[3], N. PROVENZA[1], E. BARTOLI[2]; [2]Neurosurg., [3]Neurosci., [1]Baylor Col. of Med., Houston, TX

Abstract: Classically, neuroscientists studying functional signals in the brain have focused on gray matter (GM) — the collection of somas and axon hillocks that are responsible for generating action potentials. The signals that can be obtained from white matter (WM) — the myelinated axons that transmit information across short and long distances — have been largely ignored, and white matter has been only considered for its structure. Evidence that functional information exists in white matter has primarily come from functional magnetic resonance imaging (fMRI), demonstrating that WM signals can be task-related, time-locked, and spatially modular, just like GM signals. Scientific studies using intracranial neurophysiology, on the other hand, have typically masked out or otherwise ignored WM contacts, presumably assuming that their information content is redundant or artifactual. Here, we aimed at testing the spectral features of intracranially-recorded WM signals by means of stereo-electroencephalography (sEEG). Methods: sEEG signals were recorded from 20 patients undergoing intracranial monitoring for drug-resistant epilepsy. We obtained data from a total of 1992 contacts, 65% located in GM and 35 % in WM. Signals were collected from awake resting recordings (5 minutes). For each contact, we computed the power spectrum using the Welch method and employed a model-based decomposition (Fitting Oscillations and One-Over-F) to separate periodic and aperiodic components. Results: The aperiodic component, representing the decay rate of power over frequency, was analyzed using a mixed-effects model (matter type - GM vs. WM - fixed effect; patients included as random effects). We found that the aperiodic component was shallower in WM versus GM, indicating a different ratio in low versus high frequency power (comparison between models with/without the fixed effect: χ^2: 5.612, df:1, p: 0.0178). Conclusion: Signals recorded from WM are characterized by different spectral features with respect to WM, indicating that WM is not simply a reflection of volume conducted signals from local or distant GM, but more likely carries unique information related to signal propagation across WM tracts. This motivates future investigations on the functional and clinical relevance of WM signals, especially in the context of disorders linked to connectivity deficits, such as several psychiatric disorders.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.03/JJ6

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: UH3 NS103549
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Title: Network-level beta dynamics underlying reward bias in depression

Authors: *S. CHAMARTHI[1], J. XIAO[1,2], R. K. MATHURA[1], S. J. MATHEW[3], W. K. GOODMAN[3], N. POURATIAN[4], S. R. HEILBRONNER[1,5], S. A. SHETH[1,2,3,5], E. BARTOLI[1,5], N. R. PROVENZA[1,5,6,7];
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Abstract: Depression is marked by a reduced ability to learn from rewarding experiences, contributing to anhedonia and motivational disengagement. These symptoms reflect dysfunctions in neural circuitry that underlie adaptive decision making. In our previous work, we found that beta-band activity in the anterior cingulate cortex (aCC) mediates reward biases and is accordingly blunted in depression. While this implicates local beta oscillations in outcome evaluation and tracking, it is unclear whether these signals reflect coordinated interactions across the reward network or how such dynamics are disrupted in depression. We investigated this interplay during the probabilistic reward task in epilepsy (controls; n = 15) and treatment-resistant depression (TRD; n = 4) patients undergoing stereo-EEG monitoring. Focusing on beta-band (12-30 Hz) interactions between the aCC and the medial (mOFC) and lateral orbitofrontal cortices (lOFC), we computed connectivity using magnitude-squared coherence and phase-locking value (PLV) during the feedback period. We found that relative to TRD patients, controls showed significantly greater aCC-mOFC beta coherence following reward (cluster = 250-521ms; two-sided cluster-based permutation test, $p<0.05$) and neutral feedback (0-252, 262-1000ms), with corresponding increases in PLV. aCC-lOFC coherence was similarly greater for controls during both reward (335-560ms) and neutral (437-589ms) feedback trials. These effects suggest that attenuated cortical communication underlies impairments in reward valuation and behavioral integration in depression. To next examine whether these patterns extended to corticostriatal interactions, we analyzed connectivity between the three prefrontal regions and the ventral capsule/ventral striatum (VC/VS) in TRD patients dually implanted with deep brain stimulation electrodes. All three regional pairings exhibited greater beta coherence and PLV during neutral compared to positive feedback trials (unpaired t-tests, $p<0.001$). Although comparative VC/VS recordings were not available in controls, prior studies indicate that healthy prefrontal-striatal connectivity increases with rewards than losses. The greater synchrony during non-rewarded trials in TRD may then reflect a maladaptive shift in motivational salience encoding. Together, these findings propose that depression is characterized by reduced prefrontal integration of reward feedback and preferential processing of non-rewards within corticostriatal networks. These insights hold implications for future development of circuit-based interventions for anhedonia.

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Janssen, Liva Nova, Levo Therapeutics, Merck, Neumora, Neurocrine, Perception Neurosciences, Praxis Precision Medicines, Relmada Therapeutics, Sage Therapeutics, Seelos Therapeutics, Signant Health, Sunovion, Xenon Pharmaceuticals, XW Pharma. **W.K. Goodman:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Medtronic. F. Consulting Fees (e.g., advisory boards); Biohaven Pharmaceuticals. **N. Pouratian:** F. Consulting Fees (e.g., advisory boards); Abbott Laboratories, Sensoria Therapeutics. **S.R. Heilbronner:** None. **S.A. Sheth:** F. Consulting Fees (e.g., advisory boards); Boston Scientific, Zimmer Biomet, Koh Young, Neuropace, Varian Medical, Sensoria Therapeutics. Other; Motif Neurotech. **E. Bartoli:** None. **N.R. Provenza:** None.

Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.04/JJ7

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: 5UH3NS103446-02
U01NS117838
Foundation for OCD Research
AE Foundation

Title: Human orbitofrontal neural activity is causally implicated in obsessive-compulsive behavioral dynamics

Authors: *Y. NHO[1], L. QIU[1], R. L. SEILHEIMER[1], C. ROLLE[3], A. HORN[4], N. WILLIAMS[3], B. PESARAN[2], D. OATHES[1], K. J. MILLER[5], K. SCANGOS[1], C. H. HALPERN[1]; [2]Neurosurg., [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Stanford Univ., Stanford, CA; [4]Harvard Med. Sch., Boston, MA; [5]Neurosurg., Mayo Clin., Rochester, MN

Abstract: Biomarkers of obsessive-compulsive disorder (OCD) symptom dynamics and related behavior could advance personalized interventions. Aberrant activity in the orbitofrontal cortex (OFC) has been implicated in symptom exacerbation in OCD. We conducted a first-in-human, intracranial monitoring assay to identify high-resolution neurophysiologic correlates of OCD symptoms in the OFC. Across three individuals with treatment-refractory OCD, we recorded cortical and subcortical signals during a personalized symptom provocation task. We found that low-gamma power (30-55 Hz) in the right anteromedial OFC (amOFC) was consistently elevated during high symptom states. This biomarker was reproducible across subjects and sessions, and specific to OCD-related distress. Furthermore, electrical stimulation of the ventral basal ganglia—specifically the nucleus accumbens-ventral pallidum (NAc-VeP) cluster—which produced the most robust acute reduction in OCD-related distress, also led to a reduction in amOFC gamma power. This effect was not observed during sham stimulation. These results causally implicate amOFC gamma activity in the moment-to-moment expression of OCD symptoms and provide mechanistic insight into the functional role of OFC in symptom

dynamics. The anatomical and functional specificity of this signal, localized to the amOFC and absent in other prefrontal areas, further supports its relevance as a state-dependent biomarker. Importantly, our findings demonstrate that effective neuromodulation at a subcortical target can acutely modulate pathological cortical activity and reduce symptoms in real time. This supports the development of biomarker-informed, closed-loop DBS systems that align stimulation with brain states to enhance efficacy, reduce side effects, and enable symptom-specific targeting. This study lays the groundwork for precision neuromodulation strategies in OCD by linking clinically relevant symptom expression to modifiable neural activity. Our approach highlights the potential of individualized, network-guided treatment strategies for neuropsychiatric disease. Future studies are needed to validate this biomarker in larger cohorts and evaluate its utility in chronic DBS systems.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

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Program #/Poster #: PSTR465.05/JJ8

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: NIH Grant UH3 NS100549

Title: Approach-avoidance Behavior Modulates Ventral Striatum Theta-Alpha Power in Obsessive Compulsive Disorder

Authors: *R. A. BECHTOLD[1], M. OCHOA[3], J. R. ALTMAN[3], K. MANSOURIAN[3], S. SOUBRA[3], T. HAMRE[3], T. MERK[3], H. P. COWLEY[5], R. BOSE[5], H. YI[5], E. STORCH[4], W. K. GOODMAN[4], S. A. SHETH[3], N. R. PROVENZA[3], J. A. HERRON[2];
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Abstract: Obsessive Compulsive Disorder (OCD) is characterized by intrusive thoughts and repetitive behaviors aimed at reducing distress, often resulting in a heightened avoidance of perceived threats—even when such avoidance is recognized as excessive or irrational and may interfere with goal-directed behavior. Dysfunctional reward processing in OCD has been linked to reduced nucleus accumbens activity, suggesting diminished reward sensitivity and a decision-making style driven more by avoidance of aversive outcomes than by pursuit of potential rewards. Behavioral evidence suggests that symptom improvement in OCD may involve a shift from avoidance-driven responses to more reward-oriented decision-making, although the

underlying neurobiological mechanisms remain unclear. In six patients undergoing deep brain stimulation (DBS) for treatment-resistant OCD, we recorded neural activity from the ventral striatum (VS) during a probabilistic approach-avoidance task to examine the neural correlates of reward- and avoidance-driven behavior. During the task, patients evaluated and selected between pairs of options that varied in potential risk and reward. High-conflict trials required patients to choose between two alternatives: one with a high probability of yielding either a reward or an aversive stimulus (high-risk, high-reward), and another with a low probability of either outcome (low-risk, low-reward). Selection of the high-risk, high-reward option was interpreted as reward-driven behavior, whereas selection of the low-risk, low-reward option reflected avoidance-driven behavior. Initial results revealed elevated avoidance in symptomatic OCD patients, exaggerated approach behavior in a disinhibited patient, and more balanced choices in treatment responders, suggesting that symptom improvement may be associated with a shift toward reward-driven decision-making. During DBS stimulation, VS activity exhibited a significant increase in theta-alpha power 1-4 seconds prior to a reward-driven decision compared to an avoidant decision (n=4). This increase in theta-alpha activity occurred relatively independent of OCD symptom intensity, suggesting a common modulatory effect of approach-avoidance on VS activity. To investigate the influence of risk/conflict on the observed increase in theta-alpha power, we compared reward-driven decisions involving high risk and low risk. Reward-driven behavior elicited a significant increase in delta power during high conflict (high risk) conditions compared to low conflict (low risk) conditions (n=2), suggesting that risk/conflict modulates reward-related VS activity.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

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Program #/Poster #: PSTR465.06/JJ9

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: NIH BRAIN UH3NS136631

Title: Increased neural variability in the ventral striatum predicts response after deep brain stimulation for obsessive-compulsive disorder

Authors: *J. ZHOU[1], R. R. HANISH[2], A. ALLAM[3], R. A. BECHTOLD[6], K. MANSOURIAN[3], H. BENTLEY[3], S. SOUBRA[3], T. HAMRE[3], K. A. KATLOWITZ[3], B. J. MICKEY[8], B. KIOUS[9], B. SHOFTY[10], B. Y. HAYDEN[3], E. STORCH[4], W. GOODMAN[4], J. A. HERRON[7], S. A. SHETH[3], A. PATEL[5], N. R. PROVENZA[3];
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Abstract: Treatment-resistant obsessive-compulsive disorder (OCD) burdens many patients with severe, persistent symptoms that mar their everyday lives. The rapid rise and commercialization of neuromodulatory devices, particularly deep brain stimulation (DBS) systems, have provided an outlet for patients to gain relief. Through intracranial recording capabilities of the Medtronic Percept devices, we previously introduced low frequency neural variability as a novel biomarker of clinical response after DBS for OCD in 12 patients (Provenza et al. 2024). Here, we validate our findings in an expanded cohort including 11 additional patients, highlighting the robustness and implications of increased neural variability as a biomarker of clinical response after DBS for OCD. Improvements and simplifications to our autoregressive (AR1) model enabled us to forecast neural activity using a single learnable parameter to compare against true neural data. We verified the ability of the simplified model's goodness of fit (R^2) to distinguish predictable symptom-burdened vs. unpredictable, unburdened states, validating neural variability as a marker of response to DBS for severe OCD. Two classification models were utilized, a daily and delta regression model, with a leave-one-patient-out cross validation to predict clinical status on a given day. The daily model (AUROC = 0.79) trained and tested on patients' daily R^2 values whereas the delta model (AUROC = 0.88) normalized each patient's R^2 values with their pre-DBS mean. The improved performance of the delta model suggests that there may be a personalized shift toward variable neural activity that corresponds with an improvement towards healthy behavior in responders. We also found alterations in neural variability across the patient cohort that both preceded OCD symptom alleviation ($p < 0.0001$) and, when occurring acutely within weeks after DBS activation, correlated with eventual magnitude of symptom relief ($p = 0.02$). The ability to forecast response before phenotypic changes months in advance allows clinicians to determine if patients' treatment strategies are targeting the correct circuitry. For OCD patients locked into ritualistic behaviors, DBS therapy could act as the key intervention that triggers circuit-wide reorganization, enhancing plasticity to promote reassociation of distressing triggers. The characterization of neural variability as an OCD signature enables us to explore specific brain-behavior relationships in OCD and understand the mechanistic basis of DBS treatment.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.07/JJ10

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Multi-side neural circadian rhythmicity tracks symptom states in psychiatric and movement disorders

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Abstract: Understanding the temporal dynamics of neural activity in neuropsychiatric disorders is key to advancing brain stimulation therapies. In this study, we report circadian rhythmicity patterns in local field potentials from four patients implanted with dual-site deep brain stimulation for treatment resistant obsessive-compulsive disorder (OCD) and Tourette syndrome (TS). Stimulation was delivered simultaneously to two targets: the white/gray border of the ventral capsule and ventral striatum (VC/VS) for OCD, and the globus pallidus internus (GPi) for TS. Using chronic neural recordings onboard the DBS devices, we recorded low frequency spectral power across 919 days. Two out of four patients achieved clinical response after DBS in terms of both OCD and TS. Reproducing previous findings in OCD patients, we found that stimulation responders exhibited robust decreased neural circadian variability quantified by linear autoregressive modelling of chronic recorded 9 Hz power in the VS. The dual-target sensing allowed us to quantify the presence of independent circadian rhythmicity across two subcortical regions, the VS and GPi, within the same patients. We present that circadian variability was decreased with clinical response in both targets (pre-stimulation Linear autoregressive R^2 59.85 ± 12.94, post-stimulation 23.1 ± 14.67, Welch t-test p=5e-11), and that for a subset of patients (N=2) both rhythms showed a consistent multiple-hour phase lag. These data suggest that our previous findings related to the association between clinical response after DBS and increased VS neural variability in low frequencies may generalize to other basal

ganglia structures (specifically, the GPi). This research characterizes neural chronobiology in neuropsychiatric diseases and highlights novel biomarkers of therapeutic improvement.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.08/JJ11

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: National Science Foundation Graduate Research Fellowship under Grant No. DGE-1842494
NIH UH3NS100549
NIH UH3NS136631
McNair Foundation
Gordon and Mary Cain Pediatric Neurology Research Foundation

Title: Real-world data-driven biomarker discovery in psychiatric deep brain stimulation

Authors: *T. P. KUTCHER[1], T. FRACZEK[2], Y. ZHOU[2], K. MANSOURIAN[2], R. A. BECHTOLD[6], S. CHAMARTHI[3], W. K. GOODMAN[4], S. A. SHETH[5], J. A. HERRON[7], N. R. PROVENZA[5,1];
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Abstract: Deep-brain stimulation (DBS) for severe psychiatric illness is entering an era in which chronic neural sensing, consumer wearables, and mobile self-report can be combined to capture the lived experience of the patient. We present an integrated framework that couples (i) continuous local-field-potential (LFP) recordings from the ventral striatum (Medtronic Percept RC), (ii) daily behavioral metrics from commercially available wearables (Oura Ring; sleep, activity, heart-rate), and (iii) behavior-triggered ecological momentary assessments (EMAs) delivered by SMS. Finally, we discuss preliminary findings of neural and behavioral biomarkers in patients with DBS for OCD.
In a pilot study of a patient with severe treatment-resistant obsessive-compulsive disorder, our pipeline ingested wearable data daily, computed nightly total-sleep duration, and automatically distributed an EMA whenever sleep deviated > 25% from the individual's 7-day mean. Over 28 days, 21 EMAs were sent and 11 completed (52% compliance). Our sleep-deviation triggered EMA revealed essential context for interpreting objective neural and behavioral data, showing that significant shifts in neural and sleep patterns were due to a post-surgical depressive oversleeping episode and early work commitments while also revealing hypomanic states. We

also show preliminary findings on the link between wearable-sensed behavior and physiology and theta/alpha power power in the ventral striatum of 15 OCD patients. Our previous work identified a neural biomarker of clinical response after DBS for OCD that hinged upon the predictability and variability of 9 Hz power. We fit a linear autoregressive model to the 24/7 theta/alpha power and computed the correlation between the model residuals and continuous behavioral features acquired via Oura ring. We found statistically significant ($p<0.001$) associations between model residuals (i.e., increased neural variability) and metabolic activity and sleep phases.
Our future work will extend these methods in an ongoing clinical trial investigating DBS for bipolar disorder, along with future OCD patients. By anchoring neural biomarkers to real-world context, the approach enables data-driven discovery and paves the way for adaptive, patient-centred psychiatric neuromodulation.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.09/JJ12

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: NIH BRAIN Initiative contract UH3NS136631
McNair Foundation
Gordon and Mary Cain Pediatric Neurology Research Foundation

Title: Artifact identification and mitigation strategies for longitudinal neural data collection onboard the Medtronic Percept DBS device

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Abstract: Deep brain stimulation (DBS) is a neurosurgical procedure that involves implanting electrodes into the brain to deliver electrical stimulation and treat neurological or psychiatric conditions. Recent advances in DBS devices have enabled the ability to capture continuous neural recordings concurrently with stimulation therapy in the background of everyday life. These recordings provide the opportunity to investigate neural biomarkers of various behaviors or clinical status. However, they are susceptible to artifacts that can obscure and limit our ability to interpret neural signals. A cohort of 23 patients underwent DBS for obsessive-compulsive disorder (OCD) with the Medtronic Percept device, and we recorded longitudinal neural recordings, measuring average local field potential (LFP) power of the 9 Hz band with a resolution of 10 minutes. In these recordings, we identified an artifact in longitudinal neural recordings that occurs when the detected voltage exceeds the device's maximum sensing capabilities. When such an event occurs, the device inserts a flag value of 0xFFFFFFFF in the neural power stream. We found that overvoltage events are significantly more common in patients implanted with legacy Medtronic 3387 leads than those with newer Medtronic SenSight leads, but they do not necessarily co-occur in both hemispheres collected on a single DBS device. We demonstrate a best practice, principled strategy -- Overvoltage Event Removal (OvER) -- for correcting samples affected by overvoltage events to preserve the ability to analyze the data. This approach uses knowledge of the device's data acquisition to mathematically reconstruct the true average LFP power, excluding the effect of flag values. We show that this approach improves upon simple interpolation by maintaining the 24-hour circadian pattern commonly observed in longitudinal LFP power recordings, where the daily peak of Gaussian-smoothed LFP power data occurs at a more consistent time each day in data corrected with OvER than with interpolation. Finally, in a subset of patients who wore an Oura Ring concurrently with neural recordings (N=14 patients, 25 leads), we found that overvoltage events were more likely to occur during greater physical activity ($p=6.08\times10^{-53}$), based on the two-sample Kolmogorov-Smirnov (KS) test with a correction for autocorrelation. We also saw that low-frequency LFP power is positively correlated with physical activity in 68% of leads and negatively correlated in just 8%. This result suggests that movement artifacts may elevate low-frequency neural power. Future work will analyze the relationship between specific motions and the occurrence of overvoltages.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.10/JJ13

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: National Institutes of Health (NIH) NINDS BRAIN Initiative
UH3NS100549
McNair Foundation

Title: Deep Brain Stimulation for Obsessive-Compulsive Disorder leads to Improved Performance on the Multi-Source Interference Task and Changes in Neural Activity

Authors: V. E. GOBO[1], M. OCHOA[5], S. RAJESH[2], N. DIAB[2], A. D. GANDHI[2], E. M. DASTIN-VAN RIJN[9], M. AVENDANO-ORTEGA[3,6], G. P. BANKS[4], B. SHOFTY[10], J. A. HERRON[11], B. Y. HAYDEN[12,2,6], E. A. STORCH[3], W. K. GOODMAN[3,6], S. A. SHETH[2,6,7,8], *N. R. PROVENZA[1,6,7,8];
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Abstract: Deep brain stimulation (DBS) of the ventral capsule and ventral striatum (VC/VS) provides substantial clinical benefit in approximately 66% of participants with severe, treatment-resistant obsessive compulsive disorder (OCD). However, neural mechanisms underlying successful treatment are not well understood. One prevailing hypothesis suggests that DBS improves OCD symptoms by disrupting hyperactive connections between the VC/VS and prefrontal regions responsible for cognitive control and decision-making. To investigate the effect of VC/VS DBS on cognitive control in OCD, we used the Multi-Source Interference Task (MSIT), a well-established paradigm designed to probe cognitive control deficits by requiring participants to attend to relevant stimuli while ignoring distractions. During the task, participants are shown sets of three numbers, with one number differing from the other two. Participants are asked to press the button that corresponds with the identity of the unique number, ignoring its position. Trials are classified as congruent when the target's identity matches its position, and incongruent when they do not. Eight OCD participants completed the MSIT task at various time points (μ=16.8 ±0.77 sessions) ~1 month before and 16 months after VC/VS DBS. Seven of the eight participants achieved responder status (>35% symptom reduction), and the remaining participant was a partial responder (>25% symptom reduction).All patients had a significant reduction in reaction time for both congruent ($p = 0.03$) and incongruent trials ($p = 0.04$) following DBS. Throughout the task, we captured simultaneous local field potential (LFP) recordings that we synchronized to task behavior, and computed evoked response potentials for

congruent and incongruent trials. Analyses of pre-DBS neural data reveal a significant increase in low frequency (2-8 Hz) VS power immediately after stimulus presentation during incongruent vs. congruent trials. These findings suggest that VC/VS DBS modulates neural circuits involved in cognitive control. Our future work will investigate how this neural signature changes with changes in OCD symptom severity and task performance after VC/VS DBS.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.11/JJ14

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: NIH Grant UH3NS103549

Title: Deep Brain Stimulation Mediates the Relationship between Cognitive Control and Major Depression

Authors: *J. C. MYERS[1], A. ALLAWALA[6], S. SOUBRA[1], S. R. HEILBRONNER[2], R. MATHURA[1], E. BARTOLI[3], A. WATROUS[4], B. Y. HAYDEN[1], W. GOODMAN[5], S. J. MATHEW[5], N. POURATIAN[7], N. R. PROVENZA[4], S. A. SHETH[4];
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Abstract: Diminished cognitive control is a hallmark of major depressive disorder (MDD). People with MDD often find difficulty regulating behaviors, thoughts, and emotions in a goal-directed manner. As part of an ongoing clinical trial using deep brain stimulation (DBS) for treatment-resistant MDD, we applied DBS to the subgenual cingulate cortex (SCC) and the ventral capsule/ventral striatum (VC/VS) as patients (N = 5) performed a parametric attention control task. The task was comprised of a random dot kinematogram where patients attended to target stimuli while suppressing distractor stimuli. The task was performed iteratively (n = 29) across 9-11 days of post-neurosurgical monitoring, and DBS was delivered during 16/29 (55%) of the task sessions across patients. Depression symptom severity was also measured via the

computerized adaptive test (CAT-DI) across this duration. Results indicated a negative correlation between performance accuracy and CAT-DI, where patients performed more poorly when reporting more severe depressive symptoms, $z(23) = -4.52$, $p < 0.001$. We also observed a statistical interaction between DBS (on vs. off) and performance accuracy, where DBS reduced both symptom severity and the correlation between severity and cognitive control, $z(23) = -3.37$, $p < 0.001$. These results provide promising evidence that DBS can ameliorate cognitive control deficits in patients with MDD.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: PSTR465.12/JJ15

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

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Gordon and Mary Cain Pediatric Neurology Research Foundation
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NIH Grant R24DA064430

Title: Demonstration of a clinical monitoring platform for neuro-modulation studies

Authors: *T. M. FRACZEK[1], Y. ZHOU[1], R. HANISH[3], J. ZHOU[4], T. P. KUTCHER[3], T. MERK[2], L. DIAZ[5], N. GUITTARI[6], N. E. TREGONING[6], R. T. HIDER, Jr.[9], H. YI[10], E. C. JOHNSON[7], B. A. WESTER[8], W. K. GOODMAN[11], S. A. SHETH[1], J. A. HERRON[12], N. R. PROVENZA[1];
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Abstract: Data from distributed wearable devices is becoming increasingly critical to translational research, as it offers a unique perspective into the daily well-being of the patient, but effective integration into research and clinical practice requires a robust data management platform. This is particularly important in research involving psychiatric DBS, where symptoms can be managed by changes in stimulation, but side effects and the patient's response to stimulation outside of the clinic are still a matter of investigation. When combined with neural data, data from wearables can provide the context essential to understand patient state and train predictive models of symptoms to optimize treatment. However, the collection of multimodal data has strict requirements and demands extensive infrastructure to support both clinical and research needs. To address this need, we developed a new open-source framework to support the use of wearable data to monitor patients continuously and to aid in patient compliance and safety during a clinical trial. The system supports data processing in a reliable and automated way which is made available in the proper format, in both clinical and research contexts. For research purposes, both processed and raw data for all modalities are made available for programmatic access in a standardized and query-able way. This data can be exported for sharing alongside publications or with research collaborators via archives such as DANDI or EMBER. For clinical purposes, a combination of heuristic, standard clinical practice, and novel model-based metrics of patient state are readily available at any time to aid clinical partners in decision making regarding patient treatment. Moreover, clinicians are alerted of any significant deviations that could indicate worrying changes in the patient's condition. We present a demonstration of all these capabilities in a modular set of software packages capable of managing the end-to-end analysis pipeline from data collection, to warehousing, indexing, analysis, and presentation via a web app.

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Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.13/JJ16

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: SECIHTI CF-2023-I2663
INPRFM NC24208.0

Title: A 12 month clinical follow up of a patient diagnosed with depression revealed changes in serum serotonin levels subsequent to SSRIs treatment.

Authors: *G. PÉREZ SÁNCHEZ[1,2], L. AGUILAR GÓMEZ[2], E. BECERRIL[2], M. PONCE[3], S. JACINTO[2], L. PAVON-ROMERO[2];
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Abstract: A 12-month clinical follow-up of a patient diagnosed with depression revealed changes in serum serotonin levels subsequent to SSRIs treatment. Context. Major depressive disorder (MDD) is a prevalent and debilitating mental health disorder that affects millions worldwide. Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed to regulate serotonin levels, a key neurotransmitter associated with mood regulation.However, the long-term impact of SSRIs on serum serotonin levels remains an area of ongoing investigation. This study presents a 12-month clinical follow-up of a patient diagnosed with depression, analyzing their changes in serum serotonin levels after SSRIs treatment, fluoxetine and sertraline. By examining the biochemical response over an extended period, this research aims to contribute to a deeper understanding of the physiological effects of SSRIs and their potential implications for individualized treatment strategies. Additionally, the potential usefulness of serum serotonin as a biomarker for patients with MDD is evaluated. **Methods**. The 23-year-old male patient was diagnosed with MDD and consented to participate by signing the informed consent form in accordance with the guidelines established by the ethics committee. Blood samples were collected on a monthly basis until the twelfth month of the study. The blood sample was obtained by venipuncture in the forearm and collected in a tube without an anticoagulant; the serum was then obtained by centrifugation at 1,125 x g for 10 minutes. The levels of serum serotonin and its precursor, tryptophan, were quantified using high-performance liquid chromatography (HPLC). This case report follows the patient for 12 months. For the first six months, the patient was treated with 20 mg/day of fluoxetine. However, when there was no improvement in his clinical symptoms, his treatment was changed to 50 mg/day of sertraline. The Beck Depression Inventory was used to assess depressive symptoms. **Results**. Over the course of six months of treatment with fluoxetine, there was no observable improvement in either the clinical symptoms or the serotonin levels of the patient. However, both of these outcomes exhibited a substantial improvement following sertraline treatment. Concurrently, there was an increase in serum serotonin levels and a decrease in tryptophan levels as the sertraline treatment continued. The tryptophan-to-serotonin ratio (Trp/5-HT) exhibited a decrease during sertraline treatment. A comparison of the Trp/5-HT ratio during fluoxetine and sertraline treatment revealed significant differences, with the ratio being lower in the sertraline treatment group ($p = 0.003$).

Disclosures: G. Pérez Sánchez: None. **L. Aguilar Gómez:** None. **E. Becerril:** None. **M. Ponce:** None. **S. Jacinto:** None. **L. Pavon-Romero:** None.

Poster

PSTR465: Human Studies: Psychiatry, Imaging, and Biomarkers

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.14/JJ17

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: Herman Dana Foundation

Title: Mononuclear Cell miRNA Expression Levels in Postpartum Depression

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Abstract: Background: The pathophysiology of post- partum depression (PD) remains elusive, with microRNAs (miRNAs) implicated as possible players. Aim: We compared mononuclear cell miRNA expression levels in venous blood sampled after delivery between mothers who developed PD and those reporting no affective symptoms upon prospective follow-up as resilient controls. Methods: Delivering mothers presenting to the Hadassah Mt. Scopus Hospital with an uncomplicated pregnancy and delivery were approached for participation and assessed prospectively using structured clinical interviews. Mononuclear cell miRNA expression levels sampled in the venous blood collected shortly after delivery were compared between prospectively assessed PD and resilient control mothers. Results: Several hundred miRNAs that showed valid expression in mononuclear cells, among which several showed nominal expression differences between PD and controls. None of the differentially expressed miRNAs passed False Discovery Rate (FDR) correction for multiple testing. However, applying a blind hierarchical clustering algorithm to the list of nominally significant miRNAs showing differential expression immediately after delivery, we were able to correctly classify all sample into their respective PD and control groups with a single mistake. Significance: Our encouraging preliminary results demonstrate an informative signal in mononuclear cells sampled immediately after delivery for predicting a post-partum depressive episodes. Given the large number of miRNAs expressed in mononuclear cells, a larger sample is required to replicate these exploratory results and locate miRNAs surviving stringent multiple testing required for validating these results. Implicating a unique miRNA expression signature during the triggering of PD may shed light on immune involvement in its pathogenesis, and provide objective biomarkers for its early diagnosis.

Disclosures: T. Goltser: None. **R. Segman:** None.

Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.01/JJ18

Topic: H.08. Drugs of Abuse and Addiction

Support: R00DA043573

Title: Genetic vulnerability and resistance determine the effects of environmental impoverishment on the striatal and hippocampal transcriptomes in Collaborative Cross mice

Authors: *M. LEONARDO[1], V. MAGALHAES BORGES[2], T. SALISBURY[2], S. AKTER[2], A. Q. NATO, Jr.[2], P. E. DICKSON[2];
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Abstract: A critical factor predisposing individuals to develop addiction is environmental adversity. Genetic vulnerability partially underlies the probability of developing an addiction disorder following exposure to these adverse events. The mechanisms underlying this effect are largely unknown. Systems genetics using mouse recombinant inbred (RI) panels provides an approach for discovering these mechanisms. The Collaborative Cross (CC) RI panel is an advanced genetic population encompassing ~90% of the allelic variation in mice. Therefore, strains from the CC panel manifest extreme variation on many heritable phenotypes, including vulnerability to the effects of the environment on disease. In the present study, we used a set of four CC and four CC founder strains to identify genetic mechanisms underlying effects of environmental impoverishment on the striatal and hippocampal transcriptomes. We focused on transcriptomic changes because shifts in gene expression are foundational to higher-level changes in neurophysiology, neurochemistry, and behavior. We focused on the striatum and hippocampus because they are implicated in addiction-like behaviors. We used environmental enrichment (large cage, social housing, toys, wheels) to model a "normal" environment; we contrasted this with environmental impoverishment (small cage, isolation housing, no enrichment items) to model environmental adversity. Mice were randomly assigned to these conditions at weaning and remained housed in this way for 10 weeks. Brain tissue was then collected, and RNA-seq was performed. Our analysis yielded three primary conclusions: First, environmental impoverishment is capable of causing robust changes in striatal and hippocampal gene expression. Second, this effect is dependent on strain in that some strains were resistant to impoverishment-induced gene expression changes, whereas others were vulnerable. Third, the strain-dependent vulnerability was brain-region specific. Specifically, some strains were vulnerable in both regions, others in only one region, and some in neither. Collectively, these data reveal a genetically determined and brain-region specific effect of environmental impoverishment on the striatal and hippocampal transcriptomes. Most importantly, because the effects of brain perturbation on behavior are known to be profoundly region specific, our findings suggest that the behavioral consequences of environmental impoverishment are likely to vary significantly across individuals — both in the types of behaviors affected and in the magnitude of those effects.

Disclosures: M. Leonardo: None. **V. Magalhaes Borges:** None. **T. Salisbury:** None. **S. Akter:** None. **A.Q. Nato:** None. **P.E. Dickson:** None.

Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.02/JJ19

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA057931

Title: Intravenous fentanyl self-administration and fentanyl-induced effects on patch-clamp electrophysiology in mice from the genetically complex Collaborative Cross recombinant inbred mouse panel

Authors: *C. J. TREADWAY[1], M. LEONARDO[1], N. C. BOLEN[1], J. SISCO[1], A. KASTIGAR[1], S. BRUNTY[1], B. GOURLEY[2], S. BRUNTY[3], A. WALDEN[1], J. L. LIPOVICH[4], B. J. HENDERSON[1], P. E. DICKSON[1];
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Abstract: The ongoing opioid epidemic underscores the urgent need to understand the complex polygenic factors underlying opioid use disorder (OUD), a heritable disease with devastating public health consequences and limited effective treatments. In this regard, the interplay between genetic background and neuroadaptations to opioids that drive individual differences in resistance or vulnerability to drug dependency remain poorly understood. To address this critical gap, we integrated gold-standard behavioral and neurophysiological assays to identify genetic variation associated with the development of addiction-like behaviors and their neurophysiological correlates. To capture maximum genetic complexity, we used mice from the Collaborative Cross (CC) recombinant inbred panel and their founder strains. Using these mouse strains, we quantified intravenous self-administration (IVSA) of fentanyl and, in a separate group of mice, patch-clamp electrophysiology of the nucleus accumbens (NAc) following experimenter administered fentanyl exposure. IVSA is the gold-standard preclinical model for studying voluntary drug intake, closely mirroring aspects of human drug-taking behavior and providing a robust platform for assessing individual differences in drug-seeking and consumption. In this study, mice were surgically implanted with indwelling jugular catheters. Mice then underwent standardized fentanyl IVSA protocols. Behavioral phenotypes were quantified across acquisition, dose-response, escalation, extinction, and reinstatement phases to capture the full spectrum of addiction-like behaviors. To identify the cellular and synaptic adaptations in the NAc caused by fentanyl exposure, a separate group of CC and CC founder mice was exposed to either fentanyl (500 μg/kg IP once per day for 10 days) or saline in the context of a locomotor fentanyl sensitization assay. Twenty four hours following the final fentanyl exposure, we used whole-cell patch-clamp electrophysiology to measure intrinsic excitability and synaptic transmission in medium spiny neurons in the NAc. We analyzed these data using ANOVA with post hoc correction for multiple comparisons. Our results reveal variation in fentanyl self-administration behavior and corresponding neuronal activity in the NAc across genetically complex populations. These findings demonstrate that genetic complexity profoundly influences both fentanyl self-administration and its neurobiological correlates. This approach advances the field by leveraging genetic complexity within a translational experimental framework to dissect the complex biology of opioid addiction.

Disclosures: C.J. Treadway: None. **P.E. Dickson:** None.

Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.03/JJ20

Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA057931

Title: Fentanyl-induced locomotor sensitization in male and female mice from the genetically complex Collaborative Cross recombinant inbred panel and founder strains

Authors: *N. C. BOLEN, M. LEONARDO, J. SISCO, C. J. TREADWAY, P. E. DICKSON; Dept. of Biomed. Sci., Marshall Univ., Huntington, WV

Abstract: Fentanyl addiction is a highly heritable disease and a critical public health crisis of unknown etiology. In this regard, the genetic mechanisms underlying fentanyl-induced locomotor sensitization (FILS), a behavioral index of the neuroadaptations caused by repeated fentanyl exposure, are unknown. Although FILS itself is not addiction-like behavior, the genetic mechanisms driving FILS may overlap with the genetic mechanisms driving the addiction-like fentanyl seeking that can be quantified using the gold-standard intravenous drug self-administration (IVSA) paradigm. For example, fentanyl-induced changes in neurochemical regulation, synaptic plasticity, and gene expression may all be critical to the development of drug addiction, and fentanyl-induced changes to these systems may be detectable using the less technically demanding FILS assay. Because of the high-throughput nature of the FILS assay relative to the IVSA paradigm, FILS may provide a shortcut for identifying genetic underpinnings driving addiction-like fentanyl seeking. Moreover, FILS, in contrast to fentanyl IVSA, provides a platform in which fentanyl exposure is held constant; this allows for discovery of the genetic mechanisms driving fentanyl-induced variation in many neuronal endpoints that may underlie addiction-like fentanyl seeking (e.g., gene expression, neurophysiology, neurochemistry). With these strategies in mind, we quantified FILS in male and female mice from the genetically complex Collaborative Cross (CC) recombinant inbred panel and the eight CC founder strains. Collectively, the CC encompasses ~90% of all known genetic variation within the Mus musculus species. Used in the context of a systems genetics approach, the genetic complexity provided by the CC allows for the discovery and dissection of mechanisms underlying gene-by-environment interactions. In the present study, FILS was assessed in the CC founder strains and a subset of CC strains to establish the existence of a gene-by-environment interaction. Mice were tested in Med Associates open fields once per day for 10 days. Immediately prior to being placed in the open field, mice were treated with either fentanyl (500 μg/kg, IP) or saline. All sessions were 60 minutes. Resulting data revealed robust interactions among session, fentanyl treatment group, strain, and sex. Collectively, these data indicate strong effects of strain and sex on FILS and, in concert with the fentanyl IVSA paradigm, lay the groundwork for systems genetics discovery and dissection of the genetic mechanisms driving variation in the neuronal systems that underlie addiction-like fentanyl seeking in mice.

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Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.04/JJ21

Topic: H.08. Drugs of Abuse and Addiction

Support: P30DA060810
P50DA037844

Title: Genome-wide association study (GWAS) in heterogeneous stock rats reveals genetic architecture of attention and impulsivity

Authors: *T. MISSFELDT SANCHES[1], C. P. KING[4,5], K. ISHIWARI[6,4], A. S. CHITRE[2], B. JOHNSON[2], O. POLESSKAYA[2], L. SOLBERG WOODS[7], D. M. DIETZ[4], A. A. PALMER[2,3], P. MEYER[5];
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Abstract: The Reaction Time (RT) task is a behavioral paradigm for assessing attention and action impulsivity, two core dimensions implicated in numerous neuropsychiatric conditions, including substance use disorders (SUDs). Defining the genetic architecture of these traits can reveal biological mechanisms underlying individual variation in cognitive control and inform the development of targeted interventions. To identify genetic factors influencing RT behavior, 2369 outbred Heterogeneous Stock (HS) rats were phenotyped for RT. In each trial, rats accumulated a required hold duration (0.1-1.6 s) by maintaining their snout in a central port; hold times increased over 15 training sessions. After the hold requirement was met, an imperative stimulus light appeared above the left port. Rats then had three seconds to respond with a correct snout poke into the left port to receive a 30 µL water reward. We quantified RT-derived phenotypes, including reaction time (attention), false alarms (action impulsivity), and correct trials (performance). All animals were subsequently genotyped at ~5.5 million biallelic SNPs, and the resulting dataset was used for genome-wide association analysis (GWAS). RT-derived traits showed moderate heritability (10-25%) and similar behavioral variability across sexes. GWAS revealed 45 significant quantitative trait loci (QTLs) associated with the RT-derived traits. To refine gene prioritization within each QTL, we colocalized ($R^2 > 0.90$ with lead SNPs) the loci of interest with: (1) known missense and loss-of-function variants, and (2) variants associated with gene expression (eQTL) and splicing (sQTL) across nine brain areas. Furthermore, we tested for colocalization with over 700 addiction-relevant behavioral QTLs, identifying loci with shared genetic architecture between RT and SUD related-traits. We then aggregated the colocalization

results across coding, regulatory, and behavioral QTLs to prioritize genes with the strongest neuropsychiatric relevance. We identified multiple candidate genes, including: *Nts* (modulates dopaminergic transmission), *Vrk2* (stress signaling, neurodevelopment), *Runx1t1* (neural differentiation regulator), *Trio* (regulator of synaptic development), *Grm5* (mediates synaptic plasticity), *Cdh18* (synapse-specific cadherin), *Scn2a* (voltage-gated sodium channel), and *Rgs7* (GPCR synaptic signaling modulator). These findings provide a foundation for functional validation using CRISPR knockouts or artificial selection and highlight molecular targets for future pharmacological exploration.

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Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.05/JJ22

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA P30DA060810
NIDA U01DA044451
NIDA P50DA037844

Title: Genome-wide association study of oxycodone self-administration in Heterogeneous Stock rats

Authors: *M. K. LARA[1], L. L. CARRETTE[4], T. MISSFELDT SANCHES[2], O. POLESSKAYA[5], A. S. CHITRE[3], B. JOHNSON[1], E. KEUNG[1], K.-M. NGUYEN[6], D. OTHMAN[2], M. BRENNAN[6], E. A. SNEDDON[7], L. SOLBERG WOODS[8], M. KALLUPI[9], G. DE GUGLIELMO[7], A. A. PALMER[6], O. GEORGE[10];
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Abstract: The opioid epidemic is a critical public health crisis in the US, with oxycodone misuse and addiction contributing to the rise in opioid-related overdoses and fatalities. While previous genetics studies in both humans and animal models have highlighted the role of genetic factors influencing susceptibility to opioid addiction, the identification of specific genes mediating risk for opioid use disorder (OUD) remains limited. Here, we conducted a genome-wide association study (GWAS) to identify novel genetic loci associated with OUD-like behaviors using

Heterogeneous Stock (HS) rats. HS rats are an outbred population with vast genetic and phenotypic diversity, making it an ideal model system to study complex traits such as addiction. Over the past 8 years we have comprehensively phenotyped approximately 1,000 HS rats for oxycodone addiction-like behaviors, employing an extended access model of oxycodone self-administration. HS rats exhibit a range of addiction-related behaviors, reflecting individual differences in addiction vulnerability and resilience. By leveraging the genetic and phenotypic diversity of HS rats, we performed a GWAS of these opioid addiction-like behaviors. This analysis provided heritability estimates and identified novel genetic loci associated with specific dimensions of oxycodone use. These genetic associations highlight candidate genes and biological pathways that contribute to individual variation in opioid addiction-like traits.

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Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.06/KK1

Topic: H.08. Drugs of Abuse and Addiction

Support: P50DA037844
P30DA060810

Title: Genome-wide association study (GWAS) of locomotor activity in more than 7,600 outbred HS rats identifies 25 loci

Authors: *A. S. CHITRE[1], T. MISSFELDT SANCHES[2], H. BIMSCHLEGER[5], D. CHEN[6], K. ISHIWARI[7], B. JOHNSON[1], C. D. MARTIN[8], D. MUNRO[3], K.-M. NGUYEN[4], B. PENG[4], C. ST. PIERRE[4], D. PULLMANN[9], A. ROBERTS[10], D. SEVIGNY-RESETCO[11], J. JIANG[13], P. MEYER[14], B. N. KUHN[10], P. W. KALIVAS[15], S. H. MITCHELL[12], T. C. JHOU[16], T. E. ROBINSON[17], S. B. FLAGEL[18], H. CHEN[19], D. M. DIETZ[20], O. POLESSKAYA[21], A. A. PALMER[22];
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In Neurosci., Baltimore, MD; [17]Dept Psychol, Univ. of Michigan Dept. of Psychology, Chicago, IL; [18]Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI; [19]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN, ; [20]SUNY At Buffalo, Clarence Center, NY, ; [21]Psychiatry, Univ. of California - San Diego, La Jolla, CA; [22]Psychiatry, UCSD, La Jolla, CA

Abstract: Understanding the genetic basis of locomotor activity is crucial because this trait covaries with anxiety, substance-abuse liability, and sensation-seeking. We quantified open-field distance travelled in 7,679 heterogeneous-stock (HS) rats from six cohorts that differed in age, arena, tracking modality, and prior drug exposure. SNP heritability (h^2) estimated with GCTA-GREML ranged from 0.26 to 0.41, and bivariate GREML revealed genetic correlations (r_g) of 0.01 - 0.74 (SE 0.08 - 0.24), indicating both shared and cohort-specific genetic influences. Genome-wide discovery used two complementary approaches: (i) a mega (univariate) GWAS with GCTA, employing a linear mixed-model framework with a leave-one-chromosome-out procedure; and (ii) a multivariate GWAS based on a common-factor Genomic SEM fitted to cohort-specific genetic covariance matrices generated with the REML-based MPH software. The univariate scan detected 9 loci, whereas the multivariate analysis uncovered 25 loci, 5 of which overlapped with the univariate results. Some of the loci contained genes that encode receptors for neurotransmitter systems that are modulators of locomotor behavior such as GABAergic signalling (*Gabra1*, *Gabra6*) and dopaminergic transmission (*Drd5*), while others encoded genes for transcriptional regulation (*Lmo4*) and other biological processes that likely represent novel biological insights. The Genomic SEM workflow, adapted here for use with HS rats with MPH, is generalisable to other model-organism datasets where LD-score regression assumptions fail. These findings show that multivariate GWAS markedly boosts locus discovery over univariate GWAS and provides experimentally tractable targets for probing the neural circuitry linking exploratory behaviour to addiction and anxiety-related phenotypes.

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Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.07/KK2

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant P50DA037844
NIH Grant P30DA060810

Title: Sex-dependent associations between intake escalation and cocaine incentive sensitization in heterogenous stock rats

Authors: *N. AMISSAH[1], C. P. KING[1,2], B. M. THOMPSON[1], E. A. RAKOWSKI[1], K. T. REYES[1], L. T. HANNAN[1], A. S. CHITRE[3], T. MISSFELDT SANCHES[3], B. PENG[3], O. POLESSKAYA[3], H. CHEN[4], L. SOLBERG WOODS[5], A. A. PALMER[3,6], P. J. MEYER[1]; [1]Psychology, Univ. at Buffalo, Buffalo, NY; [2]Clin. and Res. Inst. on Addictions, Buffalo, NY; [3]Psychiatry, Univ. of California San Diego, La Jolla, CA; [4]Pharmacol., Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [5]Intrnl. Med., Wake Forest Univ. Sch. of Med., Winston Salem, NC; [6]Inst. for Genomic Med., La Jolla, CA

Abstract: Addiction vulnerability is characterized by escalation of drug intake and incentive sensitization; however, these features are dependent on several factors. In this study we examined intravenous cocaine self-administration using 103 heterogenous stock (HS) rats. We hypothesized that escalation and incentive sensitization depends on the pattern drug exposure. Before testing began, a light/dark box test of baseline anxiety was conducted. Rats were then trained to acquire cocaine self-administration in ten 2-hour short-access sessions and then tested on for initial cocaine motivation using a progressive ratio test. Rats were then trained on either intermittent access (IntA) or long-access (LgA) schedules of cocaine self-administration for fifteen sessions (6 hours per session), after which a second progressive ratio test was performed. As expected, there was substantial variability in the magnitude of escalation of cocaine intake in both schedules. We therefore categorized rats into two phenotypes: high-escalators and non-escalators and compared motivation after fifteen sessions of cocaine exposure. Our results revealed similar levels of motivation in rats that were trained on IntA and LgA, but escalation was significantly related to increased cocaine motivation during the second progressive ratio test, particularly in males. Also, the tendency to escalate cocaine intake was independent of initial cocaine motivation measured during the first progressive ratio test. These findings suggest that the tendency to escalate cocaine intake is associated with the incentive sensitization to the reinforcing effects of cocaine in male HS rats, despite other studies showing that escalation is not required for incentive sensitization to occur (Allain and Samaha, 2019). Ongoing work is focused on identifying genomic loci and expression profiles linked to incentive sensitization to cocaine, and on validating the specific candidate genes identified using these approaches.

Disclosures: N. Amissah: None. **C.P. King:** None. **B.M. Thompson:** None. **E.A. Rakowski:** None. **K.T. Reyes:** None. **L.T. Hannan:** None. **A.S. Chitre:** None. **T. Missfeldt Sanches:** None. **B. Peng:** None. **O. Polesskaya:** None. **H. Chen:** None. **L. Solberg Woods:** None. **A.A. Palmer:** None. **P.J. Meyer:** None.

Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.08/KK3

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA P50DA037844

Title: Socially Acquired Nicotine Self-administration in Adolescent Outbred Rats Identifies Candidate Genes Shared with Human Smoking GWAS

Authors: A. GARCIA MARTINEZ[1], T. MISSFELDT SANCHES[2], A. S. CHITRE[3], C. JONES[4], L. SOLBERG WOODS[5], O. POLESSKAYA[6], A. A. PALMER[7], ***H. CHEN**[1]; [1]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [2]Psychiatry, Univ. of California San Diego, San Diego, CA; [3]Dept. of Psychiatry, Univ. of California San Diego, La Jolla, CA; [4]Univ. of Tennessee Hlth. Sci. Center, Memphis, TN, Memphis, TN; [5]Wake Forest Univ. Sch. of Med., Winston Salem, NC; [6]Psychiatry, Univ. of California - San Diego, La Jolla, CA; [7]Psychiatry, UCSD, La Jolla, CA

Abstract: The social environment significantly influences cigarette smoking behavior. To investigate this in rodents, we developed a socially acquired nicotine intravenous self-administration (IVSA) procedure in adolescent rats. In this model, nicotine delivery is paired with a contingent flavor cue. Crucially, social transfer of the nicotine-associated odor cue is prerequisite for initiating nicotine self-administration. We performed a genetic association study on socially acquired nicotine IVSA in a large cohort of outbred heterogeneous stock rats (n=2000), comprising approximately equal numbers of males and females. Our analysis identified 30 loci associated with various aspects of nicotine IVSA. Many of these nicotine-associated loci contain genes with human orthologs linked to smoking-related phenotypes. For instance, *Cacna1c*, found within a locus associated with time spent with a social partner prior to nicotine IVSA, also correlates with nicotine consumption and has been associated with smoking initiation in humans. These findings elucidate the complex interplay between social context and genetic predisposition in nicotine addiction, offering insights into underlying neurobiological mechanisms and potential avenues for targeted interventions.

Disclosures: A. Garcia Martinez: None. **T. Missfeldt Sanches:** None. **A.S. Chitre:** None. **C. Jones:** None. **L. Solberg Woods:** None. **O. Polesskaya:** None. **A.A. Palmer:** None. **H. Chen:** None.

Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: PSTR466.09/KK4

Topic: H.08. Drugs of Abuse and Addiction

Support: P30DA060810
5R37DA054370-04

Title: Gwas of addiction-related behaviors in heterogeneous stock rats identifies novel associations for cocaine avoidance, reward-seeking behavior, and locomotor activity

Authors: *Z. TATOM[1], M. EID[3], T. MISSFELDT SANCHES[4], A. S. CHITRE[5], D. CHEN[7], B. JOHNSON[6], R. AVILA[4], N. SUZUKI[4], O. POLESSKAYA[8], T. C. JHOU[9], A. A. PALMER[2]; [1]UCSD, San Diego, CA; [2]Psychiatry, UCSD, La Jolla, CA; [3]Med. Univ. of South Carolina, Charleston, SC; [4]Univ. of California San Diego, San Diego, CA; [5]Dept. of Psychiatry, [6]Univ. of California San Diego, La Jolla, CA; [7]Bioinformatics and Syst. Biol., UC San Diego, La Jolla, CA; [8]Psychiatry, Univ. of California - San Diego, La Jolla, CA; [9]Neurosci., Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD

Abstract: Cocaine, as with many substances of abuse, has been demonstrated to produce initial rewarding effects (euphoria) followed by a longer period of aversive effects including anxiety, craving, anhedonia, and withdrawal. Dysregulation of these effects has been suggested to contribute to the etiology of cocaine use disorder, as repeated cocaine use is thought to desensitize the rewarding effects and sensitize the aversive effects of cocaine. Human and animal genome-wide association studies (GWAS) have been employed to identify variants and genes associated with cocaine use, dependence, and cocaine use disorder with most of the attention has been spent understanding the rewarding effects of cocaine rather than the aversive effects despite both being thought to play a role in addiction. We hypothesize that GWAS of cocaine avoidance and addiction-related behaviors in Heterogenous Stock (HS) rats will enable estimation of the heritability of these behaviors and identify new loci associated with them in rats. 1,074 HS rats (379 male, 695 female) were anaesthetized and surgically fitted with indwelling intravenous catheters inserted into the right jugular vein and passed to a guide cannula exiting the back, then allowed to recover for 7 days before being exposed to behavioral testing including runway operant cocaine-seeking, progressive ratio and punishment testing, locomotion, and conditioned place preference (CPP) and conditioned place avoidance (CPA) assays. Behavioral data were analyzed using linear models to identify covariates (such as sex, cohort, age, technician) and quantile normalized. Genotyping was completed using DNA isolated from postmortem spleen tissue. GWAS was performed using Mixed Linear Model Analysis with significance thresholds estimated by permutation analysis (1000 permutations). SNP-based heritability (h^2) and genetic correlations (r_g) between traits were estimated. Heritability estimates for behavioral phenotypes ranged from 0.0-0.307. Significant ($p < 0.05$) quantitative trait loci (QTL) were identified for punishment testing on both chromosomes 5 and 6, with additional QTL on chromosome X for locomotion, cocaine avoidance, cocaine avoidance in females only, and time to run start in runway task in males only. Candidate genes identified from punishment task include genes previously associated in human GWAS with brain morphology (*Dpysl5, Slc35f6*); externalizing behaviors like age at first sexual encounter and educational attainment (*Kcnk3*); and nicotine dependence (*Cib4*). Additional genes and loci represent novel findings which may further our understanding of the genetic architecture of aversion-related behaviors.

Disclosures: Z. Tatom: None. **M. Eid:** None. **T. Missfeldt Sanches:** None. **A.S. Chitre:** None. **D. Chen:** None. **B. Johnson:** None. **R. Avila:** None. **N. Suzuki:** None. **O. Polesskaya:** None. **T.C. Jhou:** None. **A.A. Palmer:** None.

Poster

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NIH GM140964
NIH GM148302
NIH TR001450

Title: Long Noncoding RNA form R-loops to shape emotional experience-induced behavioral adaptation.

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Abstract: Emotional experiences often evoke neural plasticity that supports adaptive changes in behavior, including maladaptive plasticity associated with mood and substance use disorders. These adaptations are supported in part by experience-dependent activation of immediate-early response genes, such as Npas4 (neuronal PAS domain protein 4). Here we show that a conserved long noncoding enhancer RNA (lnc-eRNA), transcribed from an activity-sensitive enhancer, produces DNA:RNA hybrid R-loop structures that support three-dimensional chromatin looping between enhancer and proximal promoter and rapid Npas4 gene induction. Furthermore, in mouse models, Npas4 lnc-eRNA and its R-loop are required for the development of behavioral adaptations produced by chronic psychosocial stress or cocaine exposure, revealing a potential role for this regulatory mechanism in the transmission of emotional experiences. In this conference, we aim to discuss the function and underlying mechanisms of R-loops in the context of neuroscience.

Disclosures: M. Taniguchi: A. Employment/Salary (full or part-time): Medical University of South Carolina.

Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

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Program #/Poster #: PSTR466.11/KK6

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH MH219521

Title: Molecular mechanisms of DNA:RNA hybrid R-loops-mediated gene expression

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Abstract: In neuroscience, understanding the functional mechanisms of gene expression underlying long-term behavioral changes has long been a fundamental point of research. In the context of learning and memory, gene expression plays a critical roles, however, dysregulation of gene expression in response to pathological experience, such as exposure to drugs or stressors, can lead to maladaptive behavioral changes and sometimes contribute to the development of mental disorders. Recent advances in sequencing technology have revealed the complexity and precision of epigenetic mechanisms regulating gene expression. These include histone protein modifications, DNA methylation, and noncoding RNAs, and that they have been implicated in the dysregulation observed in individuals with mental disorders. Among these epigenetic mechanisms, this study we focuses on the role and functional mechanisms of long-noncoding RNA(lncRNAs). Our previous work demonstrated that lncRNA can form DNA:RNA hybrid triple strand structure, known as R-loops, in response to emotional experiences, such as exploration in the novel environment or exposure to stress. The R-loops structure forms at the activity-sensitive enhancer of immediately early gene Npas4, and facilitates the formation of three dimensional chromatin loop structure that connect the enhancer to proximal promoters. LncRNA and its R-loops are essential for the activity-dependent gene expression and emotional experience-induced behavioral plasticity. Despite their key role in the behavioral plasticity, the physiological and pathological roles of R-loops in the brain are only in the beginning to be explored in neuroscience. To expand ton our findings, this project aims to investigate genome-wide R-loops structures in brain tissue. Additionally, the precise molecular mechanisms by which R-loops initiate transcription in the brain, including associated proteins and other molecular factors is still largely unknown. We hypothesize that identifying key proteins associated with R-loops in neurons will allow us to develop a more detailed understanding of the mechanisms of addiction. The novel insights will significantly contribute to the understanding gene expression mechanism and provide a better understanding in the long-term behavioral plasticity.

Disclosures: C. Worley: None. **S. Simmerson:** None. **M. Taniguchi:** None.

Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

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Topic: H.08. Drugs of Abuse and Addiction

Support: R01 DA062540
R01 DA051390

Title: Distinct dorsolateral prefrontal cortex and nucleus accumbens transcriptional signatures associated with phases of opioid use disorder withdrawal and remission

Authors: *N. HORAN[1], M. A. SHELTON[1], K. BARKO[1], S. SAMBARE[2], R. W. LOGAN[2], M. L. SENEY[1];
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Abstract: Opioid-Use-Disorder(OUD) affects over 2.5 million people annually in the US, with cravings persisting years into remission and relapse rates as high as 90%. This highlights a critical need to identify targetable gene pathways to support sustained abstinence. To identify gene pathways underlying addiction and recovery, we leveraged a unique postmortem cohort that allowed us to better understand the genetic pathways spanning multiple stages of opioid exposure. Bulk RNA-seq was performed on human postmortem tissue from the dorsolateral prefrontal cortex (DLPFC) and Nucleus Accumbens (NAc) of 80 subjects aged 22-69 years. Subjects were grouped into unaffected controls (UC), OUD with a positive opioid toxicology screen at TOD (OUD TOX+), OUD negative opioid toxicology at TOD (OUD TOX-), and those in remission (RM; opioid-free ≥7 months). We assessed group, sex, and their interaction using a type-3 ANOVA, followed by post hoc testing to identify pairwise group differences. Differentially expressed genes ($|logFC|>2$, $p<0.05$) were analyzed using Metascape to identify enriched pathways. We identified 1,061 genes in PFC and 880 genes in NAc with significant group effects. Post hoc comparisons revealed four distinct transcriptional profiles corresponding to stages of OUD: acute drug use, chronic drug use, withdrawal, and remission. GO analysis identified robust immune signaling in DLPFC during acute use (e.g., cytokine binding, macrophage activation), while remission-specific genes were enriched for extracellular matrix remodeling and wound healing. In the NAc, withdrawal-specific genes were strongly associated with cilium movement and axonemal dynein complex assembly, suggesting a role for altered microtubule dynamics. Notably, overlapping pathways (e.g., immune signaling, vasculature development) emerged across stages but differed by brain region and directionality. These results highlight temporally and regionally distinct gene pathways across the OUD trajectory, offering mechanistic insight into opioid addiction and potential therapeutic targets to reduce relapse vulnerability.

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Poster

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Program #/Poster #: PSTR466.13/KK8

Topic: H.08. Drugs of Abuse and Addiction

Support: R00DA045795
P30DA033934
R01DA058958
R01DA058089

Title: Investigating the stability of nucleus accumbens transposable elements as contributing to drug use behaviors in mice.

Authors: *A. HASSAN[1], J. PICONE[3], P. J. HAMILTON[2];
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Abstract: Substances with addictive potential, such as psychostimulants and opioids, manipulate the brain's reward circuitry by increasing dopamine levels and reinforcing drug-seeking behaviors within the neurons of the nucleus accumbens (NAc), a central hub for integrating reward and reinforcement behaviors across species. Despite the growing prevalence of substance misuse and increasing overdose fatalities, few FDA-approved pharmacotherapies exist for substance use disorder (SUD) treatment. This research project aims to investigate the role of transposable elements (TEs) and their KRAB zinc finger protein (KZFP) transcriptional controllers within the NAc as potential brain mechanisms that contributes to substance-induced adaptations. This research has the potential to identify novel pharmacotherapies for SUDs.TEs are DNA sequences capable of replication and reinsertion into different locations in the genome and play a significant role in genomic regulation. Recent research has discovered that KZFPs, the largest class of transcription factors, are a major biological mechanism to repress TEs replication in the genome. Our lab has synthetically re-engineered the function of TRIM28, a co-repressive factor of KZFPs, in order to virally dysregulate TEs in awake and behaving mice. By virally delivering re-engineered variants of TRIM28 to the NAc to manipulate the expression of TEs, we hypothesize that the transcriptional repression of NAc TEs enables brain adaptations to substance use, and the synthetic activation of these TEs would block substance induced brain changes. We performed a dose-response experiment using C57BL/6J mice implanted with a jugular vein catheter to operate intravenous self-administration (IVSA) of cocaine. For this experiment, we virally manipulated the NAc with TRIM28 variants directly interrogate the effects of KZFP-mediated TE dysregulation on cocaine reinforcement. Additionally, we performed conditioned place preference and RNA-sequencing of transduced TRIM28 infused NAc tissue in male and female mice with sub-chronic exposure to saline, cocaine and morphine to profile alterations in drug reward and drug-induced gene expression changes upon delivering our synthetic TRIM28 variants to the NAc. Our preliminary findings indicate that KZFP-mediated transcriptional control of NAc TEs alters cocaine self-administration at low to moderate doses and produces sex differences among differentially expressed genes (DEGs) and differentially expressed TEs (DETEs). Our studies suggest that this mechanism may contribute to the molecular processes that govern drug-taking behaviors and drug-related gene expression.

Disclosures: A. Hassan: None. **J. Picone:** None. **P.J. Hamilton:** None.

Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

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Program #/Poster #: PSTR466.14/KK9

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA R01 AA030048

Title: Precision Medicine for AUD: P2X4 Receptor Modulation Reduces Alcohol Consumption in Genetically Heterogeneous Rats

Authors: *P. CAMPO[1], M. R. DOYLE[4], R. QIAO[5], T. MISSFELDT SANCHES[6], A. A. PALMER[2], M. KALLUPI[7], G. DE GUGLIELMO[3];
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Abstract: Alcohol Use Disorder (AUD) affects ~16% of the 175 million Americans consuming alcohol annually, with genetic variations likely underlying individual differences in problematic drinking. We characterized addiction-like behaviors and performed genome-wide association studies (GWAS) in heterogeneous stock (HS) rats to identify novel therapeutic targets for AUD. Addiction-like behaviors were assessed in 500 male and female HS rats. Rats self-administered 10% ethanol (v/v) on a fixed ratio 1 schedule until stable intake, followed by evaluations of ethanol preference, progressive ratio responding, and quinine-adulterated ethanol intake. Dependence was induced using chronic intermittent ethanol vapor (14 hours/day, 4 weeks, blood ethanol 150-250 mg%). During acute withdrawal (6-8 hours post-vapor), we measured escalated ethanol intake, motivation, compulsivity, sensitivity, somatic withdrawal signs, and hyperalgesia, generating an Addiction Index. GWAS identified P2rx4, encoding the P2X4 receptor, as a candidate gene. To test its functional relevance, ivermectin, a positive allosteric modulator of P2X4, was administered (1, 2.5, 5, 10 mg/kg) or vehicle to dependent rats (n=16/sex) 4 hours before self-administration sessions. Central amygdala (CeA) electrophysiological recordings evaluated ivermectin's effects. Ivermectin significantly reduced ethanol intake at 5 and 10 mg/kg in dependent rats. Responders showed the greatest reduction, mid-responders moderate effects, and non-responders no effect. CeA recordings revealed increased sIPSC frequency post-ivermectin, with stronger effects in responders. Ivermectin's modulation of P2X4 receptors reduces alcohol consumption in genetically susceptible rats, supporting its potential as a precision medicine treatment for AUD.

Disclosures: P. Campo: None. **M.R. Doyle:** None. **R. Qiao:** None. **T. Missfeldt Sanches:** None. **A.A. Palmer:** None. **M. Kallupi:** None. **G. de Guglielmo:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: R01AA030048

Title: Nicotinic α3β4 receptor partial agonist mitigates addiction-like behaviors in ethanol dependent rats

Authors: *M. BISHARA[1], M. R. DOYLE[4], P. CAMPO[2], R. QIAO[5], A. R. MARTINEZ[3], S. DIRIK[3], C. P. WOOD[3], D. MUNRO[6], B. JOHNSON[7], N. T. ZAVERI[8], A. A. PALMER[1], M. KALLUPI[9], G. DE GUGLIELMO[3];
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Abstract: Alcohol use disorder (AUD) affects over 29 million Americans and causes more than 50,000 deaths annually in the United States. Despite its impact, effective treatments remain limited. Genetic studies have linked the CHRNA5-CHRNA3-CHRNB4 gene cluster, encoding nicotinic acetylcholine receptor (nAChR) subunits, to alcohol dependence. This study evaluated ATRX-52, a novel α3β4 nAChR partial agonist, for its ability to reduce addiction-like behaviors in ethanol-dependent rats. Using genetically diverse Heterogeneous Stock rats, we categorized animals into high and low addiction-like phenotypes based on ethanol self-administration. Systemic ATRX-52 administration dose-dependently reduced ethanol intake, particularly in high-phenotype rats, and decreased motivation and cue-induced reinstatement in both groups. ATRX-52 also lowered nicotine self-administration in ethanol-dependent rats with high nicotine intake, without affecting saccharin consumption, suggesting selectivity for drug rewards. Electrophysiological assessments in the central amygdala (CeA) showed elevated baseline spontaneous inhibitory postsynaptic current frequency in high-phenotype rats, exacerbated by ethanol and normalized by ATRX-52. CeA microinjections of ATRX-52 selectively reduced ethanol intake in high-phenotype rats. Additionally, higher predicted Chrna3 expression correlated with increased ethanol consumption, indicating a genetic influence on drinking behavior.These results demonstrate that ATRX-52 effectively attenuates addiction-like behaviors in ethanol-dependent rats, especially those with severe phenotypes, by targeting α3β4 nAChRs in the CeA. This research underscores ATRX-52's potential as a therapeutic agent for AUD, particularly in individuals with high consumption patterns, and highlights the importance of genetic factors in addiction susceptibility.

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Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

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Topic: H.08. Drugs of Abuse and Addiction

Support: RO1 – AA028879-04
R21 – AA029498-02
P60 – AA006420

Title: Identifying the differential expression profile of astrocyte-expressed genes in the amygdala during alcohol withdrawal

Authors: *K. GEORGE[1], M. L. LOGRIP[2], E. P. ZORRILLA[1];
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Abstract: Alcohol use disorder affects 29 million Americans annually[1, 3, 6, 7]. Studies suggest that astrocytic proteins in the amygdala drive relapse-related negative emotional withdrawal symptoms and uncontrolled intake[4, 5]. Dependence-associated changes in astrocytic gene expression in the central nucleus of the amygdala (CeA) and basolateral amygdala (BLA) are poorly understood. We hypothesize that chronic intermittent ethanol vapor exposure (CIE) elicits differential expression profiles in astrocyte-expressed genes across withdrawal stages in amygdala nuclei. Adult male Wistar rats (n=46) underwent CIE [5 weeks; blood alcohol levels: 175-225 mg%]. Rats were sacrificed during acute (8-10 hours) or protracted alcohol withdrawal (6 weeks)[2]. To identify withdrawal-related astrocyte candidates (Gfap, Lcat, Tnc, Ankrd29, Map3k19, Wdr49, and Veph1), I performed qPCR. In the CeA, Wdr49 increased 11-fold after protracted withdrawal ($p<0.0001$). In the BLA, Wdr49 increased 7-fold in acute withdrawal ($p<0.0001$); Tnc, Map3k19, and Wdr49 increased 5, 7, and 9-fold respectively in protracted withdrawal ($p<0.05$). Principal component analysis showed regional changes in marker covariances across withdrawal stages; CeA Ankrd29 was uncorrelated with other CeA markers in controls, positively correlated in acute withdrawal, and inversely correlated in protracted withdrawal. In acute withdrawal, k-means clustering discriminated CIE subjects with increased BLA Wdr49, Lcat and Tnc. BLA Wdr49, Tnc, and Lcat became intercorrelated, unlike in controls; CeA Map3k19 became correlated with CeA Tnc. In protracted withdrawal, k-means clustering discriminated CIE subjects with increased CeA Wdr49 and BLA Wdr49, Map3k19, and Ankrd29 expression. BLA Map3k19 and Ankrd29 became associated with BLA Gfap, Tnc, and Wdr49; conversely, the normal BLA Map3k19-Veph1 association decreased. CeA Wdr49 became strongly correlated with BLA Map3k19, Wdr49 and Gfap. Finally, CeA and BLA Gfap were no longer correlated, unlike in other groups. We will investigate the functional significance of the amygdala nucleus- and withdrawal stage- specific changes in (co)-expression profiles of these astrocyte-expressed genes. By identifying, testing, and translating the causal role of CIE withdrawal-associated astrocyte proteins, this project may help to identify novel non-neuronal targets to reduce withdrawal symptoms and relapse risk in patients with AUD. This project was supported by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) (RO1 - AA028879-04, R21 - AA029498-02, P60 - AA006420).

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Poster

PSTR466: Addiction: Genetics, Epigenetics, and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: PSTR466.17/KK12

Topic: H.08. Drugs of Abuse and Addiction

Title: Investigating chromatin-mediated alterations in ventral tegmental area astrocytes following drug exposure

Authors: *L. CEDILLO[1], A. MILLER[2], A. JUMAMYRADOVA[2], B. GARCIA-CASTAÑEDA[2], A. RAMOS[2], M. J. WANAT[2], A. A. SOSHNEV[2];
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Abstract: Ventral tegmental area (VTA) dopamine neurons and their projections to the striatum modulate drug-dependent behaviors. Astrocytes are increasingly recognized as critical regulators of neuronal activity that also undergo drug-mediated adaptations. Recent data from our lab has demonstrated that prior drug exposure functionally alters how VTA astrocytes regulate dopamine-dependent behavior. Specifically, we found that chemogenetic activation of VTA astrocytes facilitates the development of a cocaine conditioned place preference (CPP) in drug-naïve animals but suppresses cocaine CPP in rats with prior cocaine experience. This data led us to hypothesize that cocaine exposure alters the epigenetic and transcriptomic landscape in VTA astrocytes. To test this hypothesis, we analyzed chromatin accessibility changes in specific cell populations in the VTA, using an assay of transposase-accessible chromatin followed by short-read sequencing (ATAC-Seq). Following VTA excision *en bloc*, bulk nuclei were isolated and stained for astrocyte (Sox9), neuronal (NeuN), and oligodendrocyte (Olig2) nuclear markers using fluorophore-conjugated primary antibodies. FACS sorting accounting for particle size, shape, and DNA content robustly identified three distinct subpopulations, as well as mixed populations representing double-and triple-stained nuclei. ATAC-Seq analyses validated expected chromatin states at neuronal (e.g. *Mapt*, *Aldh1a1*), oligodendrocyte (e.g. *Olig2*, *MBP*), and astrocyte (e.g. *GFAP*, *Sox9*) genes, providing integrative chromatin accessibility profiles across key VTA cell populations. This establishes an optimized protocol for ATAC-Seq analyses in a distinct brain region and a foundational approach for exploring epigenetic responses to drug exposure across neuronal and glial VTA cell populations.

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

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Program #/Poster #: PSTR467.01/KK13

Topic: H.08. Drugs of Abuse and Addiction

Support: ERC Starting Grant
Einstein Center for Neuroscience Berlin PhD Fellowship 2022

Title: Did you hear that? Neural signatures of psilocybin-induced hallucination-like perception in rat auditory cortex.

Authors: *D. KASSYBAYEVA[1], E. LONERGAN[2], R. DE FILIPPO[2], T. OTT[3,4];
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Abstract: Hallucinations are veridical perceptions experienced in the absence of corresponding external stimuli. Hallucinations have been hypothesized to arise from the abnormal weighting of prior expectations relative to sensory evidence, but their neural circuit basis is unknown. Hindrance to this research has been a lack of reliable animal models and methods for inducing hallucinations. In this study, we used an auditory detection task augmented with a behavioral measure of decision confidence in rats, allowing for the identification of hallucination-like perception (HALIP) as high-confidence false alarms. We combined the task with the administration of psilocybin, a serotonergic hallucinogen, and electrophysiological single-unit recordings in the primary auditory cortex (A1) to investigate the neural signatures of psilocybin-induced HALIPs. Rats (n = 6; 4 male, 2 female) were chronically implanted with Neuropixels 1.0 or 2.0 probes in A1 and performed multiple sessions of the detection task under control (saline) or psilocybin (1 mg/kg) conditions. We found that psilocybin administration led to a significant increase in HALIPs without affecting low-confidence errors or impairing general task performance. We identified over 400 single neurons and characterized their tuning to task variables, such as signal, choice, reward, and confidence. We observed neurons encoding different trial types, including hit, miss, false alarm, and correct rejection. In preliminary analyses, we report the complex changes in activity patterns induced by psilocybin in neural populations and single neurons tracked across days and experimental conditions. Together, our findings offer critical insight into the neural circuit basis of psychedelic-induced hallucinations and predictive processing.

Disclosures: D. Kassybayeva: None. **E. Lonergan:** None. **R. De Filippo:** None. **T. Ott:** None.

Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

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Program #/Poster #: PSTR467.02/KK14

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH R01NS116080
Strategic Partnership Grant from Michigan State University

Title: N-shaped waveforms for electrochemical detection of serotonin with fast-scan cyclic voltammetry reveal the accumbal effects of ketamine and escitalopram using boron-doped diamond microelectrodes

Authors: *M. PERILLO[1], S. AULTMAN[1], I. CHRISTENSEN[1], B. GUPTA[2], W. LI[1], J. SIEGENTHALER[3], E. K. PURCELL[1];
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Abstract: Neurochemicals are often a pharmacological target for the treatment of neurological and psychiatric conditions. Fast-scan cyclic voltammetry (FSCV) is an analytical method which drives redox reactions at an electrode surface with an applied potential waveform at a high scan rate which can be used to detect neurochemicals in the intact brain in real time. The applied waveform can be altered for various detection goals, one of which is to detect serotonin (5-HT) selectively from dopamine (DA) with N-shaped waveforms. This is achieved by altering the waveform's parameters, such as the holding potential, switching potential, and scan rate. These specialized waveforms have been developed on the traditionally used carbon fiber microelectrode (CFME). Newer electrode materials are currently being explored for purposes such as reduced fouling, improved long term stability, and more. Boron-doped diamond (BDD) electrodes have been shown to exhibit reduced fouling, improved electrochemical stability, and batch fabricability. Here, we examine the effects of two different N-shaped waveforms on 5-HT and DA detection with a BDD microelectrode (BDDME) compared to the CFME and the "standard" DA FSCV waveform. Additionally, we explored the use of the extended-N waveform *in vivo* with both the CFME and the BDDME by detecting 5-HT in the rat nucleus accumbens core. As a practical application, we compared the effects of ketamine and escitalopram, two pharmacologic treatments for depression and other disorders, on stimulation-evoked 5-HT release. Our data show that the BDDME exhibits a smaller reduction in DA oxidation current with N-shaped waveforms than the CFME, indicating a surface adsorption difference and the need for material specific waveform development for neurotransmitters. Additionally, we found that the BDDME can detect 5-HT *in vivo* comparably to the CFME, while retaining its benefits of stability and fouling resistance. Lastly, we found that ketamine and escitalopram have a similar dose-response effect on accumbal 5-HT, which provides insight while also raising questions about their differing therapeutic characteristics.

Disclosures: M. Perillo: None. **S. Aultman:** None. **I. Christensen:** None. **B. Gupta:** None. **W. Li:** None. **J. Siegenthaler:** A. Employment/Salary (full or part-time): Fraunhofer USA, Inc., Center Midwest. **E.K. Purcell:** None.

Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.03/KK15

Topic: H.08. Drugs of Abuse and Addiction

Support: NIMH Psychoactive Drug Screening Program
RO1MH112205
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R37DA045657
R37DA045657

Title: Psychedelics exhibit polypharmacology and activate a spectrum of receptor-transducer pathways

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Abstract: Classical psychedelics such as LSD, psilocybin, and mescaline exert their psychedelic effects by activating 5-HT_{2A} serotonin receptors (5-HT_{2A}R). In many recent preliminary clinical studies, psychedelics display potential efficacy in many neuropsychiatric disorders and substance abuse. While these compounds are categorized as 5-HT_{2A}R agonists, they can also interact with many other druggable targets. We investigated the pharmacology of 41 classical psychedelics across tryptamine, phenethylamine, and lysergamide chemical classes and found that these compounds potently activated nearly all serotonin, dopamine, and adrenergic receptors. Recently, it was reported that psychedelics such as LSD and psilocin bind to TrkB and promote endogenous BDNF signaling. However, we did not observe any agonist or allosteric modulation of BDNF-induced TrkB activity by psilocin or LSD. Also, there was no potent interaction of LSD tested with 450 human kinases. We subsequently profiled these psychedelics against all serotonin, dopamine and adrenergic receptors with their known receptor-G protein transducer pairs. We found that all tested psychedelics activate many of these receptors, including the 5-HT_{2B}R indicating the risk of cardiac valvulopathy with chronic use. Psychedelics activated a broader range of receptor pathways compared to the non-psychedelic analogs and we found a strong correlation between 5-HT_{2A}R activation and head twitch response. The long residence time of a psychedelic does not corelate with their psychedelic effects. Several lysergamides strongly interact with dopamine receptors, and tryptamine with adrenergic receptors indicating potential therapeutic and adverse off-target activities. As proof of concept to demonstrate lysergamide interactions with dopamine receptors, we solved an active state cryo-EM structure of D_2R in complex with LSD at a resolution of 2.3 Å. Our data reveal that psychedelics activate a variety of receptor-transducer pathways, some of which may be associated with their therapeutic effects. [Supported by the NIMH Psychoactive Drug Screening Program, RO1MH112205, RO1DA055656 and R37DA045657 to BLR]

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.04/KK16

Topic: H.08. Drugs of Abuse and Addiction

Support: MITACS
NSERC RGPIN-2019-06104

Title: The effect of high and low dose psilocybin administration on cell proliferation in the hippocampus

Authors: *G. O'REGAN, A. KIT, H. BHATTI, H. HENRY, B. R. CHRISTIE;
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Abstract: Psychedelics are novel, promising candidate molecules for clinical use in the treatment of a variety of psychiatric disorders. Mechanistic studies report that psilocin, the active component of psilocybin, acts as an agonist for serotonin receptors, particularly the 5-HT2AR receptors in the peripheral and central nervous systems. 5-HT2AR is primarily responsible for anti-depressive and neuroplastic changes. Studies indicate that a single administration of psilocybin can induce rapid changes in synaptic plasticity and neurogenesis via activation of pro-plasticity intracellular signaling cascades and consequent changes in gene expression. Studies in the psychedelic space work to reduce the stigma surrounding hallucinogens and provide alternatives to traditional anxiety and depression treatments. Our study assigned 60 C57BL/6 mice randomly into one of 5 varying dose treatment paradigms (12/group), then injected with thymidine analogue bromodeoxyuridine (BrdU) 24 hours before perfusions and brain collection. Standard immunohistochemistry staining and cell counting were used to quantify cell proliferation in the subgranular zone (SGZ) and the granular cell layer (GCL) of the hippocampus. Between-subjects ANOVA analysis was conducted independently for each of the 5 treatment groups, and a Tukey post-hoc test was used to correct for type 1 error for multiple comparisons. Preliminary analysis of the data indicates significant increases in cell proliferation observed in both male and female mice following a high dose of psilocybin ($p = 0.03$). Furthermore, using statistical estimation analysis, we observed a trend of increased cell proliferation in the high-dose psilocybin group and the 14-day low-dose psilocybin group. While nonsignificant, the estimation statistics may provide support for the benefits of microdosing psilocybin. The ANOVA findings demonstrate that high-dose psilocybin has rapid effects on adult neurogenesis in the hippocampus, a brain region associated with memory, learning, and mood. Mechanistically, these findings may provide insight into the drug's antidepressant

properties, providing vital insights for further exploration and understanding of the novel treatment of psychiatric disorders.

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.05/KK17

Topic: H.08. Drugs of Abuse and Addiction

Title: Investigating signatures of psilocybin-induced phenomenology and excitability with EEG

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Abstract: The serotonergic psychedelic psilocybin induces glutamatergic neural plasticity and profoundly alters consciousness. Midazolam, a benzodiazepine sedative and positive allosteric modulator of $GABA_A$ receptors, blunts neural plasticity and induces conscious amnesia. The balance of excitation and inhibition (E/I balance) and signal complexity are properties of cortical neural activity that vary with changes in consciousness and neural plasticity. Complexity and E/I balance can be measured from resting state EEG activity using Lempel Ziv complexity (LZC), which measures the compressibility of time-varying signals, and spectral exponent (SE), which measures the decay of EEG signal power with frequency. Both LZC and SE decrease with depth of sleep and anesthesia and increase upon administration of serotonergic psychedelics. Computational models suggest that SE varies with E/I balance. Whether the same is true for LZC is unclear. In our recent open label pilot study (n=8; https://pubmed.ncbi.nlm.nih.gov/39266503/), co-administration of midazolam with psilocybin (25 mg) impaired memory of the psychedelic experience without blunting its subjective quality. During the dosing session, we monitored brain activity (high density EEG), sedation level (Observer's Assessment of Alertness Sedation Scale (OAA/S)), and the intensity of the subjective experience (six questions from the Altered States of Consciousness (ASC) questionnaire). Here, we measured normalized LZC (LZCn) and SE at several timepoints during dosing session. We sought to test: 1) whether psilocybin-induced changes in LZCn and SE remain with co-administration of midazolam, and 2) how LZCn and SE relate to OAA/S and ASC scores.We ran linear mixed effect models predicting LZC and SE using time as a fixed

factor and subjects as a random effect. At 15 minutes post-dosing, before the onset of psilocybin's subjective effects, SE significantly decreased from baseline ($p < 0.0001$). From 30 to 210 minutes post-dosing, LZCn significantly increased from baseline ($p < 0.015$ all timepoints). SE significantly increased from baseline from 90 through 360 minutes ($p < .0.0001$ all timepoints). When OAA/S and ASC were added as fixed effects to the model, ASC significantly predicted LZCn ($p = 0.044$) and SE ($p = 0.003$) beyond the influence of time and OAA/S.The results suggest that LZCn and SE track acute neural effects of psilocybin when co-administered with midazolam. The effect of midazolam on SE before the onset of the acute effects of psilocybin may reflect a midazolam-mediated decrease in E/I balance. It remains unclear how different aspects of the subjective experience of psilocybin are explained by LZCn and SE.

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.06/KK18

Topic: H.08. Drugs of Abuse and Addiction

Support: R35NS097287
R01NS118461

Title: Psychedelic-induced infra-slow oscillations during a "paradoxical wake" state organize mesoscale neural activity to promote rapid plasticity of sensory representations

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[1]Inst. of Neurosci., [2]Inst. of Neurosciecne, Univ. of Oregon, Eugene, OR

Abstract: Psychedelics alleviate depression and drug addiction in humans, and reopen critical periods of brain plasticity in rodents[1]. However, the neural activity and mechanisms underlying these therapeutic effects are unknown. We sought to fill this gap in the field by performing mesoscale 2p imaging of up to ~10,000 excitatory neurons at a time across all of mouse dorsolateral cortex[2] during spontaneous behavior in the presence of the psychedelic 2,5-Dimethoxy-4-iodoamphetamine (DOI; 1-10 mg / kg). After an initial period of neurobehavioral "disorganization" (43.5 ± 6.6 min) characterized by 1 Hz rhythmic whisker twitching, mice entered a period of infra-slow pupil oscillations (ISO; 0.032 ± 0.002 Hz, duration = 48.9.0 ± 8.3 min) characterized by a high amplitude (56.8 ± 4.2% depth modulation) and striking regularity (0.005 ± 0.001 Hz wave period STD). This phenomenon, which was blocked by 5-HT2a antagonists and enhanced by 5-HT1a antagonists, was highly reliable, occurring in 35/40

sessions from 23 mice in the presence of DOI, and 0/35 sessions in 27 mice following sham injections. Similar ISOs were observed after administration of 25C-NBOH (an LSD analog; n=3), and 4-acetoxy-DMT (metabolized to psilocin; n=5). ISOs with longer and more variable periods are prevalent during non-REM sleep (Yuzgec et al, 2018[3]). During DOI-induced ISO mice exhibited brief walking bouts at the peak of each oscillation and were nearly still at each trough. Standard sleep scoring with EMG and EEG identified peaks as "active wake" and troughs as "quiescent wake", although spindle oscillations, characteristic of NREM, were regularly observed at troughs. Neural activity recorded with mesoscale 2p imaging (~3-10 Hz; CaMKII-Cre x GCaMP6s or 8m) during the pupil ISO was traveling wave-like and involved areas implicated in the rodent default mode network (DMN[4,5]), with retrosplenial/visual/auditory areas activated at the peak of the pupil ISO, and somatomotor areas activated at the trough. There were clear subpopulations of "pupil ON" and "pupil OFF" neurons that exhibited spatial overlap. We are currently performing mesoscale 2p imaging of NE and AChR axons across cortex to examine the relationship between cortical neuromodulatory tone and ISO pupil phase under DOI. In addition, we are developing a closed-loop behavioral paradigm whereby DOI can reopen the critical period for ocular dominance plasticity and cause rapid learning that is accelerated by visual stimulus presentation at specific phases of the pupil ISO when cortical norepinephrine signaling and cAMP levels are elevated. Refs: [1]Nardou at al, 2023. [2]Vickers & McCormick, 2024. [3]Yuzgec et al, 2018. [4]Raichle et al, 2001. [5]Raichle, 2015.

Disclosures: E.D. Vickers: None. **D. Hulsey:** None. **D.A. McCormick:** None.

Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.07/KK19

Topic: H.08. Drugs of Abuse and Addiction

Support: R35NS097287
R01NS118461

Title: Organization of sequential sigma-band dynamics across multiple cortical communities during NREM and psychedelic states

Authors: *J. GUENZA-MARCUS[1], D. HULSEY[2], E. D. VICKERS[3], D. A. MCCORMICK[3]; [1]Biol., Univ. of Oregon, Inst. of Neurosci., Eugene, OR; [2]Inst. of Neurosciecne, [3]Inst. of Neurosci., Univ. of Oregon, Eugene, OR

Abstract: Memory encoding and retrieval are fundamental cognitive processes through which past experiences shape future behavior and decision-making. Prior work identifies the retrosplenial cortex (RSC) in mice as a neural "hub," characterized by extensive bidirectional connectivity as well as involvement in memory encoding and retrieval (AS Alexander et al.,

2023). Sleep spindles are 0.5 - 3 s bursts of 10 - 15 Hz sigma-band oscillations and a hallmark of non-rapid eye movement (NREM) sleep. Sleep spindle research has advanced our understanding of sleep-related mechanisms of memory consolidation, with their atypical presentation linked to disorders such as schizophrenia, Alzheimer's, and autism. While thalamic generation of spindles is well studied (LMJ Fernandez, A Lüthi, 2023), their spatiotemporal cortical dynamics remain not well understood.Here, we aimed to determine how behavioral measures provide context to cortical sigma expression and spindle activity during NREM sleep as well as post-administration of psychedelic DOI (2,5-Dimethoxy-4-iodoamphetamine). We hypothesized that the RSC functionally acts as a community hub, mediating the transition between periods of spindle occurrence in other regions of cortex. To study sigma-band activity and spindle occurrence across dorsal cortex, we used wide field imaging to analyze spontaneous neural activity of mice expressing the genetically encoded calcium indicator GCaMP8m in excitatory cells. Concurrently, we collected behavioral measures such as pupillometry, locomotion, and whisking.To analyze the rich imaging datasets, we devised a novel computational pipeline to classify sigma-band activity patterns into discrete neural activity states, which identified lawful sequences of pan-cortical sigma-band activity. These distinct states form temporally linked 'communities' which have unique phase and amplitude relationships with pupil diameter during NREM and DOI-induced infra-slow (ISO) oscillations. We find that communities form a clear anatomical division between anterior (motor-somatosensory) and posterior-lateral (Auditory-Visual) networks of cortex. Finally, we find that states with RSC activity tend to act as 'bridge' states, mediating state transitions and hence sigma-band expression across cortex. These findings reveal discrete, cortex-wide sigma-band expression patterns and help elucidate the spatio-temporal regulation of global spindles. This study provides insight towards systems-level mechanisms linking thalamic spindle generation to patterned global cortical expression and lays groundwork for future investigation of the role of RSC in memory processing.

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.08/KK20

Topic: H.08. Drugs of Abuse and Addiction

Support: R35NS097287
R01NS118461

Title: Spatiotemporal dynamics of thalamocortical oscillations during Non-REM sleep and DOI exposure

Authors: *D. HULSEY[1], J. GUENZA-MARCUS[3], E. D. VICKERS[2], D. A. MCCORMICK[2]; [2]Inst. of Neurosci., [1]Univ. of Oregon, Eugene, OR; [3]Univ. of Oregon, Inst. of Neurosci., Eugene, OR

Abstract: During non-rapid eye movement sleep (NREMS) the nervous system exhibits prominent infra-slow oscillations (ISO, ~0.02Hz) in activity patterns. These ISOs also occur during psychedelic exposure (psilocybin, DOI). The ISO presents as a lawful temporal organization of neuromodulatory tone, hippocampal ripples, sleep spindles and more, and is reflected in pupil size fluctuations. Disruption of these dynamics inhibits memory functions, and atypical spindle activity marks neurological disorders such as Schizophrenia and Alzheimer's. The spatial occurrence of 'local' and 'global' spindles have been documented, but their observation typically relies on cortical EEG, which provides limited, spatially diffuse signals, and an underdeveloped understanding of their regional progression and interactions. To begin addressing these gaps in knowledge, we developed a protocol for measuring oscillatory neural activity across the entire right dorsal cortex of naturally sleeping, head fixed mice. GCamp8m imaging of calcium fluctuations in excitatory neurons (CaMKII-Cre) through the intact cleared skull at high frame rates (60+ Hz) reveals delta (0.5-3 Hz), putative alpha (3-5 Hz), and sigma band oscillations rapidly shifting throughout cortex during natural sleep. To our knowledge, this is the highest resolution preparation allows resolution of sigma band oscillations (10-16Hz). Their occurrence is negatively correlated with pupil diameter during ISOs, in keeping with recent findings regarding their occurrence during NREMS. We also performed concurrent electrophysiological recordings (Neuropixels) in visual cortex, hippocampus and visual thalamus allow for temporal alignment of cortical events, thalamic bursting and hippocampal ripple events with sigma band activity throughout cortex. Preliminary (N=2 mice) indicate the presence of two distinct cortical networks with similar dynamics in both the putative alpha and sigma bands, each with unique phase relationships to ISO of pupil diameter. The first is a motor-somatosensory network, in which sigma and spindle activity peaks during pupil constriction, and the second a retrosplenial-visual-auditory network, with peak activity at the trough of pupil diameter fluctuations. Ongoing experiments will probe shifts in the rapidly shifting dynamics following visual and auditory guided spatial tasks, and effects of their disruption on memory retention. Further observations of these patterned activations in disease models of mice may reveal more specific deficits.

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.09/KK21

Topic: H.08. Drugs of Abuse and Addiction

Support: Tiny Blue Dot Foundation

Title: Brain-wide Survey of Mouse Transcriptomic Cell Types Activated by Acute Psilocybin and Ketamine Injection

Authors: *D.-W. KIM, S. VARGAS, C. LEE, T. CASPER, M. CLARK, A. JORDAN, M. JUNGERT, R. A. MCCUE, E. PHILLIPS, D. BERTAGNOLLI, T. CARDENAS, A. CHAKKA, R. CHAKRABARTY, R. FERRER, J. GOLDY, J. GUZMAN, K. JAMES, B. NGUY, D. B. ROCHA, A. TORKELSON, K. SMITH, N. DEE, Z. YAO, J. T. TING, C. KOCH, H. ZENG; Allen Inst. for Brain Sci., Seattle, WA

Abstract: Major depressive disorder is a debilitating psychiatric condition, but current antidepressants are neither fast-acting nor effective, particularly in cases of treatment-resistant depression. As alternatives, classical psychedelics (e.g., psilocybin) and the dissociative ketamine have shown therapeutic potential in early-stage clinical trials. Yet their underlying neural mechanisms remain largely elusive, in part due to limited systematic animal studies. We performed large-scale (~18 brain areas) Act-seq experiments ~1 hour after acute intraperitoneal injection of either psilocybin (1 mg/kg) or ketamine (10 mg/kg) in single-housed male mice. Right after injection, we observed drug-induced behaviors in all mice (head-twitch for psilocybin and increased locomotion for ketamine). Act-seq, a variant of single-cell RNA-sequencing, enables the identification of transcriptomic cell types (t-types) activated by a specific manipulation, by measuring endogenously induced immediate early gene (IEG) expression. After rigorous data QC, we obtained transcriptomic profiles from 837,414 neurons across 167 Act-seq libraries. The data were mapped to our whole mouse brain taxonomy (ABC atlas), revealing neuronal t-types with significantly altered IEG expression following drug treatment relative to saline control. Overall, both drugs induced distinct and partially overlapping region- and cell-type-specific IEG activation patterns. Psilocybin robustly activated deep-layer excitatory cortical t-types, particularly layer 4/5 intratelencephalic (IT) neurons, with a strong bias toward anterior cortices (medial prefrontal, primary motor, insular, somatosensory), whereas minimal IEG activation was observed in posterior cortices (primary visual, auditory, temporal association). In contrast, ketamine elicited weaker but more spatially localized IEG activation in layer 5/6 IT and layer 6 corticothalamic (CT) neurons of somatosensory and insular cortices. In subcortical regions, we observed sparse but selective IEG activations in specific t-types. For example, “PVT-PT Ntrk1 Glut_2” in anterior thalamus (responsive to both drugs), “OT D3 Folh1 Gaba_1” in ventral striatum (ketamine only), and “STR D2 Gaba_6” in dorsal striatum (psilocybin only). To validate a subset of the activated t-types identified by Act-seq, we also performed c-Fos immunohistochemistry combined with cell-type-specific enhancer-AAV labeling after acute psilocybin injection, confirming robust and selective c-Fos induction in L4/5 IT neurons of the primary motor cortex, in strong agreement with the Act-seq data.

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.10/KK22

Topic: H.08. Drugs of Abuse and Addiction

Support: Shanahan Foundation Funding

Title: Cell-type-specific changes in psilocybin-induced psychedelics states

Authors: *Y. WANG[1], A. M. SHELTON[2], L. MARKS[3], D. WYRICK[4], S. R. OLSEN[3], M. A. BUICE[3], U. SÜMBÜL[3], I. REMBADO[3], C. KOCH[5];
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Abstract: While psychedelic drugs induce dramatic changes in consciousness in human users, their effects on the brain at the cellular level remain poorly understood. Recent research demonstrates that psilocybin induces acute changes in cortical L5p neurons in mice. To investigate this, we used Sim1-Cre;Ai32 and Tlx3-Cre;Ai167 transgenic mice to label ET and IT L5p neurons for optotagging, injected them (i.p.) with either saline or psilocybin (3 mg/kg), and recorded their electrophysiological properties using Neuropixels Ultra probes. Since optotagged units were sparse, we developed a data augmentation technique to classify IT neurons in Sim1-Cre sessions and ET neurons in Tlx3-Cre sessions. By combining supervised learning with a contrastive learning strategy to automatically extract waveform features, we achieved state-of-the-art classification accuracy of 0.83 for optotagged units without fine-tuning.
We found that a large proportion of IT units exhibit increased burstiness at the onset of psilocybin injection, while ET units and other non-optotagged regular-spiking units decrease their burstiness. We then investigated burstiness and its network-level effects of changes in spiking dynamics among L5p neurons across multiple brain regions (e.g., SSp, MOs) using a multi-population recurrent switching linear dynamical system. The model discovered a stark state change, several minutes after the i.p. injection, across multiple psilocybin experiments in different brain regions, hinting at the existence of a regular, waking state and a second, distinct state associated with the psychedelic experience in mice. On the other hand, the model did not show such a change for the control saline injection.

Disclosures: Y. Wang: A. Employment/Salary (full or part-time): Allen Institute. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Shanahan Foundation Fellow. **A.M. Shelton:**

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

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Program #/Poster #: PSTR467.11/LL1

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant MH135565
Department of Anesthesiology, University of Michigan

Title: Biophysical modeling of anesthesia reversal by a serotonergic psychedelic

Authors: *E. BUTEL-FRY[1], E. HUELS[3], D. PAL[4], V. BOOTH[2], M. R. ZOCHOWSKI[5]; [1]Physics, [2]Mathematics & Anesthesiol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [3]Anesthesiol., [4]Dept. of Anesthesiol., [5]Dept. of Physics and Biophysics Program, Univ. of Michigan, Ann Arbor, MI

Abstract: General anesthetics, such as propofol and isoflurane, produce sedative effects by increasing network-wide inhibitory signaling. Meanwhile, serotonergic psychedelics strongly promote excitation through 5HT2A receptor activation. Recent data[1] suggest that intravenous delivery of 2,5-Dimethoxy-4-Iodoamphetamine (DOI), a synthetic serotonergic psychedelic that acts via 5HT2A receptors, can induce wakefulness and reverse anesthesia despite continued delivery of isoflurane and propofol. Importantly, behavioral arousal induced by DOI is accompanied by restoration of EEG functional connectivity and network structure, suggesting that DOI produces a functional recovery from anesthesia. To investigate potential mesoscopic mechanisms of psychedelic-mediated anesthetic reversal, we present a biophysically motivated, in-silico model. In a small-world network of Hodgkin-Huxley pyramidal cells and Wang-Buzsaki parvalbumin+ interneurons, we model anesthesia as a network-wide increase in inhibitory synaptic signaling and model psychedelic 5HT2AR activation as an increase in spontaneous excitation. We report changes in gamma-band coherence, power, and frequency that recapitulate experimental findings. Finally, we find changes in local functional connectivity that are consistent with large-scale, whole-brain recordings. Together our results suggest a possible bottom-up mechanism of anesthesia reversal by psychedelics. [1] Psychedelic-mediated Reversal of General Anesthesia and Restoration of Brain Dynamics in Rat. Emma R. Huels, Nicholas Kolbman, Christopher W. Fields, Amanda G. Nelson, Hazel Jackson, Tiecheng Liu, George A. Mashour, Dinesh Pal. bioRxiv 2025.01.22.632279; doi: https://doi.org/10.1101/2025.01.22.632279

Disclosures: E. Butel-Fry: None. **E. Huels:** None. **D. Pal:** None. **V. Booth:** None. **M.R. Zochowski:** None.

Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.12/LL2

Topic: H.08. Drugs of Abuse and Addiction

Support: University of Michigan Department of Anesthesiology
CTSA Postdoctoral T32 Training Award from the University of Michigan (grant no. T32TR004764)

Title: The Effect of the Atypical Psychedelic Salvinorin A, a Selective Kappa-Opioid Agonist, on Brain Dynamics in Rats

Authors: *E. HUELS[1,2], H. WANG[1], T. LIU[1], D. PAL[1,2,3,4];
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Abstract: Amid the psychedelic renaissance, salvinorin A—the primary psychoactive component of Salvia divinorum and a highly selective kappa-opioid agonist—has remained understudied compared to serotonergic psychedelics. Herein, we used a within-subject design to determine the effect of intravenous delivery of low (0.2 mg/kg) or high (2 mg/kg) dose salvinorin A or vehicle control on brain dynamics in adult Sprague Dawley rats (n= 2 male, 1 female). Rats were surgically equipped to record high-density (30 channel) electroencephalogram (EEG) across the cortex and receive an intravenous infusion (5 minutes) of salvinorin A or the vehicle control (14:26:60 DMSO:PEG400:saline). On different days, EEG data were collected (0-300 Hz, sampling rate of 1 kHz) before, during, and after administration of low dose salvinorin A, high dose salvinorin A, or vehicle control. Artifact-free 1-5 minute EEG epochs from before and immediately after salvinorin A or vehicle were assessed for changes in brain dynamics using the following measures: weighted phase lag index (wPLI, a measure of non-directional functional connectivity), normalized symbolic transfer entropy (NSTE, a measure of directional functional connectivity), and node degree (a measure of centrality). The data are presented as the percent change (mean ± SD) from the 1-5 minute epoch immediately before the delivery of salvinorin A or vehicle. Our results show that the delivery of either dose of salvinorin A increased high gamma (125-165Hz) global wPLI (low dose: 100.00% ± 25.36%; high dose: 88.93% ± 5.44%). Salvinorin A also increased feedforward (parietal-to-frontal) and feedback (frontal-to-parietal) connectivity (NSTE) (low dose feedforward: 26.45% ± 9.84%; low dose feedback: 29.73% ± 22.06%; high dose feedforward: 24.79% ± 8.98%; high dose feedback: 24.72% ± 15.71%). Finally, both doses of salvinorin A increased global node degree in the high gamma band (low dose: 208.10% ± 138.55% high dose: 189.06% ± 84.03%), with the greatest changes occurring at frontal electrodes. Vehicle administration did not produce similar changes in any of the EEG measures. These changes in brain dynamics are similar to those reported by us in a recently concluded study of psilocybin, a serotonergic psychedelic. Altogether, the data from this study

and the findings from previous studies with serotonergic psychedelics suggest that there may be a common unitary EEG signature representing a psychedelic-like state in animal models.

Disclosures: E. Huels: None. **H. Wang:** None. **T. Liu:** None. **D. Pal:** None.

Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.13/LL3

Topic: H.08. Drugs of Abuse and Addiction

Title: Developmental changes in brain structure, function, and sensory perception following oral psilocybin exposure during adolescence

Authors: *A. N. MAHESWARI[1,2], T. CHUKWUEMEKA[2], R. UTAMA[2], E. K. BRENGEL[3], R. J. ORTIZ[4], P. P. KULKARNI[3], C. F. FERRIS[2];
[1]Biotech., [2]Ctr. for Translational Neuroimaging, [3]Psychology, Northeastern Univ., Boston, MA; [4]Northern Illinois Univ., Northern Illinois Univ., DeKalb, IL

Abstract: Psilocybin is a serotonergic psychedelic and partial 5-HT2A receptor agonist, associated with distinct neuroanatomical, molecular, and behavioral modifications**.** This study examines developmental neuroanatomical and functional alterations following adolescent psilocybin exposure. Female and Male C57BL/6J mice received multiple oral doses of 3.0 mg/kg psilocybin or vehicle beginning on postnatal day P51. Between P90 and P120, mice underwent multimodal neuroimaging and behavioral assessments targeting cognitive and motor function. Diffusion-weighted imaging revealed widespread increases in fractional anisotropy (FA) across the midbrain and hindbrain, indicative of potential alterations in microstructural architecture, axonal coherence and myelination. Functional MRI(FMRI) showed decreased positive BOLD responses in dopaminergic regions associated with reward signaling, suggesting reduced sensitivity to motivational salient stimuli. Concurrently, increased negative BOLD responses were detected in the prefrontal cortex, implicating altered responsivity to fear-related stimuli. Resting state functional connectivity rs(FC) revealed significant whole brain connectivity alterations, notably in prefrontal cortex, a region critical during adolescence, a period characterized by heightened neural plasticity and vulnerability. Sex based differences were observed in whole brain diffusivity and in open field behavior assessment where female mice exhibited greater exploratory locomotor activity compared to males and psilocybin significantly reduced exploratory behavior in females reduced compared to males. These findings suggest that psilocybin exposure during adolescence leads to long-lasting changes in brain microarchitecture and function, particularly within the mesolimbic and prefrontal pathways, emphasizing the importance of adolescent development and sex in shaping long-lasting psychedelic responses.
Acknowledgement: We thank the National Institute on Drug Abuse, Drug Supply Program and

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Disclosures: A.N. maheswari: None. **T. Chukwuemeka:** None. **R. Utama:** None. **E.K. Brengel:** None. **R.J. Ortiz:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C.F.F and P.P.K have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI Atlases, and analytical software for use in awake animal imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C.F.F and P.P.K have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI Atlases, and analytical software for use in awake animal imaging..

Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.14/LL4

Topic: H.08. Drugs of Abuse and Addiction

Support: We thank the National Institute on Drug Abuse, Drug Supply Program and the Research Triangle Institute for providing the 5-MeO-DMT used in these studies.

Title: Dose-dependent changes in global brain activity and functional connectivity following exposure to 5-MeO-DMT: a BOLD MRI study in awake rats.

Authors: *P. P. KULKARNI[1], N. CAVALLARO[2], D. AKINS[1], P. RAI[2], M. T. NASSEEF[3], S. SOLTANPOUR[4], R. J. ORTIZ[5], C. FERRIS[6];
[1]Psychology, [2]Northeastern Univ., Boston, MA; [3]Dept. of Mathematics, Prince Sattam Bin Abdulaziz Univ., Al-Kharj, Saudi Arabia; [4]Sch. of Information Technol., Carleton Univ., Ottawa, ON, Canada; [5]Northern Illinois Univ., Northern Illinois Univ., DeKalb, IL; [6]Psychology, Northeastern Univ. CTNI, Boston, MA

Abstract: 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a naturally occurring tryptamine found in the parotid gland secretions of the toad, *Incilius alvarius,* that primarily acts as an agonist at the 5-HT1A and 5-HT2A receptors. However, 5-MeO-DMT differs from most other serotonergic psychedelics in having 100- to 1,000-fold higher affinity for the serotonin 5-HT1A receptor over the serotonin 5-HT2A receptor. This unique receptor profile contributes to its distinct subjective effects compared to other classical psychedelics. When smoked, the duration of the effects of 5-MeO-DMT can be as little as ten minutes making it notably shorter-acting than other psychedelics. The subjective effects of 5-MeO-DMT are described as distinct from those of DMT and other psychedelics characterized by a relative lack of visual effects but

profound mystical experiences and ego dissolution. To characterize the immediate effects of 5-MeO-DMT on global brain activity and resting state functional connectivity we conducted a phMRI study on fully awake male and female rats. During the scanning session rats were given an IP injection of vehicle, 0.01, 0.1, or 1.0 mg/kg 5-MeO-DMT. The effect on BOLD signal was almost immediate with a global dose-dependent increase in negative BOLD. This occurred within the first 10 min of treatment and recovered by the end of the 30 min imaging session. Interestingly, the visual and auditory cortices were unaffected as were much of the cerebellum. The connectivity was decreased but only for the 0.1 mg/kg dose of 5-MeO-DMT and then only limited to the cortex, thalamus and hypothalamus as compared to vehicle and other drug doses. In previous studies on LSD, psilocybin and mescaline we reported a global increase in connectivity using the same imaging protocol. This difference may be due to selectivity for the 5HT1A receptor versus the 5HT2A.

Disclosures: **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging.. **N. Cavallaro:** None. **D. Akins:** None. **P. Rai:** None. **M.T. Nasseef:** None. **S. Soltanpour:** None. **R.J. Ortiz:** None. **C. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging.

Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.15/LL5

Topic: H.08. Drugs of Abuse and Addiction

Title: Dose-dependent modulation of global brain activity and functional connectivity by ibogaine in awake rats: A BOLD fMRI study

Authors: ***B. AXE**[1,2], N. CAVALLARO[2,3], P. P. KULKARNI[2,4], C. F. FERRIS[2,4]; [1]Bioengineering, [2]Ctr. for Translational Neuroimaging, [3]Pharmaceut. Sci., [4]Psychology, Northeastern Univ., Boston, MA

Abstract: 12-Methoxyibogaine (Ibogaine) is a naturally occurring psychoactive indole alkaloid found in the root bark of the plant, *Tabernanthe iboga*, that primarily acts on μ-opioid and κ-opioid receptors, and non-competitively antagonizes NMDA receptors, unlike the mechanisms of classical 5HT hallucinogens. The subjective experiences of Ibogaine have been described by deep introspection and ego-dissolution, yet the neurobiological mechanisms are still poorly understood. When orally administrated in humans, the distinct visionary phase can last 4-8 hours, however its introspective phase extends to as long as 48-72 hours making it notably longer acting

than other psychedelics. To characterize the acute effects of Ibogaine administration on global brain activity and resting state functional connectivity (rsFC), we conducted a pharmacological MRI (phMRI) study on fully awake male and female rats. Animals underwent a 5-day acclimation period to minimize stress and motion artifacts during imaging. During the scanning session, rats were given an intraperitoneal (IP) injection of vehicle, 1.0, 5.0, or 25.0 mg/kg of Ibogaine HCl in 0.9% NaCl saline. Results reported a dose-dependent response in BOLD activity, in global and region-based signaling over the 30-minute fMRI session. This was followed by a 15-minute rsFC EPI scan, which reported global changes in functional connectivity. Drug-specific connectivity changes were compared to previously-characterized 5HT2A receptor agonists such as psilocybin and LSD. This study demonstrates ibogaine's distinct activation and connectivity patterns and reflects the multimodal pharmacology compared to classic psychedelics; elucidating its acute hemodynamic profile may inform its therapeutic application in substance use disorders.
We thank the National Institute on Drug Abuse, Drug Supply Program and the Research Triangle Institute for providing the Ibogaine used in these studies.

Disclosures: B. Axe: None. **N. Cavallaro:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C.F.F and P.P.K have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI Atlases, and analytical software for use in awake animal imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C.F.F and P.P.K have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI Atlases, and analytical software for use in awake animal imaging..

Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.16/LL6

Topic: H.08. Drugs of Abuse and Addiction

Title: Mescaline-induced modulation of global brain activity, functional connectivity, and fear and reward pathways: a BOLD MRI study in awake rats

Authors: *N. CAVALLARO[1], P. RAI[1], D. AKINS[1], R. UTAMA[1], C. R. CODY[1], B. AXE[1], A. MAHESWARI[1], R. J. ORTIZ[2], P. P. KULKARNI[1], C. FERRIS[1];
[1]Northeastern Univ., Boston, MA; [2]Northern Illinois Univ., Aurora, IL

Abstract: Mescaline is a psychoactive alkaloid found in peyote, acting as a 5-HT2A agonist and inducing hallucinations and euphoria through sensory system effects. Sensory perception, dominated by olfaction in rodents, interprets external stimuli. This study used BOLD pharmacological MRI (phMRI) in awake Sprague Dawley rats (n=24; 12 male, 12 female) to

investigate the effects of mescaline (50 mg/kg, i.p.) on global brain activity, functional connectivity, and activation of fear- and reward-related pathways. Changes in BOLD signal were recorded over a 20-minute window following injection. Approximately 25 minutes post-injection, resting-state fMRI data were acquired to assess functional connectivity, followed by odor-evoked scans using benzaldehyde (innate reward cue) and mountain lion urine (innate threat cue). All imaging data were registered to a 3D rat MRI atlas comprising 173 distinct brain regions, enabling region-specific analysis of both BOLD signal and connectivity changes. Compared to vehicle controls, mescaline induced widespread reductions in positive BOLD signal and increases in negative BOLD signal across multiple brain regions, most notably in the cerebellum and cortex, indicating a global suppression of neural activity. Despite this reduction in regional activation, mescaline significantly increased functional connectivity across networks, particularly between the cerebellum, thalamus, hippocampus, and somatosensory cortex. Odor-evoked fMRI revealed blunted BOLD responses to benzaldehyde following mescaline, while responses to mountain lion odor remained comparable to vehicle, suggesting selective dampening of reward-related processing without altering innate fear responses. Degree centrality analysis further confirmed increased global integration under mescaline. These results highlight mescaline's capacity to induce a unique neurofunctional state marked by decreased regional activation and enhanced large-scale connectivity, with ongoing studies aimed at identifying behavioral and dose-dependent correlates.
We thank the National Institute on Drug Abuse, Drug Supply Program and the Research Triangle Institute for providing the mescaline used in these studies.

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.17/LL7

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH/DA053817
NIH/GM152169

Title: Effects of psychedelics on locomotion in C. elegans

Authors: *S. R. LOCKERY[1,2], A. M. WHITE[2], A. BAUER[2], S. FAUMONT[2];
[2]Inst. of Neurosci., [1]Univ. of Oregon, Eugene, OR

Abstract: Psychedelics have recently re-emerged as promising treatments for psychiatric conditions such as depression, PTSD, and substance use disorder. A vigorous effort is now underway to improve the efficacy and accessibility of psychedelic therapies. At present, this effort is taking place without a detailed understanding of the mode of action of psychedelics. Genetically tractable invertebrate models, such as Drosophila and *C. elegans*, with short generation times and a wealth of molecular genetic tools, offer a key adjunct to mode-of-action studies currently underway in rodents. The first step in establishing these models in psychedelic research is to identify behavioral phenotypes associated with psychedelic exposure. Classic psychedelics fall into three main types: tryptamines, ergolines, and phenethylamines. Using locomotion (crawling) as a readout, we screened two tryptamines (dimethyltryptamine (DMT) and psilocin (PSI), the active metabolite of psilocybin), one ergoline (lysergic acid diethylamide (LSD)), and one phenethylamine (2,5-dimethoxy-4-iodoamphetamine (DOI)) for behavioral effects in *C. elegans*. Synchronized young adult worms were exposed to the drug at a concentration of 0.5 mM in M9 buffer for 30 minutes, placed individually in 1 cm diameter NGM arenas, then tracked for five minutes. Control worms were exposed to M9 only.Tracking data were analyzed in terms of forward speed, reverse speed, and the probability of reverse locomotion. DMT and DOI had no effect on any of the metrics. PSI caused a 22% increase in reverse probability. LSD caused a 33% and 112% increase in reverse speed and reverse probability, respectively. Thus, at least two psychedelic drugs have behavioral effects in *C. elegans*. We chose LSD for further study because it had the greatest effect on locomotion. The effect of LSD on reverse probability was still detectable two hours after exposure. We mapped the LSD dose-response curves (DRCs) for each metric from 0.01-1 mM. The DRC for reverse probability showed increasing effects from 0.05-0.5 mM. The DRCs for forward and reverse speed were complex, with slowing at some doses and acceleration at others. Psychedelics are serotonin receptor agonists. Deletion of serotonin-receptor genes ser-1, ser-5, ser-7 attenuated the effects of LSD on forward speed and reverse probability. In contrast, deletion of ser-4 amplified the effects of LSD on these metrics. Thus, serotonin receptors are required for the normal responses to LSD. We conclude that *C. elegans* is a viable model for psychedelic mode-of-action studies.

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Poster

PSTR467: Hallucinogens and Dissociative Anesthetics: Brain States, Network Activity, and Underlying Pharmacology

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Set and Setting in a Preclinical Rat Model of Psychedelic Drug "Therapy" for Trauma

Authors: *K. LAWSON[1], H. VU[1], A. DHAMI[1], N. COLE[2], S. V. MAHLER[3];
[1]UC Irvine, Irvine, CA; [2]Howard, Washington, DC; [3]Neurobio. and Behavior, Univ. of California, Irvine, Irvine, CA

Abstract: Depression, PTSD, and addiction are common mental health disorders that affect millions of people worldwide. Risk of developing these disorders is increased in those with a history of stress during childhood, or trauma as an adult. To determine the causal mechanisms of adversity-induced brain changes with relevance to psychiatric disorders, and to test potential new therapeutics, we have established a robust rat model of adulthood trauma that robustly alters fear learning, allowing us to test novel treatment strategies. In the last few years, psychedelic drugs like LSD, psilocybin, and DMT have re-emerged in psychiatry, with apparent potential for treating depression, addiction, and other psychiatric disorders. These promising initial clinical findings inspired us to develop a new rat model of “psychedelic therapy”, in hopes of studying mechanisms by which they exert therapeutic actions in the brain. We show that a single dose of the psychedelic serotonin 2A (5-HT2A) receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI; 1mg/kg) persistently reverses trauma-induced fear hypersensitivity in both sexes for at least 3 days. Importantly, we found that DOI’s actions were subject to influences related to both “set” and “setting,” in that fear-reducing effects of the psychedelic was only seen in rats with prior aversive experiences (i.e. trauma-like “mindset”), and when the drug was delivered in a comfortable, but not uncomfortable “setting.” We also examined the brain-wide neural circuits underlying these “psychedelic therapy-like” effects using brain clearing and mapping of whole-brain c-Fos expression patterns. Results demonstrate that preclinical models of psychedelic therapy should consider contextual and experiential factors, even when studying rodents. In this way, we can better translate mechanistic rodent work to the clinic, in hopes of developing efficient, effective therapies for humans with stress-related disorders who are desperately in need of novel approaches for treatment.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.01/LL9

Topic: I.01. Attention

Support: Human Frontier Science Program RGP0008/2017
ERC 833504-SPANUMBRA
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Title: Emergence of numerical representation by individual neurons in days-old zebrafish

Authors: P. LUU[1], A. NADTOCHIY[2], M. ZANON[1], J. MO[1], Z. DU[3], M. JONES[1], K. KEOMANEE-DIZON[4], C. H. BRENNAN[7], S. E. FRASER[5], ***T. V. TRUONG**[6];
[1]USC, Los Angeles, CA; [2]Biol. Sci., USC, Salt Lake City, UT; [3]molecular and computational biology, [4]Translational Imaging Ctr., [5]Mol. & Computat. Biol., [6]Mol. and Computat. Biol., USC, Los Angeles, CA; [7]Queen Mary Univ. of London, London, United Kingdom

Abstract: Number sense, the ability to quickly assess the quantity of objects in a set (also known as its numerosity), without sequential counting, is a key cognitive function that is critical for animals and humans alike to survive, reproduce, and thrive. Considered by many researchers to be one of the foundations of human mathematical ability, number sense is believed to be mediated by number neurons that fire selectively when the organism is presented with specific numerical stimuli, such as a visual scene containing multiple discrete dots. While the existence of number neurons has been supported through electrophysiological measurements in animals and humans, direct visualization of these cells through imaging has not been achieved. Further, little is known about how these number neurons develop in the brain. To look for number neurons in the developing brain of larval zebrafish, we combine advanced whole-brain light sheet microscopy, at single-neuron resolution, and state-of-the-art computational tools to comprehensively interrogate the entire brains of zebrafish larvae as the live animals are visually presented with different number of dots. We find, remarkably, number neurons in zebrafish larvae as young as 3-days-old, essentially as soon as their vision develops. Neurons selective for 1 are most abundant, followed by 2, 3, 4, and 5, with older animals having more neurons selective for higher numbers. We map the number neurons' distribution throughout the whole brain, and demonstrate through a machine-learning decoder that we can use the ensemble firings of individual number neurons to successfully predict how many dots the animal is seeing at any given time during the experiment. We believe our discovery of number neurons in zebrafish will open exciting avenues to further the study of how organisms develop and execute their perception of discrete quantities. Future work includes further testing the robustness of number neurons' response to different types of numerical stimulus, and how number neurons participate in behaviors that involve numerosity-choice-driven tasks.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.02/LL10

Topic: I.01. Attention

Support: The McDonnell Center for Systems Neuroscience SGP FY24

Title: The habenula orchestrates neural and behavioral responses to competing prey in larval zebrafish

Authors: *S. ZHU, M. LEVENDOSKY, G. J. GOODHILL;
Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Hunting offers a powerful model for investigating the neural circuits underlying sensory processing, attention, and decision-making. In natural settings, larval zebrafish hunt small, free-swimming zooplankton and often encounter multiple competing prey. Here, we examine how the presence of competing prey alters both behavior and brain-wide neural representations. Behaviorally, competing stimuli reduced hunting success and altered initial orienting turns. At the neural level, competing stimuli suppressed visually evoked activity across multiple brain regions, including the tectum, pretectum, nucleus isthmi, and habenula, with the strongest modulation observed in the habenula and nucleus isthmi. These two regions also showed the greatest differences in neural population trajectories between single and competing prey conditions, and yielded the highest decoding accuracy for stimulus context. Competition significantly altered inter-regional communication between the habenula and other brain regions. Notably, habenular activity was also the earliest predictor of behavioral responses and best distinguished whether a stimulus was presented alone or with a competitor. Ablation of the habenula impaired hunting behavior and reduced the distinction between single and competing stimuli in other brain regions. Together, these findings identify the habenula as a key node in the brain-wide network mediating stimulus competition.

Disclosures: S. Zhu: None. **M. Levendosky:** None. **G.J. Goodhill:** None.

Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.03/LL11

Topic: I.01. Attention

Title: Mediodorsal thalamus projections to Prelimbic and Anterior Cingulate cortices are differentially modulated by predictive cues

Authors: *K. RUNYON, K. SANDERS, A. HARTLE, W. M. HOWE;
Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: Deficits in attention are central to many psychiatric and neurodevelopmental disorders. Attention guides decision-making by prioritizing sensory cues for further processing.

Such cue detection relies on the precise coordination of neural circuits, with the mediodorsal thalamus (MD) playing a pivotal role by relaying sensory information to the prefrontal cortex. The prefrontal cortex encompasses multiple subregions, including the prelimbic cortex (PrL) and dorsal anterior cingulate cortex (dACC), which differentially contribute to attentional control. Here, we tested the hypothesis that the MD output pathways form unique information channels to the PrL and dACC, respectively, to support cue detection. Retrograde tracing with Cholera Toxin B injections into PrL or dACC (n=4 each) revealed that while both MD-PrL and MD-dACC neurons originate from the same lateral portion of the MD, there is a previously uncharacterized separation on an anterior to posterior gradient, with MD-PrL projections from the anterior portion and MD-dACC projections from the posterior portion. Additionally, MD axon terminal recordings (PrL n=6, dACC n=6) during a Pavlovian cue-association task show detected cue-specific responses in the MD-dACC and MD-PrL pathways. Activity in MD inputs to dACC increases in response to cues and is then suppressed once the animal initiates reward approach. In contrast, MD-PRL activity remains elevated until the reward presentation, regardless of the animal's response. Finally, when the association between the predictive cue and the reward is broken (extinction), projections to dACC show heightened activity during cue presentation, reflecting a possible role in error detection, whereas PrL responses to the cue gradually decrease. These findings uncover previously unrecognized anatomical and functional distinctions within MD-prefrontal circuits and highlight their differential contributions to cue processing, learning, and behavioral adaptation. This work advances understanding of thalamocortical mechanisms underlying executive function and may inform novel approaches to treat cognitive deficits in psychiatric disorders.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

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Program #/Poster #: PSTR468.04/LL12

Topic: I.01. Attention

Support: JSPS Grant 24KJ0566

Title: An experience-dependent cortico-cortical top-down input modulates associative learning rates

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Abstract: Animals selectively learn associations of external stimuli based on their experience. A well-known example is blocking, in which a previously learned association of one stimulus (phase 1: CS1 → US) prevents the formation of an association of a different stimulus (CS2 → US) during compound conditioning (phase 2: CS1 + CS2 → US). Blocking is classically explained from two perspectives. Rescorla and Wagner (1972) proposed that it results from a reduced reward prediction error (RPE) during phase 2. In contrast, Mackintosh (1975) suggested that reduced attention to CS2, due to heightened attention to CS1, leads to a lower learning rate for CS2. While the neural mechanisms underlying RPE have been extensively studied, those for attentional modulation of learning rates remain largely unknown. Here, we hypothesized that the attentional modulation of learning rate is mediated by cortico-cortical top-down inputs on CS2. To study the attentional modulation apart from RPE, we established a novel blocking paradigm with head-fixed mice for quantifying each animal's learning rate under constant RPE, using an auditory stimulus for CS1 and a tactile stimulus for CS2. As a CS2-related top-down input, we focused on a projection from the dorsal frontal cortex (dFC) to the primary somatosensory cortex (S1), which is involved in tactile processing (Manita et al., 2015) and its memory consolidation (Miyamoto et al., 2016). To investigate how tactile processing relates to the learning rate, we performed electrophysiological recordings of regular spiking (RS, excitatory) and fast spiking (FS, inhibitory) units in dFC and S1, and examined the excitatory-inhibitory (E/I) balance in phase 2. We found that the learning rate was more reduced in animals whose S1 E/I balance tipped toward inhibition. To investigate whether the top-down input affects S1 E/I balance and the learning rate, we optogenetically suppressed the top-down input in phase 2. This manipulation shifted the S1 E/I balance toward excitation and increased the learning rate. Finally, we confirmed that this top-down modulation of S1 E/I balance is experience-dependent by fiber-photometry recording of the calcium responses of S1 pyramidal and parvalbumin-positive neurons to an optogenetic dFC activation during phase 1. These results indicate that the top-down input dynamically changes during phase 1 to inhibit the primary sensory cortex, thereby reducing the learning rate for new associations in phase 2. This demonstrates the idea of attentional modulation of learning rates as proposed by Mackintosh (1975).

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Poster

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Topic: I.01. Attention

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Title: Cholinergic modulation of frontal sensory cortical projections supports post-error attentional adjustment

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Abstract: Maintaining attention after errors is a fundamental aspect of cognitive control. The anterior cingulate area (ACA), a subregion of the medial prefrontal cortex, plays a critical role in performance monitoring and attentional regulation. Projections from ACA to the visual cortex (ACAvis) have been shown to causally contribute to post-error attentional adjustment (Norman et al., Neuron 2021). However, the specific upstream neuromodulatory inputs that activate ACAvis neurons during this process remain poorly understood.To address this, we expressed genetically encoded biosensors in ACAvis neurons and monitored their inputs using fiber photometry while mice performed the five-choice serial reaction time task (5-CSRTT). We separately performed calcium imaging from ACAvis neurons during attentional behavior. These experiments revealed that acetylcholine input exhibited the strongest task-related increase. Using linear regression models, we quantified how much each input contributed to ACAvis neuronal activity during the anticipatory attention period and found that acetylcholine input significantly explained a large portion of the variance in ACAvis activity. This statistical evidence supports a key role for acetylcholine in modulating ACAvis activity during post-error attentional adjustment.To test causality, we optogenetically manipulated cholinergic projections from the basal forebrain to ACA selectively during the anticipatory attentional period of the 5-CSRTT. Inhibiting this input impaired attentional performance on trials following errors, while activating the same pathway enhanced it. These results demonstrate that cholinergic input to ACAvis neurons is both necessary and sufficient for post-error attentional adjustment.Together, these findings identify a targeted neuromodulatory mechanism supporting cognitive control after errors. This work advances our understanding of how frontal circuits dynamically modulate attention and may offer insight into mechanisms of attentional dysfunction in neuropsychiatric disorders.

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Poster

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Topic: I.01. Attention

Support: NIH-NIMH R00MH128892

Title: Tracking attentional vigilance across development in C57BL/6J mice

Authors: *H. D. KIM[1], B. R. FERGUSON[2];
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Abstract: Attention—the capacity to prioritize and selectively process sensory input—is fundamental to goal-directed behavior. Attention is disrupted in a range of neurodevelopmental and neuropsychiatric disorders, including autism and schizophrenia. Despite its clinical importance, the neural circuits underlying attention remain poorly understood. Mice provide a genetically tractable system for probing attention at the microcircuit level, however existing approaches are limited. To address this, we developed a simple battery of operant attention tasks that isolate three dimensions of attentional control: sensory engagement, vigilance, and resistance to distraction. We utilized these tasks to characterize the performance of male and female C57BL/6J mice at three timepoints—late adolescent (P45-60), young adult (P65-90), and middle aged adult (P130-290). Here, we present the findings from the vigilance task. In training, mice initiate trials by poking their noses through a center port, which triggers a 5 second (s) light cue in a left or right target port. Correct target port choices deliver a milk reward, whereas incorrect choices result in doors closing and a 15 s time-out. After achieving stable performance during training, we introduced a variable delay prior to the cue and tested their performance. Developmental analysis revealed sensitivity (cue discriminability) increases between adolescent and young adult mice. Aged mice also exhibited slower reaction times, but no difference in sensitivity in comparison to young adults. Additionally, adolescents and aged adults showed lower rates of consecutive correct responses than young adults. To investigate circuit dynamics, we recorded bulk calcium activity from glutamatergic neurons in the prelimbic medial prefrontal cortex (PL), a brain region previously implicated in attentional regulation. Activity tracked cue onset, was modulated by accuracy, and predicted trial outcome, suggesting the PL regulates performance. Future directions involve exploring inhibitory neuron subtypes in PL in health and disease.

Disclosures: H.D. Kim: None. **B.R. Ferguson:** None.

Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR468.07/LL15

Topic: I.01. Attention

Title: Development and rescue of a mouse model of cognitive dysfunction in methamphetamine-induced psychosis

Authors: *N. BAJWA[1], A. MUKHERJEE[2], J. SCOTT[3], N. REDDER[3], M. HALASSA[3];
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Abstract: Methamphetamine (METH) use represents a growing public health concern across the world, with recent evidence suggesting use has risen to an all-time high. Moreover, nearly half of chronic users in a treatment setting report some psychotic symptoms. This METH-induced psychosis is often confounded by underlying neuropsychiatric conditions like schizophrenia, impeding upon effective therapeutic interventions. Here, we aim to further characterize the features of METH-induced psychosis using a chronic METH regimen in mice.
Our findings demonstrate that, using a pharmacological strategy to sensitize and chronically treat mice with METH, we are able to recapitulate working memory and task-switching deficits often seen in meth-induced psychosis patients. We find that this protocol parametrically affects prefrontal cortex (PFC) dependent tasks in which animals must hold a rule in mind, as well as in a task where animals must flexibly switch between task contexts. Molecularly, this treatment leads to decreased levels of the neuronal K+/Cl- co-transporter KCC2 in the PFC, suggesting METH use is associated with GABAergic deficits in the PFC. Physiologically, chronic METH treatment appears to reduce the fidelity of PFC signal transmission with repeated recruitment of its neural ensembles. Critical to our therapeutic objective, we next demonstrated that treatment with a recently FDA approved M1 agonist specifically improves both working memory and task switching ability in METH-treated mice. Surprisingly, we find that this effect is unique to METH-treated animals, as both wild-type and schizophrenia mouse models are not improved by this treatment. Overall, our findings characterize a pharmacological model for METH-induced psychosis, its features, and provide a promising new therapeutic target for restoring cognitive function in chronic METH users.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

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Title: Disruptions in prefrontal processing during competing cognitive task demands in mouse behavior

Authors: *C. QIAN[1], W. ZHIKUN[1], C. ZHOU[2], W. YUNG[3], Y. KE[1];
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Abstract: The ability to allocate attention across competing demands as they arise is fundamental to both animal and human behavior. However, research demonstrates that dividing attention in this way typically incurs performance costs. Despite extensive investigation into the behavior, the neural mechanisms underlying limitations behind central cognitive control remain poorly understood. To address this gap, we developed a rodent behavioral paradigm requiring divided attention and combined it with chronic electrophysiological recordings in the prefrontal cortex (PFC). Using population-level analyses and linear encoding models, we identified robust deficits at both the level of external behavior and internal neural activity. Mice exhibited performance deficits when required to divide their attention. While individual PFC neurons displayed dynamic and transient task-related activity, population-level representations remained highly stable in a quantitative manner. Notably, we found that divided attention altered the dimensionality of neural population dynamics in a manner predictive of task outcomes. Furthermore, competing demands selectively disrupted only certain types of encoding—including of abstract representations for information critical for decision-making within task conditions. These results provide new insights into how the PFC manages limited attentional resources and reveal principles governing activity during cognitively demanding behaviors.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

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Program #/Poster #: PSTR468.09/LL17

Topic: I.01. Attention

Title: Efficacy and Pharmacokinetics of SUVN-I6107, A Muscarinic 1 Receptor Positive Allosteric Modulator (M1 PAM) in Animal Models of Cognition

Authors: *R. MEDAPATI, V. BENADE, V. PALACHARLA, R. ABRAHAM, V. GOYAL, S. JETTA, R. SUBRAMANIAN, S. PETLU, A. K. SHINDE, I. KALAIKADHIBAN, R. NIROGI; SUVEN LIFE SCIENCES, HYDERABAD, India

Abstract: The muscarinic 1 acetylcholine receptor (M1) has been implicated in various cognitive disorders. Currently, the allosteric site rather than the orthosteric site is being targeted in drug discovery to avoid the cholinergic side effects. SUVN-I6107 is a new chemical entity that acts as a positive allosteric modulator with affinity for the allosteric site of M1 receptors (M1- PAM). The effects of SUVN-I6107 on the allosteric site of the M1 receptor were evaluated using a calcium mobilization assay. The effect of SUVN-I6107 on neuronal spike rate in coronal hippocampal slice electrophysiology was studied in agonist and PAM modes of testing. The

pharmacokinetic properties of SUVN-I6107 were evaluated in rats, dogs and monkeys. The effect of SUVN-I6107 on cognition was assessed using time induced delay, and scopolamine induced memory deficits in rats using social recognition task (SRT). Effects of SUVN-I6107 on neuronal markers like soluble amyloid precursor protein (sAPPα) and inositol 1 phosphate (IP-1) levels were studied in rats. SUVN-I6107 was assessed for its effects on salivation in order to evaluate cholinergic side effects. SUVN-I6107 showed allosteric potency at the M1 receptor with very good selectivity against the orthosteric and allosteric site of M2-M5 receptors. It also improved the hippocampal neuronal firing, when tested in combination with EC20 of carbachol. SUVN-I6107 was found to be orally bioavailable in rats, dogs, and monkeys. In a rat model of cognition, SUVN-I6107 reversed the delay and scopolamine induced amnesia in SRT. Treatment with SUVN-I6107 produced significant increase in the levels of cortical sAPPα and striatal IP-1 in rats. On treatment with SUVN-I6107, there was no increase in salivation which was measured using cotton balls. From the results, we conclude that SUVN-I6107 may have therapeutic utility in various cognitive disorders. SUVN-I6107 is currently being evaluated in a Phase 1 clinical trial (NCT06705088) to assess its safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy human subjects.

Disclosures: R. Medapati: A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **V. Benade:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **V. Palacharla:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **R. Abraham:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **V. Goyal:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **S. Jetta:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **R. Subramanian:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **S. Petlu:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **A.K. Shinde:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **I. Kalaikadhiban:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment. **R. Nirogi:** A. Employment/Salary (full or part-time): SUVEN LIFE SCIENCES LTD, Full-time Employment.

Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR468.10/LL18

Topic: I.01. Attention

Title: A Drug for All Ages: Levetiracetam Enhances Attention in Both Young and Aged Rats

Authors: *P. MOAZEN[1], C. MACMILLAN[2], L. SILENIEKS[3], G. A. HIGGINS[4];
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Abstract: Levetiracetam (LEV) is an antiepileptic primarily used to treat seizure disorders. By binding to the SV2A protein LEV modulates synaptic transmission and reduces excessive neuronal firing. In addition to the epilepsies, this property may be of benefit to the treatment of some cognitive disorders such as mild cognitive impairment, early Alzheimer's disease, and Autism Spectrum Disorder. Due to the diverse age-related nature of these cognitive disorders, we used male, Long-Evans rats at two distinct life stages, young (Y: 3- 9 months) and aged (AG: > 18 months). Rats were trained to the five-choice serial reaction time task (5-CSRTT), a behavioral test widely recognised for evaluating drug effects on domains such as attention, response control, reaction time, and motor function. Once performance under standard task conditions of 0.75s SD, 5s ITI, and 100 trials was attained, rats were subjected to various task manipulations such as reduced ITI (2- 5s ITI, sITI), extended (10s) ITI, and extended (250) trials, each designed to tax aspects of attention and/or response control. The effect of age and LEV (10-60mg/kg) was evaluated under these task conditions. Relative to Y rats, AG rats exhibited evidence of declined attentional performance, especially under the sITI condition. For example % hit was significantly reduced in the AG cohort at the 2s ITI (Y: 35.8±5.2; AG: 10±3.8; $P<0.01$). In contrast, AG rats showed improved response control as measured by premature responses in the extended 10s ITI schedule (Y: 60.3±11.2; AG: 21.8±6.9 $P<0.01$). Pretreatment with LEV improved some measures in both age groups. For example, % hit was significantly increased in either Y (38.8±6.3, $P<0.01$) or AG (25.2±3.5, $P<0.01$) animals in comparison to their vehicles (Y: 28.2±3.4, AG: 18.3±2.1). These findings indicate that LEV may have therapeutic potential for mitigating cognitive decline across multiple clinical conditions. Moreover, these data underscore the importance of age as a biological variable in preclinical cognitive assessments and support the use of the 5-CSRTT as a sensitive tool for evaluating pro-cognitive agents across the lifespan.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

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Title: Neuroimmune State Modulates Sustained Attentional Control: Evidence from an Individual Differences Model

Authors: *H. CARMON[1], J. LEE[2], P. WALDMANN[1], M. SARTER[1], N. C. TRONSON[3]; [1]Dept. of Psychology, [2]Neurosci., Univ. of Michigan, Ann Arbor, MI; [3]Dept. of Psychology, Univ. of Mchigan, Ann Arbor, MI

Abstract: Sign-trackers (STs) and goal-trackers (GTs) represent two distinct phenotypes defined by differences in behavioral and motivational responses to reward-predictive cues in the Pavlovian Conditioned Approach task. STs attribute incentive salience to such cues, directing their attention and behavior toward them, whereas GTs focus on the reward itself, or the "goal," using the cue as a predictor. These phenotypes also differ in attentional processes where STs typically exhibit poorer attentional control than GTs in the sustained attention task (SAT) and decreased cholinergic function that mediates attentional function. Recently, we have described differences between ST and GT in neuroimmune signaling, where STs have higher levels of cytokines in the frontal cortex compared to GTs (Carmon et al, 2023). Given the role of cytokine signaling on regulation of cholinergic function, here we aimed to determine the impact of these individual differences in neuroimmune state on attentional function. First, we demonstrated that in addition to higher basal cytokine levels, STs have elevated microglial activity. Compared with GTs, STs show lower *Sall1* expression, a key homeostatic regulator of microglia state, and elevated expression of *CD45*, suggesting more active microglia phenotypes in STs in the absence of immune challenge. Next, to determine the role of microglia state in sign- vs goal- tracking behavior, and attentional performance, we used chronic minocycline hydrochloride (45 mg/kg/day in drinking water) treatment to suppress microglia activity. Minocycline reduced microglial activation, for example in STs, minocycline increased *Sall1* expression and decreased *CD45* expression, consistent with reduced microglial activity. Although minocycline did not alter ST or GT phenotypes in Pavlovian conditioned approach, it did significantly improve attentional performance in STs, enhancing performance across SAT training, and rescuing performance of STs on low-demand test trials. Ongoing work using viral-vector mediated genetic manipulations to target microglia function will demonstrate the specific role of frontal cortex neuroimmune state in individual differences in attentional function. Together, these findings suggest that neuroimmune function drive individual differences in attentional performance, indicating that ST and GT phenotypes encompass not only dopaminergic and motivational systems but also cognitive functions and neural mechanisms including cholinergic signaling and neuroimmune modulation.

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Poster

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Title: Effects of Dolutegravir (DTG) and Raltegravir (RAL) on Brain function and Behavioral study. A Model for Cognitive disorder and Motor Function in C57 Black Mice.

Authors: *G. MUTHIAN[1], S. MAHAPATRA[2], P. PRAKASH[2], R. CHAKRABORTY[2], M. BALASUBRAMANIAM[2];
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Abstract: Some antiretroviral drugs (ARVs), while effective in treating HIV can also negatively impact brain function in mice leading to cognitive and motor impairments and even promoting the build- up of brain damaging proteins. However some ARVs, like lamivudine have shown promising results in improving cognition in mouse model of certain conditions. Currently used INSTI including dolutegravir and raltegravir potentially reduce viral load, emerging studies suggest that INST-antiretroviral therapy (ART), especially DTG based ART are associated with neuropsychiatric problems. Yet, the mechanism that drive these neuropsychiatric effects are unknown. Therefore, in this study we investigated whether acute exposure to ART could contribute neuroinflamation. In this study C57/ BL mice were subsequently administered a daily dose of either DTG and RAL 2.5 mg or 25 mg / Kg body weight (IP) for two weeks. After the last injection animals were subjected to behavioral study including locomotor activity, heat map test, Rota rod, and beam walking test. Following the study, mice brains were dissected and all brain regions were used to study the molecular mechanism of action. The behavioral studies showed DTG and RAL treatment lead to change in locomotion and exploratory behavior and muscle coordination in mice compared to control. And also neuro chemicals changes in the cortex of DTG treated groups. Western blot analysis showed that DTG and RAL increase the neurofilament- L expression in the cortex region of the brain. The reduced locomotor activity and the marker protein changes showed new model for motor function/ cognitive function due to the effect of DTG and RAL. Our findings therefore highlight the potential of ART to be harmful to the brain and as such these drugs may contribute the development of HIV associated neurocognitive disorder.

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Poster

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Topic: I.01. Attention

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Title: Parvalbumin-expressing interneurons-mediated photoexcitation interacts with endogenous attenton modulation in primary visual cortex

Authors: *F. FERREIRA[1], D. MYERS-JOSEPH[2], M. M. DAVEY[1], A. KHAN[1];
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Abstract: Modulation of sensory processing by attention is a fundamental aspect of cognitive function. In the visual cortex, neural activity becomes more selective for stimuli when animals direct their attention to those stimuli, compared to when the same inputs are presented without attention. This enhancement in selectivity is thought to support improved behavioural detection and discrimination of relevant sensory information and serves as a key neural indicator of cognitive control. However, the underlying neural circuitry responsible for this process is yet to be fully understood. Parvalbumin-positive (PV) interneurons, which provide strong perisomatic inhibition to pyramidal (PYR) neurons, are known to be highly influenced by attention and play a significant role in shaping cortical activity. It remains unclear whether their attentional modulation results from changes in the surrounding network or if they actively drive attention-related modulation in nearby neurons. Here, we employ an all-optical technique to selectively activate PV interneurons while monitoring neuronal activity in layer 2/3 of the primary visual cortex (V1) of mice performing in a cross-modal attention-switching task. We find that attention enhances neural selectivity in both PV and non-PV populations, through a dynamic interplay of response amplification and suppression. Additionally, optogenetic activation of PV cells alters stimulus selectivity in non-PV neurons during both attended and unattended conditions, suggesting a key role for PV interneurons in mediating attention-dependent changes in visual processing.

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Poster

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Title: Chronic cholinergic enhancement confers resilience to attentional decline after sleep loss

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Abstract: Insufficient sleep generally impairs attention, yet some individuals such as short sleepers appear resilient. Our recent findings reveal that sleep loss disrupts dopaminergic signaling in the anterior cingulate cortex (ACC), impairing attention [1]. However, the neural mechanisms supporting attention in the face of sleep loss remain unclear. Here, we demonstrate that chronic enhancement of nicotinic acetylcholine receptor (nAChR) activity in the absence of Lynx1, a protein that dampens nAChR function, confers resilience to attentional decline under sleep need. Lynx1 knockout (KO) mice exhibited constant performance on a two-choice visual attention task across the circadian cycle, which was supported by enhanced α7-nAChR action. Similarly, these mice were able to maintain attentional performance after 4-hour sleep deprivation, verifying their resilience to attentional decline under acutely increased sleep need. Both across the circadian cycle and after acute sleep deprivation, the attentional resilience in Lynx1 KO mice was associated with sustained cortical oscillatory activity in the slow-gamma range (30-50 Hz), which has been repeatedly implicated in attention. Furthermore, Lynx1 KO mice showed elevated neuronal activity in the ACC during the attention task particularly for parvalbumin-positive (PV+) interneurons, wherein both Lynx1 and α7-nAChR were enriched. Given the established role of PV+ interneurons in the generation of gamma oscillations [2], chronically enhanced α7-nAChR signaling in the absence of Lynx1 may drive sustained PV+ neuronal activity and slow-gamma oscillations, thereby maintaining attention under increased sleep need. Our results highlight a novel cholinergic mechanism by which attention can be maintained after sleep loss, offering a potential therapeutic target for mitigating cognitive decline caused by insufficient sleep. **References**: [1] Makino, Y. et al. (2024). Sci. Transl. Med. 16: eadh9763. [2] Sohal, V.S. et al. (2009). Nature, 459: 698-702.

Disclosures: Y. Makino: None. **T.K. Hensch:** None.

Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.15/MM1

Topic: I.01. Attention

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Title: Gamma-phase relations causally determine the effectiveness of information transfer between neuronal populations

Authors: *E. DREBITZ, L.-P. RAUSCH, E. DOMINGO GIL, A. K. KREITER;
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Abstract: The selective routing and processing of neuronal signals encoding behaviorally relevant information are essential for effective and adaptive behavior. This need becomes particularly evident when neurons receive competing inputs for multiple stimuli that cannot be processed simultaneously. A prominent hypothesis posits that dynamic γ-phase synchronization (30-90 Hz) between sender and receiver populations enables a flexible, selective modulation of signal routing. Supporting this, previous studies reported much stronger γ-phase synchronization between receiver neurons and those encoding the relevant stimulus, compared to others encoding distractors. However, whether this synchronization plays a causal role in selective routing or merely reflects an epiphenomenon remains debated. To answer this question, we trained two monkeys on a demanding shape-tracking task that required the selective evaluation of a cued, behaviorally relevant stimulus while ignoring a distractor. Both stimuli were placed within the same receptive field of a V4 recording site. We investigated whether the effectiveness of a small volley of spikes evoked by intracortical microstimulation (ICM) in area V2 perturbed the activity of the receiving V4 neurons and monkeys' behavior in dependence of the V4 neurons' γ-phase when this disturbing input arrived. Indeed, its effectiveness in triggering spikes at the V4 site strongly depended on the current V4 γ-phase. Moreover, the animals showed significantly increased response times and a higher likelihood of missed responses if the ICM-evoked spikes arrived during the γ-phase, in which they caused the strongest effect on V4 spiking activity. These effects were absent when ICM spikes arrived during other phases of the V4 neurons' γ-cycle. Furthermore, we investigated whether stimulus information is more effectively routed between sender and receiver populations during periods with effective γ-phase relation between granular and supragranular layers of V1. To quantify stimulus-specific information flow, we spectrally tagged the stimulus located in the receptive fields of recorded neurons by randomly changing its luminance 100 times per second and computed the spectral coherence between this flicker signal and the neuronal activity of the receiving population. During periods of stable and effective γ-phase relations with the sender population, we observed a significantly more stimulus information transfer as compared to other periods. These results demonstrate the causal role of γ-phase synchronization in selective information routing and processing.

Disclosures: E. Drebitz: None. **L. Rausch:** None. **E. Domingo Gil:** None. **A.K. Kreiter:** None.

Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.16/MM2

Topic: I.01. Attention

Title: Microtubule-stabilizer epothilone B delays isoflurane-induced unconsciousness in mice

Authors: *Z. QIU[1], X. YU[1], Y. HUANG[3], M. C. WIEST[2];
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Abstract: Volatile anesthetics are currently believed to cause unconsciousness by acting on one or more molecular targets including neural ion channels, receptors, mitochondria, synaptic proteins, and cytoskeletal proteins. Anesthetic gases including isoflurane bind to cytoskeletal microtubules (MTs) and dampen their quantum optical effects, potentially contributing to causing unconsciousness. This possibility is supported by the finding that taxane chemotherapy consisting of MT-stabilizing drugs reduces the effectiveness of anesthesia during surgery in human cancer patients; and by our previous study demonstrating anesthetic resistance in rats treated with a brain-penetrant MT-stabilizing drug. In order to experimentally assess the contribution of MTs as functionally relevant targets of volatile anesthetics in mice, we measured latencies to loss of righting reflex (LORR) under isoflurane in male and female mice injected subcutaneously with vehicle or varying doses of the brain penetrant MT-stabilizing drug epothilone B (epoB). Experimenters collecting the LORR latency data were blind to each mouse's drug condition.
Our preliminary results show significantly increased LORR latencies (i.e., anesthetic resistance) in epoB-treated mice on the day following injection, with reduced effects on post-injection days 3 and 5. The effect could not be accounted for by tolerance from repeated exposure to isoflurane. These preliminary results suggest that binding of the anesthetic gas isoflurane to MTs causes unconsciousness in mice, as it does in rats. This finding is predicted by the Orchestrated Objective Reduction (Orch OR) model that posits consciousness as a property of a quantum physical state of neural MTs.

Disclosures: Z. Qiu: None. **X. Yu:** None. **Y. Huang:** None. **M.C. Wiest:** None.

Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.17/MM3

Topic: I.01. Attention

Title: Low-cost automated setup for assessing sustained attention in rats

Authors: *B. NAMDARZADEH;
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Abstract: Sustained attention, crucial for understanding disorders like ADHD, is often costly to study. Our research introduces a low-cost, automated system for assessing this in rats, enhancing the accessibility and consistency of cognitive research. This system is designed for detailed studies of attention mechanisms, paving the way for novel therapeutic interventions. Our study utilized seven male hooded rats, adhering to ethical guidelines. The experiment involved a

bespoke, low-cost automated behavioral apparatus designed to assess cognitive behavior in response to auditory and visual stimuli. The setup is controlled by an Arduino board interfaced with MATLAB, ensuring precise execution and data capture of behavioral tasks. The tasks required rats to initiate trials by nose-poking into a center port, maintaining this position until a delayed go cue signaled them to select a side port for a reward. The difficulty of the task was progressively increased by extending the waiting period up to six seconds, systematically training the rats to enhance their sustained attention. The entire system was meticulously assembled to ensure uniformity and reliability, with continuous monitoring of task execution and environmental conditions, including temperature and humidity control, to maintain experimental integrity. In our preliminary analysis, rats demonstrated a significant improvement in their ability to maintain a center nose-poke as the delay period was extended. Specifically, the duration for which rats could hold the nose-poke increased significantly over trials, from an initial average of 0.01 second to 3.05 ± 1.65 seconds by the end of the training period. Statistical analysis using a repeated measures ANOVA indicated that these changes were significant, highlighting an enhancement in sustained attention capabilities. Additionally, variability in performance was observed across subjects, with some rats achieving maximum delay maintenance faster than others. This variability emphasizes individual differences in attentional capacity among the rats. These results demonstrate the effectiveness of our setup in measuring sustained attention improvements in rats, offering insights into ADHD and potential for broader neuropsychiatric research. The system's affordability and scalability make it a valuable tool for exploring attention mechanisms and developing targeted interventions.

Disclosures: B. Namdarzadeh: None.

Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR468.18/MM4

Topic: I.01. Attention

Support: ERC 818521

Title: Surgically induced model of spatial neglect in squirrel monkeys

Authors: *T. ORSET[1], J. ROYO[1], J. LOAYZA[1], P. BARTOLOMEO[1], P. POUGET[1], M. THIEBAUT DE SCHOTTEN[2];
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Abstract: Spatial neglect is a neuropsychological condition in which individuals fail to attend to stimuli on one side of space, often resulting from damage to the right hemisphere. Understanding this condition is essential for improving rehabilitation strategies, although its underlying mechanisms are only partially understood. Studies of brain lesions in humans indicate that

damage to the superior longitudinal fasciculus (SLF) disrupts fronto-parietal networks, which are crucial for spatial attention. Lesions affecting the SLF have been identified as significant predictors for the emergence of neglect symptoms. Still, these studies are limited by their opportunistic nature, as they involve analysing diverse lesions without control over their extent. Consequently, it is difficult to draw definitive conclusions about the role of a specific structure. We conducted a focused demyelination study involving two female squirrel monkeys to investigate the causal relationship between SLF damage and neglect-like behaviours. We induced demyelination of the superior longitudinal fasciculus (SLF) in the right hemisphere using lysophosphatidylcholine (LPC) injections. Behavioural assessment with a cancellation task paradigm and ultra-high field (11.7T) diffusion MRI scans were employed to monitor the evolution of deficits and structural changes over time. Each animal was used as its own control, thanks to reference acquisitions made prior to demyelination.
Our results revealed significant signs of contralesional neglect, such as impaired responses to visual stimuli presented in the neglected field of view. When comparing left-right omissions for the first and second weeks after demyelination, the Wilcoxon test revealed a bias in favor of the contralesional hemispace. For these two weeks, effect sizes were 0.51 and 0.52 for monkey 1, and 0.55 and 0.66 for monkey 2, respectively. ANOVA on the Center of Cancellation also revealed a significant difference, indicating a bias in favor of the contralesional hemispace in the first and second weeks post-demyelination ($p < 0.05$). Furthermore, the rapid behavioural recovery after two weeks suggests the involvement of compensatory mechanisms that warrant further exploration.
This study demonstrates that a pure disruption of conduction along the SLF is sufficient to induce ispatial neglect, thereby highlighting that the ability to attend to and perceive space emerges from the interconnection and interaction between cortical regions. Additionally, the findings underscore the value of lesion models in non-human primates for enhancing our understanding of neglect and its underlying neural mechanisms.

Disclosures: T. Orset: None. **J. Royo:** None. **J. Loayza:** None. **P. Bartolomeo:** None. **P. Pouget:** None. **M. Thiebaut De Schotten:** None.

Poster

PSTR468: Mechanisms of Attention: Animal Models

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Title: Meaning and Salience Contributions to Attentional Guidance in Macaques Viewing Natural Scenes

Authors: *O. SOYUHOS[1], T. HAYES[2], T. HAMEL[2], W. HU[2], B. SEVAK[3], J. HENDERSON[2], X. CHEN[4];
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Abstract: What determines where we look during real-world scene viewing? While attention during free viewing is typically attributed to bottom-up visual salience derived from low-level image features, recent human research underscores the importance of high-level semantic information ('meaning'). However, it remains unclear whether meaning similarly guides attention in non-human primates and how it interacts with visual salience, crucial steps for exploring underlying neural computations. To address these questions, we examined the contributions of meaning and visual salience in macaques freely viewing naturalistic indoor and outdoor scenes. Eye movements were recorded and fixation patterns analyzed, quantifying the relative influence of meaning (defined by human semantic ratings) and visual salience. Our results demonstrated significant predictive roles for both semantic meaning and visual salience in macaque fixation behavior. However, macaques relied more strongly on visual salience compared to semantic meaning, differing from humans who primarily rely on semantic guidance. Additionally, we found a negative interaction between semantic meaning and visual salience in macaques: semantic meaning exerted the strongest predictive influence in low-salience regions, whereas highly salient regions attracted fixations irrespective of semantic content. This negative interaction suggests an interdependence between meaning and visual salience-guided attention. These findings provide a robust behavioral basis for subsequent neurophysiological studies into attentional guidance mechanisms.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR468.20/MM6

Topic: I.01. Attention

Title: Independent Attention Modulation by Object and Location Value in the Primate Frontal-Collicular Circuit

Authors: *X. YU[1], A. GOPAL P A[2], K.-I. INOUE[3], M. TAKADA[4], O. HIKOSAKA[5];
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Abstract: Attention can be guided by different sources, such as the value of object features (feature-based attention) or the value of spatial locations (Spatial attention). While previous studies have identified the frontal eye field (FEF) and superior colliculus (SC) as critical hubs for attention modulation, it remains unclear whether feature-based and spatial attention are processed and transmitted independently or integrated to guide actions. In this study, we investigated this question by associating value with either object features or spatial locations, and examining how these modulations influence neural activities in the frontal-collicular circuit. Two macaque monkeys were trained to perform two value association tasks: an object value task, where specific objects were associated with high or low rewards, and a location value task, where value was linked to the spatial location of the stimuli. After training, both monkeys successfully learned these associations, as evidenced by faster saccadic eye movements and preferential choices toward high-value objects and locations. We first recorded neural activities from both FEF and SC and found significant modulation by object value and location value. Critically, these effects were independent, there was no significant correlation between the ROC-based measures of object and location value modulation within individual neurons. This suggests that feature-based and spatial attention influence neural responses via distinct mechanisms in both FEF and SC. To further examine whether this independence was maintained along the circuit, we used retrograde optogenetics to identify SC-projecting neurons in FEF, and assessed whether these output neurons integrated or independently processed feature-based and spatial attention signals. Our results showed that these projection neurons were also modulated by object and location value independently, with integration occurring only in a subset of neurons. Overall, our findings demonstrated that the feature-based attention and spatial attention modulated neural responses independently in FEF and that independence was preserved during the signal transmission to SC. This largely independent modulation by feature-based and spatial attention supports a flexible coding scheme in the frontal-collicular circuit, encoding both parallel and integrated processing of attention signals.

Disclosures: X. Yu: None. **A. Gopal P A:** None. **K. Inoue:** None. **M. Takada:** None. **O. Hikosaka:** None.

Poster

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Topic: I.01. Attention

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Title: Anterior Cingulate Cortex Links Past and Current Choice Outcomes During Information Sampling

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Abstract: The cognitive subfield of the anterior cingulate cortex (ACC) is activated when visual stimuli are attended and chosen during goal-directed behavior. Attention and choice related activity has been linked to the gathering of information, but the type of information being sampled and how information gathering activity modulates behavior remains unknown. We hypothesized that ACC activity during the fixational sampling of information reflects a combination of memory recall of previous experiences and the information of the currently sampled visual object. Such a linking process could indicate that the ACC updates internal beliefs about which visual features are behavioral relevant and optimizes future behavior. To test this hypothesis, we analyzed the neuronal encoding of choices during periods of high and low uncertainty in two macaque monkeys engaged in a feature-learning task. Trial uncertainty was quantified using choice probabilities derived from a reinforcement learning model, reflecting subjects' internal value estimates. Neuronal activity was recorded using multiple 64-channel linear probes in the ACC and the anterior striatum. Subjects learned through trial-and-error which visual feature of three presented objects was the rewarding feature in blocks of 30-50 trials. We used the coefficient of partial determination to quantify how activity encoded current and past choice outcomes time-resolved around the fixation onset of the object chosen in that trial. We found that ACC activity increased at the time of fixation onset in trials where the value of the object was uncertain, i.e. when choice probabilities were low, compared to trials with higher certainty of the chosen object value. This uncertainty-related activity predicted the outcome of the current choice and simultaneously encoded the choice-outcomes of previous trials. Thus, activity in the ACC - and to a similar but lower degree in the striatum - integrates current and past choice outcomes prior to making a choice about objects with uncertain values. This integration is linked to improved behavioral performance as activity increased, occurring most prominently when a correct choice followed a series of erroneous choices. These findings suggest the ACC updates information about visual objects when fixations sample visual information by recalling previous experiences involving those objects. We speculate this ‘linking’ of past and current choice outcome during uncertainty functions as a memory updating process needed to optimize future behavior.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

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Support: National Institute of Mental Health (R01MH123687)

Title: Decoding the Updating of Attentional Priorities in Anterior Cingulate Cortex, Prefrontal Cortex and Striatum

Authors: *C. G. GERRITY[1], R. TREUTING[2], T. WOMELSDORF[3];
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Abstract: Attention prioritizes certain objects because they have a learned value, or because their value is uncertain and needs to be learned. While learned attention recruits the lateral prefrontal cortex, amongst other regions, it has remained unclear how attentional priorities are learned. Learning of attentional priorities requires exploring options and inferring their future value. Lesion and stimulation studies have suggested that exploring and inferring values of objects is supported by the anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (PFC), and the striatum, but how these areas support the learning of attentional priorities is unresolved. We address this by quantifying how attention-relevant information is updated in the ACC, PFC, and striatum during the learning of feature-based attention.

We recorded neuronal activity in two macaque monkeys engaged in a feature-learning task using multiple 64 channel probes in the ACC, PFC, and striatum. Subjects learned through trial-and-error the rewarded feature shown on one of 3 visual objects. Objects had up to 9 unique features across 3 dimensions, with 3 features per dimension. One feature was designated the rewarded target feature in a block of ~35 trials. We devised a variational auto-encoder, which parsed time-resolved activity to extract optimized latent representations of task relevant information from >300 simultaneously recorded channels. From this latent space, the decoder classified 3 labels, one feature-class for each dimension that subjects chose on a given trial. The classifier used stratified ten-fold cross validation to estimate unbiased accuracies of the chosen target and distracting features.

We found that the decoder predicted choices starting shortly before the subjects fixated on the object chosen on that trial. Neuronal activity carried feature-specific information about both target and distractor objects. The target feature was maximally decoded during the learning period, when there was uncertainty about the target feature as opposed to when learning had completed. Consistent with this finding, choices of the target feature were best decoded when reward prediction errors were high.

These results show that neuronal ensembles in the ACC, PFC, and striatum represent feature-specific information about the likely attentional target during, but not after, the learning of feature-based attentional priorities. Feature-specific information emerged when gaze was directed to the target object and thus may guide attention to those objects. These findings suggest the ACC, PFC, and striatum support the updating of feature-based attentional priorities.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

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Title: Global synchronization in primate visual areas during spatial attention by microsaccades

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Abstract: Macaques engaged in a spatial attention task were randomly cued to attend to a target amid distracters while maintaining fixation, and rewarded for making a saccade to the target after its color changed. Spikes and local field potentials (LFPs) were recorded from visual area V4, inferotemporal (IT) cortex, and lateral pulvinar using laminar probes. Microsaccades (MS; < 1deg) were detected from gaze positions. We previously showed (Srinivasan et al., PNAS, 2025) that the direction of a MS interacted with attention in modulating firing rates and sharpening of stimulus representations. Here, we present the effects of MS on LFPs. MS onsets, irrespective of their direction, cause phase resets of low-frequency oscillations (< 25 Hz). These MS onset evoked phase resets enable the different areas to reach a common phase and synchronize their activities. Peak phase consistency was reached in these areas ~100ms *after* the MS onset. Granger analysis performed between the evoked responses and the MS velocities reveal that the low-frequency LFPs in all the areas were "caused" by the MS, i.e., the MSs are a strong predictor of subsequent LFPs. Inter-areal field-field coherence analyses between areas during MS triggered intervals recapitulate known results analyzed for the full trial periods without accounting for MSs: higher theta (3-8 Hz) and lower alpha (8-15 Hz), higher gamma (30-70 Hz) for V4-IT, and higher beta (15-30 Hz) for IT-pulvinar during attention. While confirming previous results, we show the contributions of each MS direction. V4 spike-field coherence (SFC) was analyzed during these MS triggered intervals in both superficial and deep layers. In MS towards intervals, theta increased and alpha decreased in both the superficial and deep layers, while gamma SFC was higher in the deep than in the superficial layers. In MS away intervals, theta was maintained, but alpha SFC remained high, and gamma persisted in both superficial and deep layers. Apart from their role in enhanced attention and stimulus tuning, these results show MSs can serve as a global reset in synchronizing the complex ongoing oscillations across multiple brain regions. Coherence in different frequency-bands is shown to be influenced by MS direction. These results clarify how the temporal process of attention is dynamically coordinated in an aperiodic environment across multiple brain areas.

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Poster

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Title: Laminar signatures of attentional enhancement and distractor suppression in macaque V4

Authors: J. GROOT[1], A. V. MAIER[2], J. D. SCHALL[3], ***J. A. WESTERBERG**[4]; [1]Swammerdam Inst. for Life Sci., Univ. of Amsterdam, Amsterdam, Netherlands; [2]Dept. of Psychology, Vanderbilt Univ., Nashville, TN; [3]Biol., York Univ., Toronto, ON, Canada; [4]Vision and Cognition, Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: We deploy attention to scrutinize specific objects and ignore others. Neuronally, this manifests as enhanced processing of the sensory information of attended objects and suppressed processing of distracting objects. However, whether these processes are independent in sensory cortices is unknown. For instance, do target vs. distractor processing changes manifest through the same or distinct patterns of laminar activity? We exploited the canonical microcircuitry of the visual cortex through neurophysiological recordings with laminar resolution to explore the circuit-level implementation of attentional enhancement vs. distractor suppression on sensory columnar processing. Moreover, we induced changes in target enhancement and distractor suppression by incorporating attentional priming to determine whether these changes were temporally coupled. Selection history can alter the profile of target enhancement and distractor suppression such that pertinent objects are more rapidly scrutinized, and others are more effectively ignored. To investigate the relationship between attentional enhancement and distractor suppression, monkeys performed pop-out visual search for an attention-capturing oddball stimulus. Priming was induced by having the animal repeatedly search for the same pop-out target before abruptly changing the target after a variable number of trials (i.e., priming of pop-out). Attentional selection in neural responses was present across all layers and varied in time as a function of attentional priming. However, target enhancement and distractor suppression largely did not covary in space or time. Laminar current source density (CSD) indicated that the primary source of distractor suppression was mediated through putative synaptic activity in the upper layers of cortex, where target enhancement showed a mixture of granular and extragranular sources. These findings indicate that multiple distinct priming mechanisms affect and can be dissociated across sensory columnar processing of attended stimuli.

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Poster

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Topic: I.01. Attention

Support: P50MH132642
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Title: Pulvinar object-based attention signals driven by primate superior colliculus and their impact on downstream cortical areas

Authors: *Y. WU[1], R. BOSHRA[2], M. HARRIS[3], B. MOREA[1], M. RODRIGUEZ[1], M. BERG[4], S. KASTNER[5];
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Abstract: Attention can be directed by both spatial location and object structure. When spatial locations are grouped by their connectedness, attention tends to spread within the object, prioritizing specific locations over others. However, the neural mechanisms underlying such object-based attention remain unclear. Here, we investigate the potential neural correlates of object attention by simultaneously recording neural activity from a large-scale cortical-subcortical network—including the frontal eye field (FEF), dorsal posterior inferotemporal area (PITd), pulvinar, and superior colliculus (SC)—while two monkeys performed an Egly-Driver task that manipulates both spatial and object-based attention. In this task, the target appeared at the cued location (80% valid) or at one of two equidistant uncued locations: either on the same object (connected by a bar) or on a different object. Behavioral performance revealed both spatial and object-based attention effects, with the highest hit rates at the cued location, lowest at the different-object location, and the same object location in-between. Neural activity in the pulvinar and SC mirrored these behavioral effects during the cue-target interval, while FEF and PITd showed only spatial attention modulation—suggesting a subcortical origin for object-based attention. Decoding analyses revealed that object-based attention signals in the pulvinar emerged after the onset of bottom-up sensory information and persisted throughout the delay period. To assess causality, we inactivated the intermediate and deep layers of the SC while recording from the same network. SC inactivation selectively disrupted object-based attention in both behavior and pulvinar activity, while spatial attention remained relatively intact. In the SC, both spatial and object attention effects were abolished. The reduction in object attention stemmed from disinhibition at the different-object location, a pattern that extended to cortical areas as well. Notably, decoding indicated that object-based—but not bottom-up—sensory information was impaired, dissociating these two signals. Together, these findings reveal a critical role for the SC

in mediating object-based attention and suggest that SC input enables distractor filtering in the pulvinar, offering new insights into the subcortical contributions to attention control.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.26/MM12

Topic: I.01. Attention

Support: R01MH137624
P50MH132642
RO1EY017699
C.V. Starr
NSERC

Title: Pulvinar electrical microstimulation modulates attentional performance via thalamo-cortical neural cascades

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Abstract: Primate studies have shown that pulvinar regulates information transfer between cortical areas during attention function. Pulvinar, similar to other thalamic nuclei, has neurophysiological properties that enable its cells to alter their firing mode from tonic- (> ms inter-spike interval [ISI]) to burst-mode firing (<4 ms ISI). Although burst-mode firing was traditionally-associated with states of sleep or sedation, other work has reported bursting during wakefulness in response to novel or unexpected stimuli. While theoretical work posits that these bursts may play a role in attention function, no empirical data directly support such notion. This is of particular interest in higher-order thalamic nuclei, which have been shown to have a higher propensity to burst. In this study, we recorded local field potentials and spiking activity from the pulvinar of two male macaques. To investigate the propagation of pulvinar-initiated signals and their putative effect on attention behavior, we recorded simultaneously from from the lateral intraparietal area (LIP) and the dorsal aspect of inferotemporal cortex (PITd), two cortical areas that are implicated in attention control and are anatomically connected to pulvinar. We found pulvinar burst probability to be modulated by spatial attention and unexpected targets to elicit a significantly higher burst probability compared to expected (cued) targets. To probe the causal

role of pulvinar and its bursting in attention, we stimulated pulvinar using 50 µA biphasic cathode-leading 16 pulse trains (200 Hz) at varying periods prior to target presentation in a covert spatial attention task. Results show that pre-target pulvinar stimulation enhanced target detection and triggered a thalamo-cortical cascade, eliciting bursts locally in pulvinar that were linked to cortical spiking. Lastly, we found that enhanced target detection was linked to the magnitude of the stimulation-induced bursts. These findings establish a causal role for pulvinar and its distinct firing properties in attention dynamics and suggest translational potential for attention disorders.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

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Topic: I.01. Attention

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Leibniz Graduate School for Primate Neurobiology (NEUROPRIM), Göttingen

Title: The spindle-like nature of gamma oscillatory activity and the implications of it for the phase coherence analysis

Authors: *V. ZELENKOVA[1], L. BUI[2], I. GROTHE[1], A. K. KREITER[1];
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Abstract: Spatiotemporal coordinated γ-frequency oscillations play a crucial role in flexible and selective information routing, a computational prerequisite for flexible cognitive processes such as selective attention. Especially the latter is well known to operate in a discontinuous manner, even when task demands are constant over time. This suggests that underlying oscillatory activity patterns may also occur in a transient (and not necessarily stimulus-locked) manner rather than as enduring rhythms.
Here, we investigate the temporal structure of γ-oscillatory activity in the local field potential during single trials of a demanding attention task, its impact on estimates of phase coherence (PC) between visual cortical areas V1 and V4. We find that γ-oscillatory activity does not occur as an enduring oscillation but rather as a sequence of short and discrete spindles, with a typical duration of around 40 ms and occurring with a frequency of ~14 Hz in V1 and V4. Notably, for

V1, the duration of these spindles increases significantly with attention by around 7 % and the time covered by spindles by 8%.
This transient, spindle-like behavior of γ-oscillatory activity is crucial to consider when analyzing its spatiotemporal patterns, particularly in terms of temporal and phase relations between different areas. Signals in a V1 γ-spindle arrive in V4 with some time delay. Optimal interaction with a similar γ-spindle in V4 would require a corresponding time shift between both spindles. Disregarding this time shift would mean calculating PC in part between periods of a γ-spindle in V1 and periods outside the spindle in V4. This would underestimate the PC between the V4 γ-oscillations and the afferent γ-oscillatory input arriving after a transmission delay. Time shift-dependent PC analysis reveals a significant average increase of 23 % in the V1-V4 PC for a time shift of ~15ms.
Furthermore, we investigated the combined effect of incorporating the time shift and concentrating the analysis on times when the γ-oscillation-based routing mechanism is active, as indicated by the presence of γ-spindles in both the sender and receiver areas. This improved PC values as compared to the conventional analyses, which do not take into account the time shift and periods without γ-spindles, by ~90%.
These results suggest that the γ-oscillation-based routing mechanism rests on short, highly dynamic interactions between spindle-like activity patterns, possibly controlled by modulations of PC between these spindles and their temporal extent.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

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Program #/Poster #: PSTR468.28/MM14

Topic: I.01. Attention

Support: Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) - 429934733

Title: The occurrence of microsaccades and their theta-phase locking depend on the level of attentional demand and the temporal structure of the task

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Abstract: Saccades and microsaccades (MS) are known to occur phase-locked to the ongoing theta rhythm. At the same time γ-oscillatory activity (30-90 Hz), which is strongly associated with stimulus processing and cognitive processes like attention, occurs during short periods that are also locked to the theta rhythms phase (phase-amplitude coupling). Given that saccades usually go along with a period of saccadic suppression - characterized by reduced neuronal activity and visual sensitivity - their close temporal association with periods of active cognitive

and stimulus processing is striking. This raises the question of how the brain avoids disturbance of ongoing stimulus processing by frequent MS. To address this question, we trained two macaque monkeys on a demanding shape-tracking task that required continuous evaluation of the continuously changing shape of the cued stimulus while ignoring a distractor. Both stimuli were placed within the same receptive field of neurons recorded in area V4. Their shapes morphed through several transitions, while the monkeys had to detect the reappearance of the initial shape after two, three, or four morph cycles (MC) of constant duration. We observed that, unlike in free viewing or in paradigms involving the detection of events occurring at entirely unpredictable times, the MS-rate varied systematically across the MCs. Most MS occurred in the first and last quarters of each MC. In between, their rate declined strongly to a minimum in the third quarter, where they were almost absent, i.e., in the period most critical for identifying the upcoming shape and comparing it to the initial sample. While the upcoming shape had not yet fully appeared, and the monkeys were likely still tracking the stimulus' shape, MS were strongly phase-locked to theta activity. In contrast, MS occurring after shape identification showed little to no phase locking. Time-frequency analysis revealed that MS induced a distinct pattern of the oscillatory activity of V4 neurons. Immediately after MS onset, γ-power decreased significantly for ~100 ms, while simultaneously, β-power (12-30 Hz) was significantly enhanced. After these initial 100 ms, γ-power increased above average levels during MCs while β-power returned to average levels. This pattern suggests that although MS initially suppresses γ-activity, the subsequent rebound might enhance stimulus processing. Furthermore, MS predominantly occurred during perceptually less demanding task periods and at theta phases strongly separated from those associated with high γ-activity. These features likely minimize disruption of stimulus processing around saccades and may even support it subsequently.

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Poster

PSTR468: Mechanisms of Attention: Animal Models

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Topic: I.01. Attention

Support: BMBF Grant 01GQ0705 (Bernstein Group for Computational Neuroscience Bremen)
Leibniz Graduate School for Primate Neurobiology (NEUROPRIM), Göttingen

Title: Attention-dependent modulations of gamma-frequency predict inter-areal synchrony in macaque's visual areas V1 and V4

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Abstract: Flexible rerouting of sensory input signals has been linked to changing patterns of synchrony between local gamma rhythms of distant neuronal groups. It has been proposed that attention mediates selective synchrony by increasing the gamma frequency of the sender population processing the attended stimulus, enabling it to more effectively synchronize with a lower-frequency receiver population by reaching the receiver area before slower competing inputs. However, gamma frequency fluctuates over time, varies between areas, and depends on stimulus properties—posing a challenge for entrainment between inter-areal oscillators.
Here, we investigate how attention-driven modulation of gamma frequency from two nearby V1 populations (senders) and one overlapping V4 population (receiver) supports inter-areal synchronization, quantified as inter-areal phase coherence (PC) of the local field potentials (LFPs). To this end, LFPs were simultaneously recorded from V1 and V4 while macaque monkeys performed an attentionally demanding delayed match-to-sample task. V1 activity was recorded from a chronically implanted epidural electrode array, while intracortical microelectrode recordings were used for V4.
We report attention-related changes in V1 gamma-frequency and in inter-areal synchrony between V1 and V4. Specifically, attention increased gamma-frequency in the attended V1 population and significantly enhanced the correlation of gamma-frequency between the trial-averaged time courses of V1 and V4. Remarkably, this occurred even though V4, the receiver population, had a much larger mean frequency than either sender population in V1. Attention also led to consistently stronger inter-areal synchrony, as reflected by increased gamma-band phase coherence between V1 and V4. Importantly, the frequency difference between the competing (attended and non-attended) V1 populations predicted inter-areal synchrony for the attended stimuli: greater frequency differences between attended and non-attended V1 populations were associated to greater phase coherence with V4 and stronger frequency covariation between V1 and V4. Finally, frequency covariation between V1 and V4 was predictive of inter-areal phase coherence exclusively for attended stimuli.
These results suggest that a small increase in frequency for the sender population processing the attended stimulus might help to selectively synchronize its gamma band activity with that of the receiver population. Maintenance of gamma-synchrony might be further promoted by frequency covariations between areas, which could help synchrony overcome the natural variability of gamma-frequency.

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Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Program #/Poster #: PSTR469.01/MM16

Topic: I.02. Perception and Imagery

Support: ZIAMH002783
ZIAMH002966

Title: Covertly predicting and augmenting visual conscious perception in cerebral blindness

Authors: *S. I. KRONEMER[1], A. Y. WANG[1], C. WALSH[1], C. M. LEVESQUE[1], V. E. GOBO[4], S. JAPEE[2], E. MERRIAM[1], J. GONZALEZ-CASTILLO[3], G. EDWARDS[1], B. OSBORNE[5], L. TURTZO[6], L. LATOUR[7], T. T. LIU[8], P. A. BANDETTINI[3];
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Abstract: Damage to the primary visual pathway (e.g., following traumatic brain injury or stroke) can result in cerebral blindness. The extent of vision loss in cerebral blindness is typically inferred from overt report by patients indicating the presence or absence of conscious vision across their visual field. However, subjective reporting methods have limited validity, particularly in degraded or abnormal vision. In this study, we explore eye metrics (e.g., pupil size, blinking, and microsaccades) as objective markers to predict and augment conscious visual awareness in cerebral blindness. We recruited adults with homonymous hemianopia (N = 8) to perform a visual perception task while recording eye tracking and pupillometry data. Combining traditional statistical analyses and machine learning methods applied on stimulus-evoked eye metrics, we identified two subgroups of cerebrally blind participants: those with and without visual conscious awareness in their blind field. Notably, stimulus-evoked eye metrics predicted perception in the blind field even when task performance and subjective report initially indicated complete blindness. Moreover, these physiological signatures were linked to residual, stimulus-evoked neural activity. To explore ways of enhancing perception, we next tested whether specific visual stimulus features (e.g., shape, spatial frequency, color, and contrast) could be optimized to elicit changes in physiological measures and augment conscious visual awareness in the blind field. Prior research has shown that some patients with cerebral blindness exhibit heightened sensitivity to specific image features (e.g., noticing red more than green images) that may correspond with their unique lesion profile. To efficiently test multiple image features, we designed a closed-loop model that dynamically adjusts stimulus parameters in real time based on eye metric feedback. This approach allows us to identify individualized image features that maximally modulate physiological responses with the goal of enhancing residual neural activity and conscious visual perception in the blind field. Together, these results highlight the value of eye metrics as objective indicators of conscious awareness and residual neural activity in cerebral blindness. They also suggest potential applications for restoring vision by tailoring images that bypass the specific visual deficits unique to each patient.

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Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.02/MM17

Topic: I.02. Perception and Imagery

Support: NIH Intramural Research Program ZIAMH002783

Title: Investigating eye metrics as an indicator of sensory neural processing, behavior, and conscious perception

Authors: *P. SUWANAMALIK-MURPHY[1], S. I. KRONEMER[1], V. E. GOBO[4,1], J. GONZALEZ-CASTILLO[1], A. BENITEZ[2], P. BANDETTINI[1,3];
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Abstract: Prior research has demonstrated that eye metrics, including pupil size, blinking, and microsaccades can serve as indirect but accessible markers of neural activity and associated behaviors. The goal of this study is to further clarify the relationship between spontaneous fluctuations in pupil size, blinking, and eye movements with corresponding sensory-evoked neural activity, behavior, and conscious perception. We recruited healthy adult participants (visual task: N = 33; auditory task: N = 36) to perform a stimulus-in-noise visual and auditory detection task while undergoing simultaneous eye tracking, pupillometry, and magnetoencephalography (MEG). In the visual task, images of faces appeared in visual static noise among sub- to suprathreshold opacities. In the auditory task, tones were played in auditory static noise among sub- to suprathreshold volumes. Participants pressed a button when they perceived a stimulus. Task stimuli resulted in approximately equal proportions of perceived and non-perceived conditions, and participants were accurate in locating the stimulus (i.e., the on-screen image location or the ear in which the tone was played) when perceived. Reaction time decreased on average with stimulus strength (i.e., quicker for suprathreshold versus near-threshold stimuli). By analyzing pupil size, pupil phase, pupil variance, blink rate, and microsaccade rate, we categorized behavior according to the timing of their presentation relative to the ongoing spontaneous dynamics at the onset of stimuli presentation (e.g., stimuli that appeared when the pupil was large versus small). Preliminary results indicate that eye metrics such as large pupil size, large pupil variance, reduced blinking rate, and reduced microsaccade rate are linked to increased perception rate for visual stimuli. Likewise, larger pupil size and variance for auditory stimuli were found to correspond with increased perception. Analysis of MEG signals found that the amplitude and latency of sensory-evoked field potentials correspond to the stimulus magnitude - shorter latency and larger amplitude for supra- versus subthreshold stimuli. Future analyses will assess how spontaneous changes in eye metrics modulate stimulus-level sensory neural processing across conscious and unconscious contexts. We also plan to explore how directly modulating eye metrics (e.g., real-time biofeedback) may allow for causal modulation of brain state and behavior.

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Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Topic: I.02. Perception and Imagery

Support: NIMH Grant: ZIAMH002783
NIMH IRTA Grant: ZIAMH002920–09

Title: Using afterimages as a novel approach for investigating perceptual reality monitoring

Authors: *C. M. LEVESQUE[1], S. I. KRONEMER[2], N. DIJKSTRA[4], P. BANDETTINI[3]; [1]Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Washington, DC; [2]Lab. of Brain and Cognition, [3]Section on Functional Imaging Methods, Natl. Inst. of Mental Hlth., Bethesda, MD; [4]Univ. Col. London, London, United Kingdom

Abstract: Perceptual reality monitoring (PRM) is defined as our ability to distinguish between real versus imagined or illusory sensory conscious experiences. PRM errors are common in certain patient groups (e.g., hallucinations experienced by people with schizophrenia and Charles Bonnett syndrome) and are rarely experienced in healthy individuals. Due to the difficulty of inducing PRM errors under controlled experimental conditions, the neural mechanisms of PRM remain poorly understood. To address this methodological limitation, we developed a novel PRM paradigm that utilizes afterimages - an illusory visual conscious perception that occurs following an inducing stimulus. In a recent cortical layer resolution fMRI study, we found that afterimages involve signaling in the human primary visual cortex that is distinct from visual perception of real-world images. Similarly, our and other prior work shows a link between afterimages and mental imagery vividness. Therefore, we believe afterimages can be used as a model of sensory-independent conscious perception. We developed a novel PRM paradigm where healthy adult participants (N = 16) were asked to distinguish between images and afterimages. During the task, participants perceived afterimages and physical images designed with visual features (e.g., opacity, shade, and presentation duration) that approximately matched those of the afterimages. To prevent participants from using the inducer stimulus that produces afterimages as a cue for the perception type, continuous flash suppression (CFS) was used to render the inducer invisible, without suppressing subsequent afterimages. Participants were instructed to judge whether they perceived an afterimage or a physical image, as well as their decision confidence. Initial behavioral findings indicate PRM failures were successfully induced in healthy individuals (i.e., participants mistake one type of percept for the other). Notably, participants reported similar confidence levels for accurate and inaccurate PRM. We also observed performance variability among participants that suggests unique PRM abilities, which may potentially predict perceptual traits in daily life. Future research aims to incorporate neuroimaging techniques, such as fMRI, MEG, and EEG, to investigate the neural mechanisms of PRM. Ultimately, we aim to apply these insights to guide treatment of impaired PRM.

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Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Program #/Poster #: PSTR469.04/NN1

Topic: I.02. Perception and Imagery

Support: 2022ZD0204802
2022ZD0204804

Title: Imagining an oriented line: Probing imagery in human early visual cortex using intracranial electroencephalogram

Authors: *R. YANG, G. CHEN, Q. WANG, F. FANG;
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Abstract: Visual imagery enables the generation of conscious experiences without external input, providing the basis for internal world models and cognitive functions such as memory and planning. Neuroimaging studies suggest that imagery involves early visual cortex (EVC), supporting the sensory recruitment hypothesis. However, it remains unclear to what extent imagery and perception recruit overlapping neural substrates in EVC. It is also unresolved whether imagery directly reactivates perceptual activity or relies on task-driven pathways with distinct encoding mechanisms. In this study, we use high spatio-temporal resolution intracranial EEG (iEEG) technology to investigate how EVC encodes internally generated visual representations. Participants performed a visual imagery and perception task while maintaining central fixation. They either viewed or imagined an oriented line, followed by a probe dot requiring a spatial judgement (on or off the line). Experimental conditions varied by tasks (perception or imagery), receptive field (RF) alignment (line intersected or lay outside the RF), and line orientation. Control trials had identical stimuli but required detection of a luminance change at fixation, serving as a control for confounding effects of visual cues. We recorded iEEG signals from eight epilepsy patients implanted with stereo-electrodes as they performed the tasks while maintaining central fixation. RFs of EVC contacts were measured using retinotopic mapping. We identified 29 visually responsive contacts (8 in V1, 17 in V2, and 4 in V3), among which six (in V2/V3) showed increased high-gamma activity (HGA) during imagery. Notably, this HGA increase was observed only when the imagined line intersected the RF of the recorded contact, indicating spatial specificity. We also found that orientation selectivity differed between imagery and perception, suggesting distinct encoding formats. Cross-condition decoding revealed that perception-trained classifiers successfully decoded imagined orientation, but only in contacts that showed imagery-induced HGA. In contrast, perception-trained classifiers reliably decoded imagined spatial location regardless of whether the contact showed imagery-induced HGA. These findings suggest that imagery engages spatially specific and feature-selective representation in EVC. In summary, our results reveal that imagery recruits overlapping neural substrates with perception but relies on task-driven encoding mechanisms that are distinct from

direct reinstatement of sensory-based activity, providing insight into how sensory cortex contributes to internally generated conscious experiences.

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Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Program #/Poster #: PSTR469.05/NN2

Topic: I.02. Perception and Imagery

Title: Different cortical regions decode visual location in consciously perceived versus not perceived face stimuli

Authors: *J. QU[1], A. KHALAF[2], S. I. KRONEMER[3], H. BLUMENFELD[4];
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Abstract: Perception of spatial location is fundamental to conscious visual experience, yet the neural mechanisms underlying spatial recognition, with and without the engagement of conscious awareness and participant task report, remain unclear. We analyzed data from a visual threshold perception task, in which participants viewed faces presented in one of the four quadrants of the screen with the threshold adjusted individually so that the participant perceived the stimulus 50% of the time. We investigated decoding of cortical fMRI signals for face stimuli located on the left vs. right side and categorized these locations into two conditions. Participants reported whether they perceived the face and what was the quadrant location at the end of each trial. We labeled the trials as perceived if the participant reported seeing the face and got the quadrant location correct. The trial was labeled as not perceived if the participant reported not seeing the face and got the quadrant wrong. fMRI data were preprocessed with a general linear model to determine the beta weight of each voxel for the 4 conditions (left-perceived, right-perceived, left-not perceived, right-not perceived). We then applied a whole-brain searchlight decoding to the beta weights to identify brain regions capable of discriminating between left- and right-sided stimuli.We found that regions predictive of stimulus location (accuracy between 63% to 68%, $p \leq 0.05$, n=18) differed substantially between the perceived and not perceived conditions. For perceived stimuli, discriminative information was present in the prefrontal cortex, dorsal and medial frontal cortex, medial parietal cortex, and the inferior frontal gyrus—regions typically associated with attentional processes. For not perceived stimuli, regions with comparatively high accuracy include the inferior occipital gyrus, left posterior cerebellum, medial prefrontal cortex, middle temporal gyrus, and supramarginal gyrus. Overlap of decoding for perceived and not perceived stimuli was found in primary visual cortex and intraparietal sulcus. These findings suggest that spatial information about visual stimuli is encoded in widespread brain areas both for consciously perceived and not perceived stimuli, but the specific

brain networks differ depending on perceptual awareness. Further work will incorporate additional data from a paradigm with no explicit task report to explore the role of report-dependent and report-independent networks in spatial decoding and recognition. Together, these results provide new insights for the spatial representation of visual signals in the brain modulated by conscious awareness.

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Poster

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Topic: I.02. Perception and Imagery

Support: NIH R01 NS134655

Title: Thalamic Neurostimulation Augments Transient Visual Perceptual Awareness

Authors: *Q. XIN[1], F. STOCKART[2], O. AGDALI[3], M. HOOK[6], S. MAJUMDER[4], S. AERTS[3], S. I. KRONEMER[7], D. S. JIN[3], T. YADAV[4], J. LIU[4], A. KHALAF[4], P. HADAR[8], S. SINGLA[10], A. URBAN[10], C. J. CHU[11], M. RICHARDSON[9], C. R. BUTSON[12], I. H. QURAISHI[5], H. BLUMENFELD[13];
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Abstract: The role of subcortical arousal systems in the conscious perception of transient sensory stimuli is not well-understood. In particular, the intralaminar thalamus with extensive connectivity to frontoparietal sensorimotor networks and association areas may play a crucial role. We hypothesized that intralaminar thalamic neurostimulation, precisely timed with the presentation of a transient semi-transparent face image, would augment visual perceptual awareness. To test this hypothesis, we leveraged a unique group of patients with epilepsy implanted with closed-loop neurostimulators (RNS® System, NeuroPace, Inc). We recruited six patients with RNS implants targeting the centromedian nucleus (CM). The participants were asked to report if they perceived a 50ms human face image presented with at-threshold opacity against a noise background. The participants' trials were randomized into three groups: (1) concurrent, (2) delayed, and (3) no-neurostimulation conditions. For concurrent and delayed neurostimulation conditions, a 300ms burst of biphasic square waves of neurostimulation at 100Hz was delivered either during the onset of the face image or 2 seconds after visual

presentation. The charge density of the neurostimulation was individually titrated to ensure that the participant could not feel the neurostimulation. Visual perceptual sensitivity was calculated as the percentage of trials where the participants reported that they perceived the image and subsequently identified the correct position. In four participants, we found that among the trials where the image was presented on the side of the screen contralateral to that of thalamic neurostimulation, perceptual sensitivity for the concurrent neurostimulation condition increased compared to the no-neurostimulation condition. This effect was not observed in the delayed neurostimulation condition. In the other two participants, perceptual sensitivity was not increased by neurostimulation. Based on stimulation models built from patient-specific imaging, perceptual sensitivity in the concurrent stimulation condition was positively correlated with the volume of tissues activated by the neurostimulation intersected with the CM (Pearson's R=0.75). Our preliminary results suggest that the thalamic arousal system play a causal role in regulating the perception of conscious events. With further work these investigations may shed light on both normal mechanisms of conscious perception and provide potential therapeutic targets for disorders of attention and consciousness.

Disclosures: Q. Xin: None. **F. Stockart:** None. **O. Agdali:** None. **M. Hook:** None. **S. Majumder:** None. **S. Aerts:** None. **S.I. Kronemer:** None. **D.S. Jin:** None. **T. Yadav:** None. **J. Liu:** None. **A. Khalaf:** None. **P. Hadar:** None. **C.J. Chu:** None. **M. Richardson:** None. **C.R. Butson:** None. **I.H. Quraishi:** None. **H. Blumenfeld:** None.

Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.07/NN4

Topic: I.02. Perception and Imagery

Support: Postdoctoral fellowship of the Fyssen Foundation
NIH R01 NS134655

Title: Human thalamic and report-independent alpha-beta desynchronization in response to conscious visual perception

Authors: *F. STOCKART[1], S. I. KRONEMER[2], Q. XIN[3], H. BLUMENFELD[4];
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Abstract: The cortex displays a widespread and sustained reduction in alpha and beta bands power starting ~500 ms after stimulus detection. This *alpha-beta synchronization* (ABD) has been associated with a decrease in intercortical feedback activity. It is unknown if ABD is (a) specific to the cortex and (b) to what extent it is involved in perceptual vs. report-related processes. To bridge these gaps, we analyzed data from a human dataset including scalp EEG (n

= 122) and intracranial EEG data from thalamic implants (n = 7). Participants provided detection and location reports on face stimuli presented at visual threshold. In a report and no-report paradigm, they were instructed to ignore faces presented at some locations. Conscious detection of these faces was inferred using a machine learning algorithm trained on eye movements, making it possible to study perceptual activity independently from post-perceptual processing associated with reporting one's perception. We extracted electrodes' time-frequency response locked on the onset of the face stimulus using a short-time Fourier transform. Consistently with previous studies, scalp EEG data showed a sustained decrease in both alpha and beta bands across the whole topography when participants reported perceiving vs. not perceiving a face. ABD was also observed for inferred perceived vs. not perceived faces (without report), but with a smaller amplitude and less duration than for faces on which participants provided a report. Intracranial channels in the region of the intralaminar thalamus also displayed ABD, albeit with a more modest amplitude and a later latency than observed over the cortex. This is the first evidence for ABD in the human thalamus in response to conscious detection, showing that this phenomenon is not specific to the cortex. Our results also indicate that while a part of the ABD measured on the scalp is involved in post-processing associated with reporting one's perception, another part is directly involved in perceptual processing. These findings raise important questions for further investigation regarding thalamocortical mechanisms in the ABD and the role of these signals in report-dependent and report-independent conscious perception.

Disclosures: F. Stockart: None. **S.I. Kronemer:** None. **Q. Xin:** None. **H. Blumenfeld:** None.

Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.08/NN5

Topic: I.02. Perception and Imagery

Support: NIH: F99NS139540

Title: Mapping Auditory Conscious Perception with Machine Learning Free from Subjective Report

Authors: *S. AERTS[1], S. I. KRONEMER[4], A. KHALAF[2], Q. XIN[5], A. A. SHARMA[3], K. L. CHRISTISON-LAGAY[6], H. BLUMENFELD[6];
[2]Neurol., [3]Dept. of Neurol., [1]Yale Univ., New Haven, CT; [4]Section on Functional Imaging Methods, Natl. Inst. of Mental Hlth., Bethesda, MD; [5]Yale Univ. Interdepartmental Neurosci. Program, New Haven, CT; [6]Dept. of Neurol., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Patients with disorders of consciousness (DoC) often cannot report their experiences, leading to misdiagnosis in up to 40% of cases. Research to better understand consciousness is confounded by the neural activity related to reporting of perception. We used machine learning and fMRI to identify auditory perception-related networks independent of subjective report.

Auditory stimuli (whistle, laser, water drop) were presented separately to each ear at individual perceptual thresholds. Participants reported hearing/not hearing the target ear stimulus while asynchronous sounds played in the non-target ear. Pupil size, blink rate, and microsaccade rate were recorded during fMRI acquisition. Eye metrics during reported trials trained a machine learning classifier that predicted perception in nonreported trials. For report trials (n =26), threshold stimuli were perceived in 43% of trials, with 88% correct sound identification (chance = 33%). Control/silent trials had a 10% false positive rate, and fully audible suprathreshold stimuli had an 8% false negative rate. Eye metrics significantly differed between perceived and nonperceived trials at a subset of timepoints after the stimulus: pupil dilation (200-2500 ms), blink rate (1130-1880 ms), and microsaccade rate (153-510 ms). Classifier performance reached ROC AUC = 0.88, PPV = 0.88, NPV = .86, with a 74% retention rate. Perceived stimuli evoked BOLD activation in detection, arousal, and salience networks (e.g., frontal eye fields, anterior cingulate, thalamus) at 3s post-stimulus, followed by activation in task-positive networks (anterior medial frontal gyrus, dorsal inferior parietal lobule) and deactivation in default-mode networks (ventral medial prefrontal cortex, posterior cingulate) at 6s. These results show that reflexive eye metrics can classify auditory conscious perception and combined with fMRI, dissociate perceptual awareness from report. This method can eventually be used help identify perception and neural targets for therapeutic neuromodulation in DoC patients.

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Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.09/NN6

Topic: I.02. Perception and Imagery

Support: TWFC-2022-30267 "Bifurcation Dynamics in a No-Report Paradigm"

Title: Eeg bifurcation dynamics around visual detection threshold in no-report

Authors: *A. NICOLACOUDIS, M. OPITZ, M. A. PITTS;
Psychology, Reed Col., Portland, OR

Abstract: Studies aimed at isolating neural signals linked with perceptual awareness overwhelmingly utilize a binary contrastive approach, comparing brain responses between conditions in which a subject was aware versus unaware of a stimulus. This method, while informative, often yields numerous candidate signals, likely overestimating the neural differences between perceived versus non-perceived stimuli. To better assess changes to the neural dynamics around perceptual threshold a few recent studies (Sergent et al., 2021; Cohen et al., 2024) presented stimuli across a wider range of visibility/audibility levels. Across these two studies, EEG signals from ~250-400ms showed bifurcation dynamics that matched the

psychometric functions from the behavioral reports.
Here, we present a variation of these experiments, using simpler visual stimuli (oriented gratings) and no backward masks (stimuli were embedded in random visual noise). Visibility was manipulated by varying stimulus contrast across five levels (2-below, 1-at, 2-above threshold). In a report condition, on each trial, subjects performed an objective 2AFC task on stimulus orientation, followed by a subjective clarity rating using the perceptual awareness scale (PAS). In a separate no-report condition, the same stimuli were presented while subjects performed an orthogonal task detecting infrequent red dot probes. An event-related potential (ERP) characterized by a negative-going wave over the occipital scalp at ~250-350ms (most likely the "visual awareness negativity" or "VAN") showed a pattern of amplitude change across contrast levels that closely matched the subjective PAS ratings. In addition, decoding of stimulus presence showed significant off-diagonal temporal generalization from ~200-400ms for stimuli at contrast levels above, but not below, perceptual threshold. Finally, preliminary analyses suggest there may be an increase in inter-trial EEG variability within similar time frames for the threshold-level stimuli, consistent with a bifurcation of seen and unseen trials. Together, these results confirm the close link between perceptual awareness and neural processing during this critical time window (250-400ms).

Disclosures: A. Nicolacoudis: None. **M. Opitz:** None. **M.A. Pitts:** None.

Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.10/Web Only

Topic: I.02. Perception and Imagery

Title: Entangled photons emitted by oscillating cationic arginine side chains within the hydrophobic constriction site of voltage-gated sodium channels form the quantum mechanical underpinnings of consciousness

Authors: *D. S. GUPTA;
Sch. of Pharm., South Univ., Savannah, GA

Abstract: It is known that awareness depends on cortical neuronal activities that result from the interaction of the brain with the environment. To explain the quantum mechanical basis of the awareness of interactions with surroundings, the author proposes that movements of conserved arginine amino acid residues of the voltage sensor (VS) within a hydrophobic constriction site (HCS) of the first activated voltage-gated sodium (NaV) channel at the initial axon segment produce entangled photons. The arginine residue side chain is a guanidinium cation. There is a high intensity voltage of ~8 million volts/m along the HCS. Upon reaching the action potential threshold due to depolarization, resulting from excitatory synaptic inputs, the helical VS will rotate within the HCS as it moves outward. Since the positively charged arginine side chain is aligned along electric field lines, the rotation of the VS carrying arginine side chain would

produce a torque, which will eventually overcome electrical field forces, leading to oscillations of the positively charged arginine side chain. Oscillations of the electrical charges result in emissions of photons. Further note that the transmembrane potential difference fluctuates dynamically during synaptic inputs to neurons reflecting the dynamic nature of the brain's interactions with external environment. The fluctuations in transmembrane potential difference near the action potential threshold can result in reversal in the direction of the movement and rotation of the VS within the HCS. This reversal of the movement of the VS is more likely to occur when there is interaction with a conserved phenylalanine within the HCS. Pairs of maximally entangled infrared photons will be emitted due to a shared electrical field vector at the time point of reversal. Each of these photons may interact with another oscillating arginine side chain with the same vibrational state as the one that emitted those photons, resulting in stimulated emission of a second photon, both of which will then be entangled. This stimulated emission will occur when the emitted photon interacts with an oscillating arginine side chain with the same mechanical constraints, namely, electric force vector, steric factors within the HCS, permitting only certain vibrational states of arginine side chains as the moving VS segment interacts with the conserved phenylalanine. Multipartite photon entanglement, resulting from the brain's response to various stimuli, would adequately explain the binding and qualia associated with awareness of surroundings.

Disclosures: D.S. Gupta: None.

Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.11/NN7

Topic: I.02. Perception and Imagery

Title: Fidelity and Subjective Experience in Stepwise Mental Imagery Construction

Authors: *H. SATO[1], T. TAKANO[2], K. MOGI[3];
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Abstract: Mental imagery is the cognitive ability to internally construct and manipulate visual information without direct sensory input (Pearson, 2019). This process has been linked to working memory, particularly visuospatial working memory (Keogh and Pearson, 2011). Recently, neuroscientific research has also suggested that VWM and mental imagery share overlapping neural representations in the visual cortex (Dijkstra et al., 2019). Mental imagery plays an important role in a wide range of cognitive functions, including perception (Ishai and Sagi, 1995) and moral judgment (Amit and Greene, 2012). However, the mechanisms for actively integrating information within working memory, and how these relate to subjective experience, are not yet fully understood. Furthermore, recent findings suggesting that some attributes of mental imagery can be maintained in a "non-committed" state (Bigelow et al., 2023)

are closely related to issues of working memory capacity limits and the fidelity of information representation within it. This study systematically investigated the stepwise integration process of visuospatial information in working memory, the accuracy of the mental image constructed as a result, and its relationship with participants' subjective vividness and confidence, using a task in which images were divided into multiple regions and presented sequentially. In this task, participants viewed only one region at a time. The regions were switched sequentially, and after all regions had been presented once, participants selected the original complete image from several candidate images. This process demanded that participants maintain and integrate the information from each region within their working memory to construct the final, complete image. Additionally, in each trial, participants' subjective ratings of image vividness and their confidence in their answers were assessed. We then analyzed how these subjective measures relate to objective accuracy, which is considered to reflect the precision of integration in working memory. We discuss insights into the dynamic role of working memory in mental construction processes, the mechanisms of metacognitive evaluation of these process outcomes, and the potential neural mechanisms involved.

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Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Program #/Poster #: PSTR469.12/NN8

Topic: I.02. Perception and Imagery

Support: Templeton World Charity Foundation Board, (TWCF-2021-22032)

Title: Reproducible and open-source fMRI decoding pipelines for arbitrating theories of consciousness

Authors: *A. EKHLASI[1], E. OLSSON[1], M. KLIMOVA[2], X. HUANG[2], A. SHEN[1], K. GARCIA[1], N. DIJKSTRA[3], J. MORALES[2], M. A. PETERS[1,4];
[1]Univ. of California, Irvine, Irvine, CA; [2]Northeastern Univ., Boston, MA; [3]Univ. Col. London, London, United Kingdom; [4]Canadian Inst. for Advanced Res., Toronto, ON, Canada

Abstract: How does the brain distinguish between perception and imagination? Higher-order (HO) theories of consciousness posit that this reality monitoring (RM) signal is constructed through a HO mechanism that monitors a first-order representation—a representation about the external environment—by encoding features such as its strength, reliability, or vividness. However, HO theories differ in how they treat vividness. Higher-Order State Space theory (Fleming, 2020; Dijkstra & Fleming, 2023) argues that vividness serves as a RM signal, while Perceptual Reality Monitoring theory (Lau, 2019; Lau, 2022) claims that RM is a distinct signal separate from vividness.In this work, as part of an ongoing adversarial collaboration arbitrating among these HO theories (TWCF-2021-22032) we are developing a novel approach to

formalizing these hypotheses using domain adaptation (DA), a machine learning technique which statistically aligns neural representations to evaluate the separability of the vividness versus RM HO dimensions. To move forward, we must first establish a standardized analytic pipeline against which to benchmark future DA work. Here, we present the open science infrastructure we have developed as a standard framework for adversarial collaborations more broadly, and discuss its integration with our target DA analyses to evaluate HO theories. Our reproducible pipeline combines fMRIprep, Nilearn, Neurodesk, and other standardized tools, and deploys them in a containerized and modular computing environment to meet the independent replication requirements for these adversarial collaborations. We showcase this pipeline using fMRI data from two participants (Horikawa & Kamitani, 2017), which included both visual perception and imagery tasks with trial-by-trial vividness ratings during imagery. To identify RM brain regions, we performed GLM-based beta estimation, multivariate pattern analysis (MVPA), and whole-brain searchlight decoding. We then trained classifiers to decode vividness from imagery trials, and then developed a novel ratio metric to quantify the degree to which a given brain region encodes vividness versus RM. Our analyses can reliably identify regions involved in RM, and show that these only partially overlap with regions encoding vividness. We also show how our infrastructure can be seamlessly deployed across multiple labs and data analysis sites to facilitate transparent replicability. Our findings and pipeline establish the baseline benchmark against which to develop and deploy our target DA approaches for arbitrating HO theories of consciousness in future.

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Poster

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Program #/Poster #: PSTR469.13/Web Only

Topic: I.02. Perception and Imagery

Support: Korea NRF RS-2022-NR070542

Title: Time course of mean size judgments

Authors: *S. J. JOO, S.-A. YOO;
Psychology, Pusan Natl. Univ., Busan, Korea, Republic of

Abstract: Despite psychophysical evidence that the visual system rapidly and accurately forms ensemble representations of individual items in a scene, the temporal dynamics of this process remain unclear. In the present study, we used electroencephalography (EEG) to investigate the time course of ensemble representation during mean size judgments. We recorded event-related potentials (ERPs) from 34 observers (12 male, 22 female; mean age = 22.9 years) as they performed a two-interval forced-choice mean size task, in which they compared the mean size of

two arrays of circles. On each trial, participants compared a standard array of 20 circles—whose mean size was randomly drawn from a uniform distribution between 2.1° and 2.8° of visual angle—to a test array containing either 16 or 24 circles. The test arrays were constructed so that their mean size was one of five ratios relative to the standard (0.57, 0.87, 1.00, 1.15, or 1.76). Observers judged which array had the larger mean circle size, allowing assessment of both behavioral accuracy and the ERP signatures associated with ensemble encoding at different set sizes and difficulty levels. ERPs elicited by the test array exhibited an early sensory component peaking at approximately 90 ms over occipital electrodes, and the amplitude of this component was modulated by the mean size manipulation. However, it is not clear whether this result was due to ensemble encoding or sensory encoding (the summed area of all circles) because they are confounded. To isolate the ERPs to the mean size representation, we calculated a difference wave by subtracting the ERP response to the test array from that to the standard array. The difference wave showed a systematic amplitude increase between 120-160 ms after stimulus onset as a function of test array mean size. These results suggest that initial encoding of individual item sizes might precede the formation of an ensemble representation, with aggregate size information emerging between 120 ms and 160 ms during mean-size judgments.

Disclosures: S.J. Joo: None. **S. Yoo:** None.

Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

Location: SDCC Halls B-H

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Program #/Poster #: PSTR469.14/NN9

Topic: I.02. Perception and Imagery

Title: Investigating Bifurcation Dynamics and Neural Correlates of Consciousness Using EEG and Report/No-Report Paradigms

Authors: *K. KASRAEIAN, J. SAMAHA;
Psychology, UCSC, Santa Cruz, CA

Abstract: Understanding the neural correlates of consciousness (NCC) requires isolating neural activity directly linked to conscious perception from confounding factors such as sensory encoding, attention, and post-perceptual processes. This study explores whether bifurcation dynamics—sharp transitions in neural activity between perceived and non-perceived states—serve as a general neural signature of perceptual consciousness. Using a report/no-report paradigm, we investigated bifurcation dynamics in the domain of visual perception.Participants are presented with Gabor patch stimuli varying in contrast, location, and orientation. In report conditions, participants provide subjective visibility ratings and perform an objective localization task, enabling analysis of trials with spontaneous perceptual variability. In no-report conditions, participants engage in an unrelated fixation task, minimizing task-related and reporting confounds while maintaining conscious perception of stimuli.Preliminary results indicate that around 350 milliseconds post-stimulus, a, classifier trained on no-report data and tested on report

data shows a key statistical signature of bifurcation, namely that trial-to-trial variability in the classifier output peaks at intermediate stimulus intensities.Notably, this bifurcation appears later than in analogous auditory studies, possibly due to modality-specific dynamics or reduced attentional engagement in the no-report condition. This approach offers a framework for isolating perceptual awareness and advancing our understanding of the neural dynamics underlying visual consciousness.

Disclosures: K. Kasraeian: None. **J. Samaha:** None.

Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Topic: I.02. Perception and Imagery

Support: NIH Grant R01-EY025648

Title: Unfolding spatiotemporal representations of 3D visual perception in the human brain

Authors: *Z. LU, J. D. GOLOMB;
Dept. of Psychology, The Ohio State Univ., Columbus, OH

Abstract: Although visual input is initially recorded in two dimensions on our retinas, we perceive and interact with the world in three dimensions. Achieving 3D perception requires the brain to integrate 2D spatial representations with multiple depth cues, such as binocular disparity. However, most studies typically examine 2D and depth information in isolation, leaving the integrated nature of 3D spatial encoding largely underexplored. In this study, we collected a large-scale, multimodal neuroimaging dataset consisting of multiple EEG and fMRI sessions while participants viewed stereoscopic 3D stimuli through red-green anaglyph glasses. Participants first completed a behavioral session including depth judgement tasks and a novel cube adjustment task to quantify and calibrate individual depth perception in units of binocular disparity. Then during two EEG and two fMRI sessions, participants passively viewed stimuli presented at 64 systematically sampled 3D locations (a 4×4×4 grid centered on fixation), yielding over 66,000 trials in total across ten participants. Combining this large-scale EEG-fMRI dataset with computational methods via representational similarity analysis, we not only systematically characterized the spatiotemporal representation of multiple spatial features in 3D perception but also explored how different coordinate systems (e.g., Cartesian or Polar) might be employed across brain regions and time. Our results reveal that human brains employ multiple types of spatial feature representations and coordinate systems to encode spatial locations at different temporal stages and across distinct cortical regions. In addition to strong representations of 2D space throughout visual cortex, we find unique representations for depth and 3D features in later timepoints and visual areas, including some evidence for integrated 3D processing in parahippocampus. These findings contribute to a more comprehensive understanding of the

spatiotemporal organization of neural representations that support 3D perception. Additionally, our novel dataset will be made openly available to support future research on 3D perception and spatial cognition.

Disclosures: Z. Lu: None. **J.D. Golomb:** None.

Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Program #/Poster #: PSTR469.16/NN11

Topic: I.02. Perception and Imagery

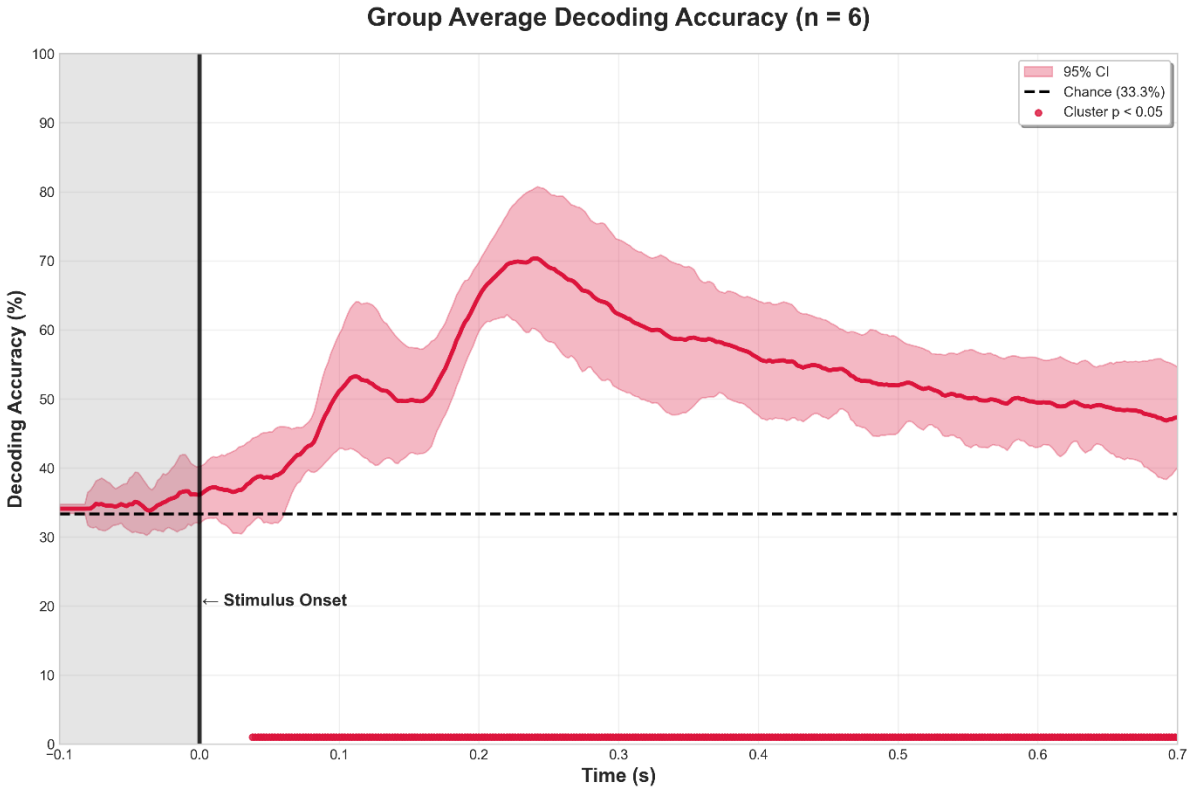
Support: Collaborative Pilot Research Grant from American University's College of Arts and Sciences
NIH 1R15EY033512-01
NSF BCS-2122961

Title: Eeg decoding reveals invariant representation of material categories of real-world objects

Authors: *V. LAVAN[1], C. LIAO[1], M. SAWAYAMA[3], L. BAYET[1], B. XIAO[2];
[1]Neurosci., [2]Computer Sci., American Univ., Washington, DC; [3]Grad. Sch. of Information Sci. and Technol., Hokkaido Univ., Sapporo, Japan

Abstract: Humans can often recognize familiar materials from images within a fraction of a second. Given the immense variation in appearance both within and across material categories, constructing material representations is challenging for the visual system. Previous work on the neural correlates of material perception has relied on isolated surface patches or computer-generated stimuli, leaving open the question of how material category representation arises from viewing complex real-world objects. Here, we investigated how the neural processing of material categories unfolds over time and tested the hypothesis that material categories emerge across variations of object-level features and scene factors. We photographed 10 objects of 3 distinct material categories that share translucent features — crystals, soaps, and squishy toys. Each image contains a single object against a wooden surface from 5 poses under consistent natural lighting. Participants (n=6; ages 18-25) viewed these images on a monitor while brain activity was recorded using a HydroCel Geodesic Sensor Net 128-channel EEG cap. Each trial started with a 750ms fixation dot followed by a 200-300ms jittered blank screen. Next, a stimulus was presented for 750ms followed by a 750ms blank screen. The recorded EEG data was preprocessed and segmented into epochs. Material category decoding was conducted within-participants using a linear one-vs-rest multiclass Support Vector Machine in 41ms sliding windows centered at each time point (+/- 20ms) and 5-fold cross-validation. Material categories could be decoded significantly above chance starting from 40ms and peaking around 200-250ms after stimulus onset (cluster-based permutation test, $p < 0.05$). Our findings provide initial evidence that the spatiotemporal patterns of brain activity have a rapid representation of

materials, allowing for the recognition of different categories of materials despite variations in appearance caused by both intrinsic properties and external scene factors.



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Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Program #/Poster #: PSTR469.17/NN12

Topic: I.02. Perception and Imagery

Support: NIH Award R01-MH128552

Title: Testing retinotopic sensitivity of human hippocampal activity via intracranial EEG

Authors: *K. A. ROSTOWSKY[1], J. L. VOSS[1], J. E. KRAGEL[2];
[2]Neurol., [1]Univ. of Chicago, Chicago, IL

Abstract: Hippocampal representations of space are not limited to an organism's physical position, but also include view-based information. However, few studies have investigated how

visual information is represented in the hippocampus. In humans, functional magnetic resonance imaging (fMRI) has suggested retinotopic sensitivity of hippocampal responses to visual stimuli, in that activity is stronger for stimuli presented in contralateral versus ipsilateral visual field. Yet, fMRI lacks the temporal resolution to assess if such sensitivity aligns with neural oscillations. Alpha desynchronization in human visual cortex is organized retinotopically, but it remains unclear whether similar theta oscillatory mechanisms contribute to retinotopic responses in the hippocampus. To test for retinotopic organization of oscillatory activity, we used intracranial electroencephalography (iEEG) to directly record hippocampal activity in humans (N=12 patients undergoing presurgical evaluation for intractable epilepsy) performing a visual field mapping task adapted from the Human Connectome Project. Complex images appeared across the display while subjects maintained gaze centrally and responded to color changes in a central fixation dot to ensure attentional engagement. We focused analyses on low (1-5 Hz) and high theta (5-12 Hz) power recorded from the left (N=48 contacts) and right (N=64 contacts) hippocampus. Low-theta power was significantly modulated by the presence versus absence of visual stimuli ($p < 0.05$ via permutation test with 10000 permutations) for 30% of hippocampal electrode contacts and high-theta power was modulated for 40% of contacts. Thus, a significant subset of recorded hippocampal locations were sensitive to the task's visual stimuli. For these electrodes, we analyzed the relationship between theta power and the left/right lateralization of the visual stimulus. Of visually sensitive electrodes, 10% had activity that correlated significantly (95% bootstrap CI with 1000 resamples) with stimulus lateralization (45% in left hippocampus, 55% in right hippocampus). These preliminary findings suggest that theta activity of human hippocampus demonstrates retinotopic sensitivity similar to what has been identified via fMRI. Ongoing analyses that will be discussed include testing for retinotopic organization beyond lateralization and characterizing whether any portions of the hippocampus (e.g., anterior versus posterior) are more retinotopically sensitive than others. Together, these findings help bridge a mechanistic gap between nonhuman electrophysiology and human fMRI studies of hippocampal visual space organization.

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Poster

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Program #/Poster #: PSTR469.18/OO1

Topic: I.02. Perception and Imagery

Support: NSF 2050833

Title: Neural Signals Reflect Differences in Perception of Illusory Faces as Opposed to Faces and Objects

Authors: *A. THOKSAKIS[1], E. F. ESTER[2];
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Abstract: Face pareidolia refers to the phenomenon where faces are perceived in inanimate objects. These illusory faces provide an excellent model for investigating the neural mechanisms underlying human face processing. Notably, few studies have examined whether classical electrophysiological signatures of face processing, such as the N170 ERP component, are modulated by illusory faces. Furthermore, research has yet to show how signals elicited by illusory faces differ from those evoked by real faces and inanimate objects. To bridge this gap, we recorded EEG in two studies where participants passively viewed or categorized faces, pareidolias, and common objects. Both studies employed a precision imaging approach, where a small number of participants viewed thousands of exemplars from each category, enabling us to quantify and compare electrophysiological signals on both within- and between-subjects bases. trials. In experiment 1, participants passively viewed stimuli over 9,216 trials. Here, our analyses revealed small but statistically robust effects of stimulus category on N170 amplitude and latency. In experiment 2, we asked participants to make overt judgements regarding whether they saw a face, illusory face, or object over 4,609 trials. This time, we observed clear N170 effects across all stimuli, with faces eliciting the greatest negativity, objects eliciting the smallest negativity, and signals elicited by illusory faces occurring intermediately. Together, these results suggest that the N170 ERP differentiates between faces, illusory faces, and objects, making it a suitable component for tracking the time course of illusory face perception.

Disclosures: A. Thoksakis: None. **E.F. Ester:** None.

Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.19/OO2

Topic: I.02. Perception and Imagery

Support: LUE postdoc fellowship
FNR Grant INTER/FNRS/17/1178524

Title: The largest frequency-tagged responses of the human brain occur to visual stimulation under 4 Hz when taking higher harmonics into account

Authors: *T. L. RETTER[1], B. ROSSION[2], C. SCHILTZ[3];
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Abstract: In electroencephalogram (EEG) frequency tagging, periodic visual stimulation at temporal frequency F generates periodic brain responses at *F* and higher harmonics (2*F*, 3*F,* etc.) in the frequency domain. These higher harmonic responses have most often been left out of

response analysis: responses are commonly assessed simply at *F* (i.e., the first harmonic = 1*F*). A simple *F* analysis is appropriate when the response is represented at a single frequency, i.e., steady-state or approximately sinusoidal in terms of voltage amplitude over time. In the visual modality, this occurs when F > 4-8 Hz, and visual stimulation at F = 10 Hz has long been known to generate the largest EEG response at *F* over the human occipital cortex. However, the traditional *F* analysis is not appropriate to measure non-sinusoidal responses occurring to lower F. When higher harmonics are taken into account through baseline-corrected amplitude summation ($F+2F+3F... = F_s$), the largest EEG responses occurs to visual stimulation at F < 4 Hz. We suggest that frequency tagging does not need to be limited to steady-state conditions to benefit from the advantages of frequency-domain analysis, notably objective identification of one or more responses with a high signal-to-noise ratio. This implies that F well under 10 Hz may be considered optimal in some contexts of fundamental and applied research, although the highest-amplitude response may not always be considered the optimal one.

Disclosures: T.L. Retter: None. **B. Rossion:** None. **C. Schiltz:** None.

Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.20/OO3

Topic: I.02. Perception and Imagery

Support: R01EY032085

Title: Probing the neural geometry of conscious object category representation in time

Authors: *A. HACHISUKA[1], T. J. BAUMGARTEN[1,3], D. SPECTOR[1], L. KOENIG[1], B. J. HE[1,2];
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Abstract: During object recognition, we derive meaning from the processing of visual inputs by integrating and abstracting low-level features. However, when and how the conscious experience of object categories emerges remains an open question. The coarse-to-fine theory of vision posits that an early perception of the superordinate category, resolved via “gist perception”, guides the filling-in of details that support perception of the basic-level category that often corresponds to the object’s common name (e.g., “cat”, “truck”). However, it is currently unclear how to reconcile these ideas with evidence showing that the basic category is prioritized and rapidly accessed. We recorded high-density EEG data from 30 human participants while they performed a threshold-level object categorization task, using regular images containing objects and animals, low-pass filtered (LSF) images to disrupt feedforward processing, and visually masked images to disrupt recurrent processing. For each image, participants were asked to report its superordinate

and basic category, as well as their perceptual awareness scale (PAS) rating. The superordinate-level categorization performance is higher than the basic-level categorization performance, suggesting that superordinate category information is more easily accessed for report. However, in all conditions, both category levels are significantly decoded at similar onset times in EEG. In normal and LSF image conditions with intact recurrent processing, investigation of neural geometry revealed that an abstract superordinate category representation emerges at a later time point (~300ms), as a result of the disentanglement from low-level features. We then tested how category representation contributes to subjective experiences by predicting PAS ratings, at a trial-to-trial level, from the distance of the neural activity to the discrimination boundary in the decoder. This analysis revealed that the strength of evidence for the basic category representation contributes to the participants' PAS ratings earlier (~50ms) than that of the superordinate category representation (~350ms). Collectively, we demonstrate that while superordinate categories are reported more effortlessly, the basic-level category representation contributes to the graded conscious experience first, followed by the late-stage, abstract superordinate category information. Our results shed light on how object categories emerge in time in the brain and become part of our subjective awareness.

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Poster

PSTR469: Neural Dynamics of Visual Consciousness and Awareness

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.21/OO4

Topic: I.02. Perception and Imagery

Support: R01EY032085
TWCF-2022-30264

Title: Neural mechanisms of visual recognition under occlusion

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Abstract: Identifying key objects in the environment, whether food or threats, is a critical behavior for all organisms, but the natural world is often chaotic and filled with ambiguous stimuli. The human visual system has evolved to correctly recognize ambiguous images even under challenging conditions. While recognition of unambiguous images has been shown to be driven by computations in the ventral visual stream, what other brain regions are required to resolve ambiguous images are currently unclear. We seek to clarify this question in this fMRI study. We recorded brain responses in 24 subjects (11 female) using whole-brain 7T fMRI while they performed an image recognition task with partially occluded images. During the task,

participants were asked to report the category (animal/building/object/person) of the presented image, and whether they could identify the specific object in the image (yes/no). We developed a custom image set for this study using greyscale natural images with randomly placed colored circles occluding 40%, 60%, or 80% of each image, and validated it in an online experiment (N=28 participants) prior to collecting fMRI data. We found that recognizing the partially occluded images was correlated with brain activity in distinct brain regions. Recognized trials and unrecognized trials elicited significantly different activation in a wide range of networks including visual cortex, the default mode network, and the anterior insula and dorsal anterior cingulate cortex of the cingulo-opercular network (CON). While most areas show greater activation during recognized trials, in CON areas activation was lower in recognized trials. Consistent with previous studies, visual areas in both the ventral and dorsal streams showed decreased activation with increasing occlusion level. By contrast, CON areas showed increased activation with increased occlusion but only during correct trials, suggesting that more challenging images require heightened engagement of CON to be successfully recognized. Finally, we found that while, as expected, decoding accuracy of image category is anticorrelated with occlusion level in visual cortex, the hippocampus had stable decoding accuracy across occlusion levels. Our findings add to a growing body of evidence showing that regions beyond the visual ventral stream contribute to visual recognition. We find that areas from early visual cortex to frontal cortex are actively involved with varying activity profiles indicating their unique contributions. These findings provide new evidence that brain regions beyond the ventral stream are involved in visual recognition of occluded objects.

Disclosures: J.D. Shor: None. **Y. Wu:** None. **D.F. Zheng:** None. **B.J. He:** None.

Poster

PSTR470: Neural Mechanisms of Decision-Making

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.01/OO5

Topic: I.08. Learning and Memory

Title: Differential activity patterns of D1 and D2 medium spiny neurons in the tail striatum develop during auditory learning

Authors: *L. CHEN[1], Y. ZHANG[3], X. PENG[2], Q. XIONG[4];
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Abstract: The tail striatum, the most caudal region of the dorsal striatum, receives inputs from both the auditory cortex and thalamus and plays a critical role in auditory-guided behaviors. However, the physiological mechanisms underlying learning in this region remain largely unknown. Using in vivo calcium imaging in freely behaving mice, we found that D1 and D2 medium spiny neurons (MSNs), the two populations of principal neurons, exhibit distinct

patterns of task-related activity. Notably, longitudinal tracking of neuronal ROIs during learning revealed that D1-MSN responses to auditory cues guiding contralateral movements became selectively potentiated and synchronized. This effect was not observed in D1-MSN responses to movement or in D2-MSN responses. Computational modeling further supported a role for D1-MSN auditory encoding in driving task performance, emerging specifically during learning. Together, these findings reveal the development of task-relevant D1-MSN activity in the tail striatum as a critical mechanism for auditory decision-making.

Disclosures: L. Chen: None. **Y. Zhang:** None. **X. Peng:** None. **Q. Xiong:** None.

Poster

PSTR470: Neural Mechanisms of Decision-Making

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.02/OO6

Topic: B.07. Network Interactions

Support: VA I01BX004500
VA I01BX002774
NIMH R21 MH125242

Title: Cortical and subcortical oscillatory and connectivity dynamics during olfactory decision-making in mice

Authors: E. B.-L. MANESS[1], M. MACIVER[1], J. T. MCKENNA[2], *J. M. MCNALLY[3]; [1]VABHS/Harvard Med. Sch., West Roxbury, MA; [2]Research/Psychiatry, VA Boston/Harvard Med. Sch., West Roxbury, MA; [3]VABHS, Harvard Med. Sch., West Roxbury, MA

Abstract: The ability to quickly and flexibly attend and respond to the demands of an unpredictable environment is important for navigating the physical world and necessitates the precise coordination of distributed brain networks across a variety of conscious states. In olfactory cognition, incoming chemosensory information must quickly traverse from primary sensory neurons in the olfactory bulb (**OB**) to regions involved in higher-order cognition and stimulus-associated behavior. Attentional processing enhances olfactory discrimination by selectively filtering bottom-up signals that convey task-relevant information and engaging top-down pathways to promote appropriate behavioral responses. The present work aims to characterize time- and performance-dependent changes in oscillatory activity and functional connectivity within and between brain regions in mice (n = 11) outfitted with multi-site local field potential electrodes during performance of a self-initiated olfactory discrimination Go/No-Go task. Overall, there was a robust suppression of high-frequency oscillatory activity (high gamma, 80-200 Hz) prior to and during attentional effort in all examined brain areas - including those associated with olfaction (OB), attention and salience (prelimbic cortex, anterior insular cortex, basal forebrain (**BF**), and visual cortex), and memory (retrosplenial cortex (**RS**) and hippocampus (**CA1**)) - indicating a widescale pre-emptive reduction of activity in anticipation of

information-bearing input. There were additionally performance-associated enhancements of lower frequency bands (e.g. theta, 4-8 Hz; beta, 12-30 Hz; and low gamma, 30-80 Hz) that varied depending on brain region (olfactory-relevant vs. olfactory-irrelevant), timing (odor sampling vs. decision-making), odor type (reward-linked vs. non-reward-linked), and behavioral outcome (correct vs. incorrect responding). Furthermore, we found that directional connectivity from the OB, BF, and CA1 to other brain regions was prominent during correct trial performance; however, olfactory outputs - particularly to the CA1 and RS - were reduced in incorrect trials, highlighting a potential disruption in olfaction-driven contextual signaling that underlies accurate task performance. Taken together, these findings reveal timely intra-regional rhythmic signatures and inter-regional coordination underlying optimal signal-driven attention, suggesting that maintaining exteroceptive awareness is a multifaceted phenomenon that necessitates the synchronized activation of large-scale cortical and subcortical brain networks.

Disclosures: E.B. Maness: None. **M. MacIver:** None. **J.T. McKenna:** None. **J.M. McNally:** None.

Poster

PSTR470: Neural Mechanisms of Decision-Making

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.03/OO7

Topic: H.03. Motivation

Title: Effects of a single injection of psilocybin on value-based decision-making behavior and prefrontal cortex perineuronal nets in rats

Authors: J. HOUFF[1], A. WILLIAMS[1], O. ALLEN IV[2], B. GISABELLA[2,3], H. PANTAZOPOULOS[2,3], *A. J. DEL ARCO[1,2,3];
[1]Univ. of Mississippi, Oxford, MS; [2]Dept. of Psychiatry and Human Behavior, [3]Program in Neurosci., Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: Clinical trials suggest that a single dose of the psychedelic drug psilocybin produces long-term therapeutic benefits as a treatment for substance use disorders. Choice impulsivity is a value-based decision-making bias and a reliable behavioral feature that anticipates the transition to substance abuse. Recent studies from our group suggest that extracellular matrix molecules such as perineuronal nets (PNNs) in the dorsomedial prefrontal cortex (dmPFC) play a role in choice impulsivity. Here we investigate whether a single injection of psilocybin modulates choice impulsivity and PNNs in the dmPFC two days after administration. Male Long Evans rats (n= 18; 3 months) were trained in a delay discounting task (DDT). This task involves a decision-making process in which the subjective value of a reward decreases as the delay in receiving it increases. Rats first learned to discriminate between a large-reward lever (LR) (3 sugar pellets) and a small-reward lever (SR) (1 sugar pellet). DDT consisted of three blocks of trials in which both levers were active, and animals had to make a choice between LR and SR. The three blocks differed on the delay to receive the large reward after pressing LR: 1 s (block 1), 10 s (block 2)

and 20 s (block 3). After stable performance, rats were injected with psilocybin (1 mg/kg, i.p.) (n= 6) or vehicle (n= 8). Two days after the injection, DDT was assessed, and rats were euthanized and their brains processed for immunofluorescence and microscopy analysis. Brain slices were labeled with wisteria floribunda agglutinin lectin to quantify the number of PNNs together with antibodies for parvalbumin (PV) neurons and c-fos as a marker of neuronal activity. Psilocybin acutely increased the number of head twitches (5.33 ±0.54; $p< 0.001$, *t* test). In the DDT, psilocybin decreased LR choices (Group: $F(1, 12)= 4.70$, $p= 0.05$) and increased the latency to LR press (Group: $F(1, 10)= 10.01$, $p= 0.010$, ANOVA) two days after administration. Importantly, these effects were not dependent on delay, which suggests that psilocybin changes reward-seeking behavior, but not choice impulsivity. In the dmPFC, we found that psilocybin increased the labeled density of PNNs + cFos (veh= 0.2 ± 0.1; psi= 0.9 ± 0.12; $p< 0.01$) and PNNs + cFos + PV (veh= 2 ± 0.89; psi= 5.6 ± 1.0 neurons/mm2; $p< 0.01$, *t* test) in deep layers compared to vehicle. These results suggest that a single injection of psilocybin decreases reward-seeking behavior in association with increased activation of dmPFC PV neurons surrounded by PNNs. These results support a role of psilocybin modulating the brain reward system in the long term through PNNs remodeling. *First two authors made the same contribution*.

Disclosures: J. Houff: None. **A. Williams:** None. **O. Allen IV:** None. **B. Gisabella:** None. **H. Pantazopoulos:** None. **A.J. Del arco:** None.

Poster

PSTR470: Neural Mechanisms of Decision-Making

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.04/OO8

Topic: H.03. Motivation

Support: NIMH BF-PV

Title: A Frontal-to-Midbrain projection promotes reflexive responding during behavioral conflict

Authors: *K. YANG[1], D. BONDA[4], M. WULF[2], J. TARANDA[5], P. OSTEN[6], A. KEPECS[3]; [1]Washington Univ. in St. Louis, St Louis, MO; [2]Dept. of Neurosci., [3]Neurosci., Washington Univ. in St. Louis, St. Louis, MO; [4]Cedars-Sinai Med. Ctr., Santa Monica, CA; [5]Neurosci., Natl. Ctr. for Tumor Dis. (NCT), Heidelberg, Germany; [6]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Adaptive behavior requires the ability to weigh competing demands, such as balancing instinctive reactions to environmental challenges with sustained goal pursuit. This form of executive control is thought to rely on neocortical modulation of evolutionarily conserved midbrain defense centers, yet the specific neural circuits that resolve such motivational conflicts remain unknown. Using a novel Threat-Reward Conflict (TRC) paradigm in mice, we identified a population of excitatory prefrontal neurons projecting from the anterior

cingulate cortex to midbrain defense centers, including the superior colliculus and periaqueductal gray, that are selectively active when defensive behaviors override reward pursuit. Viral tracing revealed no evidence of top-down inhibitory (mono- or di-synaptic) input to these targets. Optogenetic activation of this pathway enhanced escape and freezing, while its inhibition reduced these behaviors—but only under conflict. These findings reveal a top-down circuit that resolves motivational conflict by promoting, rather than suppressing, reflexive defensive behaviors.

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Poster

PSTR470: Neural Mechanisms of Decision-Making

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Program #/Poster #: PSTR470.05/OO9

Topic: I.08. Learning and Memory

Support: UF Center for Cognitive Aging and Memory
McKnight Brain Research Foundation

Title: Apoe4 genotype in a rat model mimics aging and Alzheimer's disease-like patterns of executive function and decision making

Authors: *D. ROMERO[1], K. M. GONZALEZ[2], S. N. BURKE[2], B. SETLOW[3], J. L. BIZON[4]; [2]Neurosci., [3]Dept. of Psychiatry, [1]Univ. of Florida, Gainesville, FL; [4]Neurosci., Univ. of Florida Dept. of Neurosci., Gainesville, FL

Abstract: Among the genetic risk factors for sporadic Alzheimer's disease (AD), the apolipoprotein E (ApoE) gene is the most prevalent, with different alleles having different disease implications. Compared to the "neutral" E3 allele, the E4 allele substantially increases AD risk and influences neural function decades before disease onset. While most research on E4 has focused on mnemonic functions mediated by the medial temporal lobe, less is known about effects on prefrontal cortex-mediated executive functions. To address this, we employed homozygous transgenic rats in which the human E3 or E4 allele replaces the native rat ApoE gene on a Sprague-Dawley background. Rats were evaluated on a battery of tasks assessing executive functions that are compromised in aging and AD, at both 4-8 months and 12-16 months of age. The intertemporal choice task, in which rats chose between small, immediate and large, delayed rewards, assessed choice impulsiveness. The delayed response task, in which rats had to remember the position of a response lever over short delays, assessed working memory. The probabilistic reversal learning task, which required rats to reverse lever response rules, assessed cognitive flexibility. At 4-8 months of age, E4 males showed reduced impulsive choice (greater preference for delayed over immediate reward) and impaired working memory and cognitive flexibility compared to E3 males - a pattern of performance comparable to that

observed in aged compared to young adult male wild-type rats. At 12-16 months of age, E4 males showed *increased* impulsive choice compared to E3 males (i.e., reduced preference for delayed over immediate reward) - a pattern of performance like that observed in AD. Performance in females did not differ by genotype in any task at either age. Altogether, the results suggest that, at least in males, the E4 allele promotes an "accelerated aging" cognitive phenotype at young ages, whereas at middle age, cognitive performance is more consistent with an AD-like phenotype.

Disclosures: D. Romero: None. **K.M. Gonzalez:** None. **S.N. Burke:** None. **B. Setlow:** None. **J.L. Bizon:** None.

Poster

PSTR470: Neural Mechanisms of Decision-Making

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Program #/Poster #: PSTR470.06/Web Only

Topic: H.03. Motivation

Support: NSERC

Title: Exploring the roles of mPFC and vHPC in cue/context stimulus competition

Authors: *S. RIAZ[1,2], S. WU[2], S. NARAENTHERARAJA[2], H. MAUDOODI[2];
[1]Univ. of Toronto, Scarborough, ON, Canada; [2]Univ. of Toronto, Toronto, ON, Canada

Abstract: Effective decision-making in environments with conflicting motivational information requires the integration of discrete cues and contextual features. The medial prefrontal cortex (mPFC) and ventral hippocampus (vHPC) have both been implicated in emotional memory and contextual modulation of behaviour, yet their roles in resolving cue/context conflict remain unclear. To investigate this, we developed and refined a novel stimulus competition (SC) task to examine rodent behaviour in conditions where a cue previously associated with an outcome was superimposed on a context also separately associated with an outcome. Rats were trained to associate auditory cues and distinct spatial contexts with either a sucrose reward, no outcome (neutral), or a mild foot shock. Following successful acquisition, animals were tested under extinction conditions in cue/context conflict scenarios (e.g., a reward-predictive cue presented in a shock-associated context). In separate experiments, rats received bilateral injections of DREADDs (hM3Dq, hM4Di, or GFP) targeting either the mPFC or vHPC and were tested following intraperitoneal administration of clozapine-N-oxide (CNO) or saline. Baseline behaviour confirmed robust learning, with preferential approach toward reward-predictive cues and contexts. Preliminary results showed that mPFC inactivation (hM4Di) increased responding to reward-predictive cues even in shock-associated contexts, suggesting impaired conflict resolution. In contrast, vHPC activation (hM3Dq) enhanced avoidance of shock-predictive contexts when paired with shock-predictive cues, indicating improved stimulus integration under conflict. Notably, behaviour in GFP control animals revealed that the relative influence of

context and cues on approach-avoidance behaviour could be modulated by task parameters. These findings support complementary roles for the mPFC and vHPC in integrating motivationally relevant cued and contextual information to guide adaptive behaviours. Additionally, our data continue to inform the refinement and validation of this novel behavioural task for investigating stimulus conflict resolution. These insights lay the groundwork for future research using animal models of comorbid disorders such as PTSD and addiction, where approach-avoidance conflict remains poorly understood.

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Poster

PSTR470: Neural Mechanisms of Decision-Making

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Topic: I.08. Learning and Memory

Support: JST FOREST Program JPMJFR2040
JSPS KAKENHI JP 24H02164
JSPS KAKENHI JP 23K25753
JSPS KAKENHI JP 22K18645
JSPS KAKENHI JP 20K20862
JSPS KAKENHI JP 25K00895

Title: Hippocampal acetylcholine guides flexible behavioral transitions for reward pursuit under uncertainty

Authors: *M. OGAWA[1,2], H. MUKOHIRA[2,1], S. ISHINO[1], T. KAMADA[1];
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Abstract: Humans and animals often persist in pursuing valuable outcomes despite uncertainty or delay in reinforcement, and this persistence is crucial for maximizing long-term reward in real-world environments. Reinforcement learning (RL) provides a computational framework for understanding such behavior. Standard RL models, centered on dopamine-based reward prediction errors (RPEs), effectively capture value updating from immediate outcomes. However, they fall short in explaining persistent goal pursuit across uncertain or non-rewarding states, where agents must integrate outcome history and evolving task contingencies to adaptively maintain behavior. We demonstrate that hippocampal acetylcholine (ACh) dynamically modulates flexible behavioral transitions to support sustained reward pursuit under uncertainty. We developed a series of operant tasks in rats to monitor ACh dynamics in the hippocampus and amygdala via fiber photometry, and to record activity from cholinergic neurons in the medial septum. In a probabilistic reward task, hippocampal ACh transiently increased following unexpected reward omissions and terminations, and decreased following unexpected reward receipt. These responses evolved with learning and were closely linked to

behavioral transitions. Trial-by-trial analysis revealed that ACh increases positively correlated with the latency to disengage from non-rewarded trials, suggesting a role in evaluating and updating action-outcome contingencies. These patterns were consistent across dorsal and ventral hippocampus and mirrored in most cholinergic neurons in the medial septum. In contrast, amygdala ACh showed opposing dynamics. Optogenetic activation of septo-hippocampal cholinergic projections during reward omission facilitated adaptive transitions. In a delayed-reward task requiring sustained engagement across multiple non-rewarded trials, hippocampal ACh tracked prediction errors and evolving reward expectations, and diminished as task structure became familiar. These findings reveal that hippocampal ACh supports flexible behavioral strategy updating across trials, complementing but functionally distinct from canonical dopamine RPEs. This mechanism enables persistent reward pursuit in uncertain environments.

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Poster

PSTR470: Neural Mechanisms of Decision-Making

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Program #/Poster #: PSTR470.08/OO11

Topic: H.03. Motivation

Support: Rhode Island INBRE, NIH GM103430-STAR subaward
Rhode Island Foundation 16409_139170
Providence College Provost's Faculty Fellowship

Title: Medial prefrontal cortical ensembles direct behavior in response to competing needs

Authors: F. H. SCHAUB, K. S. MCCAFFREY, M. A. ROHR, E. N. MORLEY, N. L. ASHBY, *R. J. POST;
Neurosci. & Psychology, Providence Col., Providence, RI

Abstract: Neural circuits that drive survival behaviors (e.g., food seeking) when animals face a single, specific need (e.g., hunger) are highly conserved and well-characterized. However, when animals face multiple concurrent needs, behavior selection is a result of the integration and weighting of information related to the most pressing need. Though this behavioral plasticity is essential for survival, the mechanisms by which the brain accomplishes this are not fully understood. The medial prefrontal cortex (mPFC) plays a pivotal role in action selection, and our previous work indicates that two competing stimuli—environmental threat and food—are reflected by activity in largely segregated mPFC ensembles in hungry mice. While neural activity in these distinct mPFC ensembles correlates with these different motivations, it remains unclear whether this activity actually influences behavioral selection. To determine if activity in these mPFC ensembles is sufficient to bias the animal's behavior in response to one competing need over the other, we chemogenetically activated ensembles responding to either predator odor

or food while hunger and environmental threat were in conflict. Eight-week-old male and female TRAP2-Cre mice were injected with AAV5-hSyn-DIO-hM3D(Gq)-mCherry in the mPFC. Three weeks later, hM3D expression was driven in either threat or food-responsive mPFC ensembles. Specifically, mice were injected with 4-hydroxytamoxifen (4-OHT) prior to predator odor exposure (n = 13) or following overnight food deprivation and prior to refeeding (n = 13). After three weeks of expression, mice were food-deprived for four hours and injected with CNO or vehicle in counterbalanced trials prior to a predator odor assay, in which food was only available in the presence of the predator odor trimethylthiazoline. Food consumption and time in the odor zone were quantified. Activating predator odor-responsive mPFC ensembles significantly decreased food consumption compared to vehicle trials. In the absence of predator odor, there was no effect on food consumption. While experiments activating food-responsive mPFC ensembles are ongoing, our results thus far raise the possibility that activity in independent mPFC ensembles representing competing motivations may bias the animal's behavior toward one need at the expense of another.

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Poster

PSTR470: Neural Mechanisms of Decision-Making

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Program #/Poster #: PSTR470.09/OO12

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: 1R56MH137332-01

Title: Identification of Neurophysiological Biomarkers of Risk-Taking Propensity Using an Optimized Operant Decision-Making Task in Rats

Authors: *F. FAZIO[1], H. ROSBERG[1], J. MISHLER[1], M. SALIMI[1], D. RAMANATHAN[1,2,3,4], J. W. YOUNG[1], M. ULIVIERI[1], S. C. DULAWA[1];
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Abstract: Risk-based decision-making is a critical behavioral process that varies widely among individuals and is disrupted in multiple psychiatric disorders. Heightened risk-taking is observed in conditions such as substance use and gambling disorders, while excessive risk aversion characterizes disorders like anorexia nervosa. Despite the availability of human paradigms that assess individual differences in risk-taking, preclinical models that both detect these extremes and yield reliable neurophysiological biomarkers remain limited. Here, we optimized a rodent operant task to detect both high and low risk-taking phenotypes and assessed neural oscillatory signatures using local field potential (LFP) recordings across decision-making circuits.Adult

male and female Long-Evans rats were trained on a four-phase operant task requiring initiation via nose poke followed by a choice between a small, certain reward (50 μL sucrose) and a larger, uncertain reward (170 μL at 25% or 10 μL at 75%). Testing included 50 forced-choice trials, 100 free-choice trials, and an additional 100 free-choice trials in which all reward volumes were halved to manipulate task parameters. LFPs were recorded via bilateral tetrode implants targeting the orbitofrontal, infralimbic, and prelimbic cortices, as well as the dorsomedial and ventromedial striatum, nucleus accumbens (core and shell), and basolateral and central amygdala.Halving the reward volumes significantly increased risky choices ($p = 0.01$) across sexes and shifted the behavioral distribution away from risk-averse phenotypes (<20% risky choices) toward higher-risk categories. These behavioral shifts were accompanied by changes in oscillatory dynamics across multiple brain regions involved in reward processing and decision-making.These results demonstrate that our optimized task can reliably detect shifts in risk-taking behavior and uncover corresponding neurophysiological patterns. This preclinical platform offers a robust and translationally relevant approach for identifying circuit-level biomarkers of risk-based decision-making, with potential applications in the development of targeted interventions for psychiatric disorders characterized by maladaptive risk-taking

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Poster

PSTR470: Neural Mechanisms of Decision-Making

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Title: Functional dissociation of tactile and visual value-coding neurons in the primate caudate, putamen, and ventral striatum

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Abstract: Primates rely on tactile and visual information to evaluate objects, an ability critical for survival. These inputs are relayed from distinct cortical areas to the striatum, which includes putamen (PUT), caudate (CD), and ventral striatum (VS). Our previous study (Hwang et al, 2024) showed that PUT neurons encode both tactile and visual values, likely supported by converging tactile, visual, and dopamine inputs. While CD and VS also receive these inputs, they differ in their cortical origins: PUT from sensorimotor cortex, CD from associative and visual

regions, and VS from limbic areas. Despite the overlap in input content, their distinct sources raise a key question: how do these subregions differ in processing tactile and visual value information to regulate value-guided behaviors?Monkeys were trained to discriminate the values of tactile (braille) and visual (fractal) stimuli while single-neuron recordings were conducted. We identified bimodal (52% PUT, 48% CD, 60% VS), tactile-selective (17% PUT, 15% CD, 18% VS), and visual-selective (31% PUT, 37% CD, 23% VS) value neurons, with similar proportions of the types across all regions. However, regional differences emerged in the population decoding analysis of modality-selective value neurons: tactile-selective neurons in PUT showed superior decoding of tactile value, whereas visual-selective neurons in CD and VS had better decoding in visual value. These results suggest that each region contributes differently to regulating behavior based on the value associated with each sensory modality. To test this at the behavioral level, we selectively inactivated PUT, CD, or VS by muscimol injection while monkeys made value-based choices using tactile and visual cues. Notably, PUT inactivation selectively impaired tactile-guided choices, CD inactivation selectively impaired visual-guided choices, and VS inactivation disrupted both. In addition, analysis using the Rescorla-Wagner model indicated that these deficits arise from impaired exploitation of learned values, rather than from a failure in learning. Together, these results indicate that each striatal region supports a distinct sensory modality in value-based behavior, driven by modality-selective value neurons unique to that region. Although these regions receive similar input contents, their distinct functional roles suggest that they may relay modality-specific value information to different downstream targets.

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Poster

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Topic: I.08. Learning and Memory

Title: Differential Encoding of Prediction Errors in Caudate Neurons during Associative Learning

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Abstract: While the dorsal anterior caudate is known to contribute to prediction error signaling, critical gaps persist in understanding how distinct neuronal subpopulations dynamically encode prediction error subtypes across learning phases. Prior studies have focused on phasically active neurons (PANs)—putative medium spiny neurons (MSNs)—and dopamine-dependent mechanisms, leaving unresolved whether fast-spiking interneurons (FSIs) or tonically active neurons (TANs, cholinergic interneurons) contribute differentially to unexpected versus expected

outcomes during learning and reversal. The temporal evolution of these signals as associations transition from novel to mastered states also remains poorly characterized.
We addressed these questions by recording single-unit activity in macaque dorsal anterior caudate during a saccade-based visual association task with learning, reversal, and recall phases. The animal matched four visual cues to directional targets via trial-and-error, receiving feedback events categorized using a prediction error framework: unexpectedly positive (UP), expectedly positive (EP), unexpectedly negative (UN), and expectedly negative (EN).
We hypothesized that UP-selective neurons would show response attenuation to correct feedback as associations consolidated, while UN-responsive units would show decreasing incorrect feedback responses during reversal mastery. Peri-event histograms revealed heterogeneous dynamics across responsive neurons. A subset displayed predicted attenuation patterns, while others maintained or increased activity. Most task-modulated units exhibited firing properties inconsistent with MSNs—including sustained high-frequency discharge matching FSIs. This suggests our recordings may have preferentially captured larger interneurons due to electrode sampling, though MSNs (PANs) likely remain integral to error processing. These findings underscore complementary roles of interneuron populations and dopamine-dependent mechanisms in prediction error computation. Response heterogeneity suggests functional specialization within caudate microcircuits, where distinct subpopulations—including FSIs and potentially TANs—may track different error contingencies to support flexible adaptation. While dopamine-centric models remain foundational, our data highlight the need to integrate interneuron dynamics into striatal error processing frameworks.

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Poster

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Title: Hippocampo-cortical contributions to the structured organization of task knowledge

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Abstract: Successful task switching requires resolving the interference from the old task and/or reconfiguring the representation of the new task, both of which rely on how task representations are organized in the brain. On one hand, tasks can be encoded in completely orthogonal representations to minimize interference. However, this would incur maximum reconfiguration at every task switch. Alternatively, it is possible that task knowledge is encoded under a common

reference frame, such that interference and reconfiguration costs of task switch are balanced by tuning the similarity between task representations. One candidate for such reference frames is a cognitive map, a ubiquitous organizational structure of various relationships. A cognitive map provides a mental model of relationships between given information. In the context of task representations, task features (e.g., task rules) can be coded as continuous parameters like coordinates on a map, such that each point on the map uniquely identifies a task. We test this prediction using a parametric task-switching paradigm with high spatial resolution 7T fMRI. Here we focus on the role the hippocampus and cortex jointly play in supporting the construction and organization of relational maps of task knowledge such as stimulus, response, and rule representations as these areas provide crucial support for the construction of relational cognitive maps. Leveraging hippocampo-cortical RSA, our preliminary analyses (N = 28) show multiple significant ROIs where pattern similarity scales with the similarity between tasks. Some of these areas include the posterior cingulate cortex, insula, and frontoparietal cortex, where task information is represented during execution. Furthermore, we expect that the strength of pattern similarity to task similarity correlation in the frontoparietal cortex is linked to hippocampal activation, due to the importance of the hippocampus in supporting a cognitive map. To probe how the fidelity of the cognitive map and strength of the parametric representation influences cognitive flexibility we will examine the relationship between neural measures such as RSA scores and retrieval strength, and behavioral reconfiguration costs. Understanding the organization of task rules will provide crucial insight into how the memory organization of task knowledge facilitates cognitive flexibility.

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Poster

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Title: Linking Transformer Architectures to Human Hippocampal Function in a Two-Armed Bandit Task

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Abstract: Humans exhibit remarkable rapid learning capabilities, readily adapting to novel environments and making decisions that maximize long-term rewards. To elucidate the

computational flexibility of the human brain, we analyze single-neuron recordings from humans alongside transformer-based language models, which demonstrate comparable learning efficiency on tasks commonly used to study human learning and decision-making. By comparing behavior, neural activity, and internal representations in humans and transformer models, we aim to examine how adaptive computations underlying goal-directed navigation are implemented in the brain and whether similar mechanisms arise in artificial agents. One influential theory accounting for such flexibility is the successor representation (SR), which conceptualizes the hippocampus as a predictive map encoding expected future state occupancies. When combined with a separate reward function, this representation enables rapid adaptation to changing goals. We ask whether the human brain and transformer-based models engage similar computational processes in goal-directed navigation tasks, including SR-like predictive coding, relational reasoning, and value updating. To investigate this question, we analyze 189 medial temporal lobe neurons from 12 neurosurgical patients with drug-resistant epilepsy as they perform a virtual spatial two-armed bandit task in parallel with transformer agents trained on a comparable task. The task involves navigating a virtual environment of two distinct paths comprising three connected rooms, with independently manipulated reward contingencies and transition structures. This design enables us to disentangle how changes in rewards or state transitions influence behavior, neural coding in humans, and internal representation in agents. Behaviorally, participants demonstrate rapid adaptation to changes in reward and transition structure. At the neural level, we identify neurons exhibiting predictive coding and reward-dependent remapping consistent with SR properties. In parallel, we examine whether transformer agents exhibit similar behavioral flexibility and internal representations aligned with successor representation. In these models, we test the effect of the training regime on both behavior and the extent to which SR-like properties emerged. Our results suggest that there are parallels between human spatial learning and the representational strategies adapted by transformer models in support of goal-directed navigation and rapid adaptive learning.

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Poster

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Title: Reorganization of working memory codes with increasing cognitive load

Authors: R. TUNG[1], R. KIM[3], ***N. RUNGRATSAMEETAWEEMANA**[2];
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Abstract: Working memory (WM) is a cornerstone of flexible, goal-directed behavior, supporting processes such as reasoning, learning, and decision-making. WM-based cognition is disproportionately disrupted in neuropsychiatric conditions, yet the circuit-level computations that support it remain poorly understood. In particular, the contributions of distinct cell types and the interaction between spiking activity and local field potentials (LFPs) have not been well characterized. Investigating how these circuit dynamics adapt or fail under increased cognitive demand could reveal new mechanistic insights and inform novel therapeutic targets.
To address this gap, we developed biophysically realistic spiking recurrent neural networks (RNNs) composed of excitatory and inhibitory neurons, and trained them on cognitive tasks that parallel human WM paradigms. These models serve as a computational testbed to study neural dynamics, from spiking to field-level activity, across varying task conditions and difficulty. We first trained networks on a delayed match-to-sample (DMS) task, which requires encoding two sequential stimuli separated by a delay period, followed by a decision about whether they match. Task difficulty was manipulated by varying the length of the delay. To probe the resulting network dynamics, we applied a suite of analyses including stimulus selectivity, population dynamics, and spike-field coupling. Preliminary results show that the ability to decode the identity of the first stimulus from population firing rates decreases during the presentation of the second stimulus in incorrect trials. This suggests that the disruption of memory representations is not solely due to decay over time, but may be driven by interference from subsequent sensory input. In addition, while many network neurons exhibit stimulus selectivity, we identified a subpopulation of non-selective neurons, more frequently excitatory, that may contribute to higher-order processes such as reformatting memory codes or linking sensory representations to motor outputs. We are further dissecting these circuit dynamics through targeted lesioning experiments in the model.
In parallel, we are testing the extent to which similar neural dynamics emerge in the human brain by analyzing intracranial recordings from neurosurgical patients performing conceptually aligned WM tasks. This approach provides a mechanistic framework for understanding the circuit computations that support WM-based cognition and how they may break down in disease.

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Title: Neural heterogeneity shapes the temporal structure of human working memory

Authors: *D. KUSSOVSKA, N. RUNGRATSAMEETAWEEMANA;
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Abstract: Working memory (WM) provides temporary storage of information critical for learning, language comprehension, and decision-making. Persistent neuronal firing has long been considered the primary mechanism underlying memory maintenance. However, sustained spiking is metabolically costly, raising questions about its efficiency as a strategy for supporting WM. Much of the supporting evidence has also relied on trial-averaged data and often assumes network homogeneity, with limited attention to how cell-type specificity or synaptic interactions shape population-level dynamics. As a result, it remains unclear how heterogeneous neuronal populations in the human brain maintain information over time. To address this gap, we analyzed the activity of 902 single neurons recorded from the medial temporal and medial frontal lobes of 21 intracranially implanted patients performing a WM task. Focusing on single-trial dynamics, we found that stimulus representations during encoding and maintenance occupy distinct low-dimensional geometries. This temporal reorganization suggests that information is not maintained in a static format but through evolving population trajectories. To further characterize these dynamics, we performed a burst detection analysis, revealing that neural activity during WM is temporally organized into transient, structured events that align with task epochs. These bursts provide empirical support for activity-silent models, in which brief episodes of coordinated spiking encode and preserve memory content without persistent firing. Additionally, we developed a novel cell-type classification framework to investigate how different neuronal populations contribute to memory-related dynamics. This analysis revealed that cell types exhibit distinct bursting and temporal profiles, suggesting functional specialization and complementary roles in sustaining memory representations and coordinating network states. Together, our findings demonstrate that WM in the human brain is maintained by temporally structured population dynamics and propose a mechanistic account of how heterogeneous neural circuits support flexible cognitive function.

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Poster

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Title: Two-state dynamics structure working memory in the human medial temporal lobe

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Abstract: Persistent neuronal firing during maintenance has long been regarded as a core mechanism underlying working memory (WM). However, a recent study in non-human primate (NHP) lateral prefrontal cortex revealed a two-state model, in which information-rich 'On' states of elevated spiking alternate with low-rate 'Off' states, during which memory persists in latent, ensemble-level connectivity rather than sustained firing. Whether this dynamic generalizes to humans, and how the underlying cell ensembles are organized, remains unknown.Here, we analyzed single-neuron recordings from the human medial temporal lobe (MTL) during a verbal WM task in which participants indicated whether a probe letter was part of a previously presented set (set size: 4, 6 or 8). Linear Support Vector Machines (SVMs) trained to decode memory load yielded a time-continuous confidence metric that revealed clear temporal fluctuations in decoding strength over time. Time-bins exceeding a permutation-based threshold were labeled On, with the remaining bins designated Off. Crucially, cross-validated decoding performance was robust during On states and near chance during Off states, closely mirroring prior findings in NHP.To investigate the mechanisms underlying these two-state dynamics, we examined how individual neurons contributed to stimulus-related coding and contrasted population activity patterns across states. On states were primarily driven by stimulus-selective neurons, while Off states were dominated by neurons whose collective activity confined to low-dimensional subspaces that were largely inaccessible to the original decoder - consistent with a latent storage mode. This shift in decodability may reflect not only changes in which functional subpopulations are engaged, but also in the strength of their interactions. Variations in ensemble membership and coupling strength may underlie the observed alternation between an explicit, stimulus-aligned state and a silent, mnemonic state.Together, these findings suggest that working memory in the human MTL is continuously maintained, but toggles between an energy-efficient, interference-robust silent state and a transient information-rich state in which stimulus content is explicitly readable. This cross-species evidence positions two-state coding as a potential canonical mechanism for balancing stability and energy efficiency in working memory.

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Poster

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Title: Probing adaptive decision-making under uncertainty using extended hidden Markov models

Authors: *R. SINGHA[1], J. WINSLOW[2], R. KIM[3], J. T. SERENCES[4], N. RUNGRATSAMEETAWEEMANA[1];
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Abstract: Perceptual decision-making under uncertainty depends critically on how bottom-up factors (e.g., sensory strength) and top-down factors (e.g., selective attention and prior expectation) interact to shape choice dynamics. However, their independent and combined contributions remain poorly understood. To address this gap, we designed a motion-discrimination task in which participants viewed flickering clouds of red and blue bars. On each trial, only one color cloud contained coherent motion, while the other remained entirely random. The clouds flickered at distinct frequencies with a variable percentage of bars in one color moving coherently (high/low coherence) in one of five possible directions (15°-159° in 36° steps). A color cue indicated the attention condition (focused/divided): red or blue signaled attending to one color cloud, while green cued attending to both. Expectation (expected/unexpected coherent motion) was manipulated across blocks by overrepresenting one target direction. Participants continuously reported the perceived motion direction using a 360° flight simulator joystick. Twelve human participants performed 2,880 trials each. We found that high stimulus coherence increased the speed of the response trajectory and reduced response error with the effects emerging approximately 700-1200 ms after stimulus onset. Focused attention similarly enhanced response speed and precision, with effects emerging around 200-1000 ms post stimulus. In contrast, expectation reduced pre-stimulus baseline response error from 500 ms before to 833 ms after stimulus onset. We hypothesized that the observed behavior reflected transitions between discrete underlying cognitive states. To test how these states were modulated by stimulus coherence, attention, and expectation, we fit a two-state hidden Markov model (HMM) - selected via leave-one-out cross-validation on Bayesian Information Criterion - to the continuous joystick trajectories. This approach identified two latent states, termed “accumulation” and “decision,” each exhibiting strong inertia, with about a 90% likelihood of persisting rather than transitioning. Importantly, coherence produced a stronger modulation of the joystick response patterns during the decision state (Earth Mover's Distance: decision > accumulation), accelerated transitions into this state by approximately 150 ms, and extended its dwell time. In contrast, attention and expectation led to only modest and symmetric shifts in both states. Together, these findings suggest that bottom-up and top-down factors differentially govern the latent cognitive states underlying human perceptual decisions.

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Poster

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Title: Asymmetric influence of reward and punishment on human behavior and network models

Authors: *S. IYER[1], R. L. COWAN[4], S. FUSI[2], B. SHOFTY[4], E. H. SMITH[4], N. RUNGRATSAMEETAWEEMANA[3];
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Abstract: Emotional valences (positive vs. negative), experimentally induced via rewards and penalties, are theorized to occupy *symmetrically* opposite sides of a valence-arousal space. Yet, empirical studies have demonstrated an *asymmetry* in how rewards and penalties are processed (e.g., losing 100$ may weigh heavier than gaining it). Here, we asked whether risk seeking and aversion in a reward-based perceptual task emerge from asymmetrically weighted representations of reward and penalty. We designed a classification task in which human participants viewed a shape and placed it along a continuous axis between two classes. Crucially, one shape class offers reward if correctly placed, while the other imposes a penalty if incorrect. Simultaneously, placement towards one class entails greater risk and potential reward than the other. Across task conditions, we manipulated the location of the class boundary to examine the effects of compressing or expanding one side of the valence space. Participants achieved high classification accuracy, with poorer performance for shapes near the class boundary. Individual differences in rates of false positive and negative errors reflected distinct risk-seeking and aversive strategies. Participants exhibited a tendency of placing shapes near the class boundary, suggesting that reward-based classification is a stronger driver of behavior than perceptual similarity alone. To develop a theoretical account of the circuit-level computations that support performance on this task, we trained a two-layer feedforward neural network using shape embeddings extracted from AlexNet. These embeddings were passed through a nonlinear hidden layer with outputs to separate classification and regression (placement) heads. Networks achieved high classification accuracy, showed reduced performance near the class boundary, and exhibited different rates of false positives and negatives across initializations. However, they did not exhibit a bias toward positioning near the class boundary, suggesting different mechanisms at play than in humans. Finally, we analyzed how network representations reorganized across task conditions. Representational dissimilarity matrices revealed that the hidden layer geometry shifted depending on whether the reward or penalty class was compressed - indicating sensitivity to the valence structure. Overall, we found preliminary evidence that human behavior and network representations are asymmetrically influenced by rewards and penalties. Ongoing steps involve collection and comparison of human single-neuron data to network simulations.

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Poster

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Title: Reinforcement agents predict single-neuron variability during human probabilistic decisions

Authors: *K. MEHTA[1], T. AQUINO[1], N. RUNGRATSAMEETAWEEMANA[2];
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Abstract: Deep-learning-based reinforcement learning (RL) agents are capable of learning decision policies to maximize rewards in complex environments, yet it remains unclear to what extent their internal dynamics align with computations in the human brain. Here, we test whether a recurrent RL agent, trained to perform a probabilistic decision-making task, develops internal representations that map onto single-neuron activity recorded from human participants. We focus on a two-armed bandit task in which reward contingencies change across blocks. This task has previously been shown to engage a distributed network involved in learning, inference, and value-based decision-making. We trained a gated recurrent unit (GRU)-based Q-learning agent on this task using only reward feedback. The agent had no access to neural data during training. After training, we extracted hidden-layer activations and compared them to single-neuron spike counts at trial onset from 18 neurosurgical patients (12 female; ages 17-67) performing the same task. Recordings were taken from 734 neurons across five regions: the presupplementary motor area (preSMA; 122 neurons), amygdala (232 neurons), dorsal anterior cingulate cortex (dACC; 89 neurons), ventromedial prefrontal cortex (vmPFC; 170 neurons), and hippocampus (121 neurons). Using Poisson regression with permutation testing ($p < 0.05$), we found that across five different random seeds, the model's internal representations (activations or embeddings) reliably explained trial-by-trial variability in neural firing rates on held-out trials (quantified using R^2). We also assessed whether the proportion of significant neurons per region exceeded chance using binomial tests. The proportion of neurons with significant model alignment exceeded chance in each region. The dACC and vmPFC showed the highest proportion of neurons with explained variance when averaged across the five seeds. While no region showed a markedly higher explained variance than others, the presence of above-chance signal across seeds suggests the emergence of a convergent representational structure between the model and brain. These findings demonstrate that recurrent neural network (RNN) agents, when trained on ecologically valid tasks, may spontaneously develop low-dimensional internal dynamics that resemble aspects

of biological computation. Next steps include characterizing these internal dynamics to identify the latent variables and computational motifs they may reflect.

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Title: Human single-neuron correlates of spatial episodic memory encoding and retrieval

Authors: *C. Z. HAN[1], T. DONOGHUE[1], M. TSITSIKLIS[2], L. KUNZ[3], J. JACOBS[1]; [1]Biomed. Engin., [2]Neurobio. and Behavior, Columbia Univ., New York, NY; [3]Biomed. Engin., Univ. Hosp. Bonn, Bonn, Germany

Abstract: In human electrophysiological studies, a considerable amount work has been done investigating both the spatial and memory-related functionality of the MTL - for example, investigating specific cell types that show selective spatial modulation (e.g. place cells) during virtual spatial navigation tasks as well as work studying episodic memory encoding and recall dynamics in non-spatial tasks such as free recall. However, what has been less studied is the interaction between these two functions, with less investigation connecting the single-neuron representations of spatial episodic memory encoding and retrieval during spatial navigation in complex naturalistic environments. Specifically, how do such neural responses vary across different episodic memory stages remains poorly understood. To address these questions, we recorded neural data from the hippocampus and surrounding areas in the MTL of human neurosurgical patients with implanted microwires while they performed a spatial episodic memory task named Treasure Hunt. In each trial, participants navigated an open arena, learning and later recalling the location of presented items. We first analyzed single-neuron activity for general stimulus response during item encoding and recall. We observed a highly consistent firing pattern across different stages of the task such that neurons that showed an increased firing rate during item encoding also fired more during recall prompt and recall response, potentially suggesting a reinstated neural representation during recall. Next, zooming in on the unique 'flip' feature of the task where subjects experienced item encoding and retrieval from either the same (non-flip) or opposite (flip) side of the arena, we found that the average distance error is greater and response time is longer for flip trials than non-flip ones. Additionally, we identified a significant number of cells that showed different firing patterns between flip and non-flip item recall, 60% of which had a preferred direction for flip item. This suggests different and/or additional mechanism are involved when retrieving items from a reversed perspective, for example, requiring mental rotation. Collectively, these results highlight the benefits of directly

comparing the single-neuron activity between memory encoding and retrieval to specify the flexibility/consistency of neural representations across various memory stages. Bridging between the behavioral dynamics and the neural responses during memory retrieval could further shed light on how people form/retrieve episodic memory in a complex spatial environment.

Disclosures: C.Z. Han: None. **T. Donoghue:** None. **M. Tsitsiklis:** None. **L. Kunz:** None. **J. Jacobs:** None.

Poster

PSTR471: Executive Function and Learning and Memory in Humans

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.10/PP6

Topic: I.04. Executive Functions

Support: NIH R61MH135405

Title: Building Cross-Modal Neural Representation to Reveal Multiscale Hippocampal Dynamics

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Abstract: Modern neural recordings produce high-dimensional data that reflect complex population dynamics. Representation learning provides a principled approach to reduce such complexity and can uncover low-dimensional structure when it exists, offering insight into how neural populations encode task-relevant variables. However, most existing analyses rely on a single modality, typically single-unit spiking, which captures only a microscopic view of neural dynamics. In many cases, a single experimental setup also records local field potentials (LFPs), which offer a complementary macroscopic perspective through oscillatory population activity. Integrating both signals into a cross-modal representation learning framework can enrich the resulting representations and improve physiological interpretability.We are developing a cross-modal representation learning framework inspired by advances in multiview contrastive learning. While single-modality contrastive learning embeds neural data by pulling together similar patterns and pushing apart dissimilar ones within one modality, multiview contrastive learning extends this by aligning representations across modalities, enabling unified embeddings of neural signals with complementary structure. This unified representation may reveal inter-modality phenomena such as phase locking, phase precession, and phase resetting, which are critical for hippocampal function. We aim to examine how electrophysiological features, including theta/gamma power, instantaneous phase, spatial tuning, vary across this space to validate its structure and improve interpretability.We first trained modality-specific models to learn representations of spike and LFP data separately, using hippocampal recordings from rats performing a spatial navigation task. Each modality produced a representation that reflected behavioral variables such as position and head direction. Although learned independently, the

resulting spike- and LFP-derived representations exhibited similarly organized structure. Notably, their geometries differed: spiking representations showed a clear bifurcation conditional to two directions of the linear track, while LFP representations displayed a smoother, ring-like structure. This convergence, alongside their complementary structure, motivates a single unified cross-modal representation that jointly models both modalities.This work provides a meaningful advance toward cross-modal representation learning in systems neuroscience, offering a scalable framework for integrating neural signals with multimodal recordings.

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Poster

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F31AG087649

Title: Hippocampal Population Dynamics in Reward Representations Across Movable Spatial Boundaries

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Abstract: Adaptive navigation requires the brain to represent space flexibly, accommodating environmental changes (physical, structural, reward, etc.) across time. However, how hippocampal circuits integrate shifting spatial boundaries with changing reward contingencies remains poorly understood. Here, we address this question using a spatial reinforcement learning task implemented in both humans and mice. In both versions of the task, participants navigate through a series of interconnected rooms separated by movable doors, with the environment changing dynamically across sessions through two key manipulations: (1) altered sequences of room transitions between learning and re-learning phases, and (2) reassignment of high-value rewards to different rooms. Behavioral performance exhibits highly comparable sensitivity to these manipulations in both humans and mice, supporting future comparative analyses. Our primary analyses focus on how the physical separation between rooms—mediated by door

configurations—influences the encoding of reward information in hippocampal population dynamics In mice, calcium imaging in the dorsal hippocampus captures population-level neural activity as animals adapt to these changes. We find that their neural representations of spatial boundaries are present from the first session, but are disrupted and reorganized following re-learning. By examining how hippocampal populations track the evolving structure of the environment and its reward associations, this work sheds light on the neural mechanisms that support flexible spatial representations during learning and adaptation.

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Poster

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Program #/Poster #: PSTR471.12/PP8

Topic: I.04. Executive Functions

Support: National Science Foundation

Title: Spectral Drift and Stable Trajectories of Traveling Waves

Authors: *E. ZABEH[1], S. KANG[2], M. TSITSIKLIS[3], A. DAS[4], E. H. SMITH[6], G. M. MCKHANN, II[7], C. SCHEVON[8], S. A. SHETH[9], J. JACOBS[5];
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Abstract: The Long-term stability of neuronal codes is difficult to reconcile with the gradual changes that neural activity exhibits over days, even though the brain reliably maintains task performance. Most work in this area has focused on spiking output, leaving the stability of field potentials and their spatiotemporal organization largely unexplored. Using a chronic high-resolution implant in the human prefrontal cortex, we tracked neural activity for eight consecutive days while patients performed an identical task. We found that distinct oscillatory bands map onto unique traveling-wave directions. Although oscillatory power was highly variable, traveling-wave trajectories were strikingly stable both within and across sessions and retained their behavioral relevance; particularly for theta-band waves, which remained task-modulated even when theta power was weak. A synaptic network model subjected to cross-session spectral fluctuations reproduced this robustness, indicating that trajectory stability is intrinsic to the underlying circuitry rather than to specific spectral signatures.These results show that the spatial organization of traveling waves provides an anatomically grounded scaffold for consistent neural dynamics, offering a mechanism by which the brain preserves functional performance without requiring immutable neuronal codes.

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Poster

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Program #/Poster #: PSTR471.13/PP9

Topic: I.04. Executive Functions

Support: NSF CAREER to J.J.
NSF CRCNS to B.E. and J.J.

Title: Planar, Spiral, and Concentric Traveling Waves Distinguish Cognitive States in Human Memory

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Abstract: A fundamental challenge in neuroscience is explaining how widespread brain regions flexibly interact to support behaviors. We hypothesize that traveling waves of oscillations are a key mechanism of neural coordination, such that they propagate across the cortex in distinctive spatial patterns that control how different regions interact. To test this hypothesis, we used direct brain recordings from humans performing multiple memory experiments and an analytical framework that flexibly measures the propagation patterns of traveling waves. In previous work, traveling waves were shown to play a critical role for certain behaviors such as visual processing and spatial navigation in rodents (Lubenov & Siapas, 2009, *Nature*) and non-human primates (Davis et al., 2020, *Nature*), and recently in human cognition (Zhang et al., 2018, *Neuron*; Mohan et al., 2024, *Nature Human Behavior*), however, these waves were planar waves, severely limiting their ability to rapidly and dynamically reorganize to adapt to complex behaviors in humans. Our results showed an array of complex traveling wave propagation patterns including sources, sinks, spirals, and heterogeneous directional propagation patterns that extended beyond those seen previously in humans and the currently known anatomical and functional hierarchies. Moreover, waves with specific complex shapes correlated with particular cognitive processes. Our findings of complex patterns of traveling waves converge well on recent theoretical predictions from biologically plausible neural models (Bhattacharya et al., 2021, Scientific Reports; Sato, 2022, Scientific Reports), which posit that waves can be generated locally based on the initial spatial activation of neurons, where each neuron is connected to a few of its neighbors. These locally generated waves can propagate across widespread regions between locally connected neurons and interact with other locally generated waves, to generate globally complex patterns of propagating oscillations. Crucially, we were able to robustly predict a subject's behavioral state at the single trial level based on the direction and strength of the observed patterns of complex traveling waves, for both broad behavioral states

such as encoding, retrieval, and navigation, and also specific behavioral states such as English letters “B”, “G” etc. These findings could be the potential basis for a novel brain computer interface. Our findings provide a fundamental new advance in explaining how the brain dynamically reorganizes large-scale neuronal processes that underlie complex human behaviors.

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Poster

PSTR471: Executive Function and Learning and Memory in Humans

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Program #/Poster #: PSTR471.14/PP10

Topic: I.04. Executive Functions

Support: NIA Grant R33AG078087

Title: Metabolic dysregulation and memory cognition: baseline findings using a delayed recall test

Authors: *A. R. VANDERGIESEN[1], M. G. BRUCKS[1], S. A. BILLINGER[2], S. M. LEVENS[4], A. S. BALDWIN[5], C. D. KOUROS[5], L. E. MARTIN[1,3], N. MOHAMMAD[1];
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Abstract: Background: Cognitive impairment has been associated with metabolic risk factors, such as a body mass index (BMI) over 30. Memory, critical for daily functioning, may serve as an indicator of early cognitive decline in individuals with metabolic risk factors. Metabolic dysregulation has been shown to also affect brain volumetrics in memory related regions, such as the hippocampus. Existing research focuses on older adults, leaving a gap in mid-life populations where interventions may be more effective. This study investigates the relationship between metabolic risk factors and memory in mid-life adults.**Methods:** Forty adults (ages 45-65) were recruited for a 6-week exercise intervention. Baseline assessments included BMI and cognitive assessments. Memory was evaluated using the NIH Toolbox Rey Auditory Verbal Learning Test, which measures memory recall approximately 15 minutes following learning a list of words. The relationship between BMI and memory were analyzed with a Pearson correlation.**Results:** Over 55% of participants had a BMI over 30, indicating elevated risk for developing metabolic syndrome. We found a non-significant association between BMI and memory ($r = -0.314$, $p = 0.06$). The observed trend may reflect an underlying relationship that requires further exploration.**Conclusion:** Findings suggest a potential link between higher BMI and poorer memory recall, highlighting the influence of metabolic risk factors on cognitive decline. Future analyses will examine baseline MRI data to assess memory-related brain structures, such as the hippocampus, and evaluate the individual and combined effects of metabolic factors including diabetes, hypertension, dyslipidemia, and arterial stiffness on cognitive function.

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Poster

PSTR471: Executive Function and Learning and Memory in Humans

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.15/PP11

Topic: I.04. Executive Functions

Title: Computerized cognitive training improves mental health, sleep, and executive function in Mexican university students.

Authors: *C. R. VUELVAS-OLMOS[1], L. GAMIÑO-RAMIREZ[2], N. Y. CORTÉS[3];
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Abstract: Abstract: Cognitive stimulation (CS) is a promising non-pharmacological intervention to enhance cognitive functioning and neuroplasticity. This study evaluated the impact of CS on cognitive performance and serum brain-derived neurotrophic factor (BDNF) levels in nursing and midwifery students. To assess the effect of a 12-week CS intervention on cognitive performance and BDNF levels, and to explore the influence of sociodemographic and lifestyle variables on these outcomes. Twenty-three undergraduate students participated in a structured CS program using the NeuronUP platform for over 12 weeks. Pre- and post-intervention assessments included demographic data, depression, anxiety, sleep quality, and physical activity. Cognitive domains (reasoning, memory, attention, and global performance) were evaluated alongside serum BDNF concentrations. CS significantly improved general cognitive performance, with notable gains in reasoning, memory, and attention ($p < 0.05$). A significant increase in serum BDNF levels was observed post-intervention. Correlational analyses revealed positive associations between BDNF increases and improvements in specific cognitive domains, particularly reasoning, attention, and memory. Sociodemographic and behavioral variables also showed associations with cognitive and neurochemical outcomes. A 12-week cognitive stimulation program effectively enhances cognitive performance and elevates BDNF levels in university students. These findings support the role of CS as a neuroplasticity-enhancing strategy, potentially mediated by BDNF

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Poster

PSTR471: Executive Function and Learning and Memory in Humans

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Topic: I.03. Decision Making

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NIH Grant T32MH126036
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Hearst Foundation
American Academy of Neurology (AAN) Resident Research Scholarship

Title: Load-dependent reorganization of neural dynamics during working memory

Authors: *R. J. TUNG[1], R. KIM[3], N. RUNGRATSAMEETAWEEMANA[2];
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Abstract: Working memory (WM) is foundational to goal-directed behavior. Though WM is often impaired in neuropsychiatric conditions, the neural computations underlying WM and the mechanisms by which they adapt or fail under increased cognitive demand remain poorly understood. In addition, the specific contributions of excitatory (E) and inhibitory (I) connections to these circuit computations and the role of local field potential (LFP) dynamics in complementing single-unit activity are unclear. To this end, we developed biophysically realistic spiking recurrent neural networks (RNNs) with E and I neurons and trained them on a series of complex cognitive tasks such as those inspired by WM tasks humans perform in everyday life. These models allow us to study neural dynamics during cognitive tasks with full ability to manipulate neural connectivity, neural spiking and field activity, and task parameters and difficulty. We train models to perform a delayed match-to-sample (DMS) task, which involves sequentially processing two stimuli separated by a delay period, followed by a response indicating whether the stimuli match. To manipulate task difficulty, we vary the duration of the delay period. We study circuit dynamics using analytic methods, from stimulus tuning and decoding to dynamical systems-based analysis and spike-field coupling. Preliminary results show that decodability of the first stimulus identity from population firing rates significantly decreases during the presentation of the second stimulus in incorrect trials. This suggests that while representations of the initially presented stimulus may degrade over time, they are more likely to be disrupted by the onset of a subsequent sensory input. Additionally, we find that while most network neurons are tuned to a particular stimulus identities, there are populations of non-stimulus-selective neurons, more often excitatory, that may contribute to non-sensory computations, such as reorganizing memory codes or linking sensory input to motor plans. We plan to employ systematic lesioning and silencing approaches to further elucidate the neural circuitry underlying WM computations. In parallel, we are investigating whether the changes in neural dynamics observed in our model also take place in the human brain by analyzing single-neuron and LFP data from intracranial recordings in neurosurgical patients performing similar WM tasks. This theory-guided study offers a new venue for uncovering novel mechanistic insights into human cognitive computation and its disruption in disorders.

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Poster

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Program #/Poster #: PSTR471.17/PP13

Topic: I.03. Decision Making

Support: U01NS103792
U01NS117839
BCS-2219800
AAN Resident Research Scholarship

Title: Top-down modulation of human ventral temporal cortex during goal-directed tasks

Authors: *R. KIM[1], T. AQUINO[4], C. M. REED[2], A. N. MAMELAK[3], N. RUNGRATSAMEETAWEEMANA[4], U. RUTISHAUSER[3];
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Abstract: Background Cognitive flexibility, characterized by the ability to adapt behavior in response to changing environmental demands, is a hallmark function of higher-order cortical areas such as the medial frontal cortex (MFC). This capability, also known as top-down information processing, is essential for tasks requiring context-dependent decision-making and complex reasoning. Traditionally, sensory areas such as the ventral temporal cortex (VTC) were seen as purely visual processors, with limited involvement in higher cognition. In this study, we propose that VTC also supports higher cognition via MFC feedback, a link not previously shown directly using human electrophysiology.

Methods

Single-neuron activity data recorded from eleven epilepsy patients (55% female, mean age ± stdev; 36.6 ± 9.6 years old) were included in the current study. All participants engaged in a cognitive task while we recorded single-neuron activity from VTC and MFC areas including ventromedial prefrontal cortex, dorsal anterior cingulate cortex, and pre-supplementary motor area. Participants performed a cognitive task involving two image presentations and a language-based instruction indicating which image to choose. In “early instruction” trials, the instruction was presented before the first image; in “late instruction” trials, it followed the first image. This design allowed us to compare neural responses to identical visual input with and without prior instruction. We isolated 164 VTC and 329 MFC single neurons.

Results and Conclusion

Our results revealed that VTC neurons were significantly modulated by task instruction, even when visual input was identical, providing the first direct evidence of top-down influences in human VTC. MFC neurons showed stronger and more sustained instruction encoding, suggesting it as a potential source of this modulation. At the population level, instruction

enhanced category representations in VTC, as indicated by increased pairwise distances between neural response patterns. These findings challenge the traditional view of VTC as purely sensory and highlight its capacity for flexible, context-dependent coding. Together, the results support dynamic interactions between cognitive and sensory systems, with implications for detecting residual cognitive function in patients with limited behavioral responsiveness.

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Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.01/PP14

Topic: I.07. Long-Term Memory

Title: A Further Examination of the Effects of List Composition on JOL Reactivity

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Abstract: Although judgments of learning (JOLs) are used to capture how individuals monitor their memory, previous research has shown that eliciting these judgments can have reactive influences on memory performance. One account of JOL reactivity focuses on the tradeoff between item-specific and (inter-)item-relational processing, which has also been applied to many other memory phenomena. Based on the predictions of this account, Kaya & Mulligan (2024) have found that JOL reactivity in free recall is subject to design effects: the effect is more positive in mixed than in pure lists. Critically, the item-specific/relational account suggests that design effects should not occur when other memory tests, such as cued recall or recognition, are used. The current set of experiments confirmed this prediction by demonstrating that, compared to a no JOL condition, making JOLs increases cued recall and recognition performance regardless of list composition.

Disclosures: A. Krishnan: None. **A. Jain:** None. **S. Kaya:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: PSTR472.02/PP15

Topic: I.07. Long-Term Memory

Support: National Science Foundation

Title: Eeg oscillatory correlates of the negative trade-off effect in younger and middle-aged adults

Authors: *S. KAFAFI[1], X. NIU[1], K. SANDERS[1], T. CUNNINGHAM[2], M. UTAYDE[1], E. A. KENSINGER[3], J. PAYNE[1];
[1]Psychology, Univ. of Notre Dame, Notre Dame, IN; [2]Beth Israel Deaconess Med. Ctr., Jamaica Plain, MA; [3]Psychology and Neurosci., Boston Col., Chestnut Hill, MA

Abstract: Emotional memories are typically remembered more vividly than neutral ones, yet the neural oscillations underlying this effect are understudied - particularly regarding the role of arousal in modulating encoding processes. This study investigated EEG oscillations associated with successful memory encoding of negative versus neutral scenes in a sample of young and middle-aged adults (ages 18-59). Participants completed the negative trade-off task to assess whether emotionally salient objects were preferentially remembered at the expense of their backgrounds. Heart rate and skin conductance were collected during encoding to measure physiological arousal. Behaviorally, participants demonstrated enhanced memory for negative scenes compared to neutral ones. However, both memory performance and physiological arousal decreased with advancing age. EEG analyses revealed greater alpha desynchronization and increased gamma synchronization during encoding of negative versus neutral scenes. These results suggest that gamma oscillations track the emotional salience of stimuli, while alpha desynchronization reflects heightened attentional engagement driven by emotional arousal. Together, these findings elucidate the oscillatory dynamics supporting emotional memory encoding and highlight age-related changes in these processes.

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Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: PSTR472.03/PP16

Topic: I.07. Long-Term Memory

Support: BSF Grant 2022171

Title: Reactivating spatial memories during sleep using multi-sensory cueing and an immersive virtual environment

Authors: *G. NARAYAN[1], A. SOFER[4], M. CHO[2], E. LE[2], H. ZHANG[2], C. PIEDRA[2], K. C. SIMON[3], A. AZRI[4], E. SCHECHTMAN[2];
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Abstract: Sleep plays an active role in the consolidation of memories. During sleep, the neural traces supporting newly formed declarative memories are spontaneously reactivated. Targeted memory reactivation (TMR) is a technique that uses non-invasive sensory cues, such as odors or sounds, to preferentially reactivate associated memories during sleep. One avenue of TMR research that has not yet been explored involves the combined use of odors and sounds to selectively enhance memories. Here, we examine the interactive effects of multi-modal reactivation cues during sleep on consolidation in a realistic first-person memory task. We used the Minecraft Memory and Navigation task, a first-person, engaging spatial task that demonstrates sleep's contribution to spatial memory (Simon et al., 2022). Following memory encoding of unique locations and the environment which we enriched with odors and sounds, we reactivated the encoded memories during NREM sleep using the odors, sounds, or both. We hypothesized that rich, multisensory synergetic reactivation during sleep, compared to the unisensory reactivation, would maximally benefit spatial memory recall. Additionally, we explored the effect of different cueing regimes on sleep spindles and slow oscillations during NREM sleep. Our study reveals the contribution of memory consolidation during sleep to real-life spatial memories, and provides insight into whether multisensory cueing has synergistic, additive, or competitive benefits for consolidation.

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Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: PSTR472.04/PP17

Topic: I.07. Long-Term Memory

Support: NINDS R01NS114913

Title: Eye movements are sensitive to retrieval success and memory precision for spatial locations

Authors: *M. HOU[1], L. R. PEZANKO[2], S. SROKOVA[3], P. F. HILL[3], A. D. EKSTROM[3], M. D. RUGG[2];
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Abstract: We examined whether eye fixations are associated with retrieval success and precision, two different yet important elements of episodic memory. Eye movement data were collected from 23 healthy young adults (mean age 23 yrs, 11 female) during the study and test phases of a task assessing the precision of location memory. At study, participants viewed a series of object images, each placed at a randomly selected location on an imaginary circle. At test, studied images were intermixed with new images and re-presented to the participants. Each

test image was presented for 1 second, followed by a 3-second presentation of a white circle with the same radius of the virtual circle used at study. During this phase of the test trial, participants were instructed to covertly recall the studied location of the image. They were then to move a cursor to the recalled location of the studied image, guessing if necessary, and signal whether the presented image had been studied. Memory precision was quantified as the angular difference between the studied location and the location selected by the participant. Trials associated with a correct item recognition judgment were classified as location hits or 'guess' trials according to an analysis based on a mixture model that separated trials associated with 'true' location judgments from guesses. Location hits were further categorized as high vs. low-precision trials. For each test trial, eye fixation data acquired from the onset of the test image to the end of the covert recall phase was included in the analyses. The area used to identify location-related fixations was defined as a circular band that excluded the central area potentially associated with image-related fixations. Compared to guess trials, location hits were associated with a greater number of fixations, earlier fixation onset, and longer total fixation duration. Moreover, fixation precision, which was estimated as the average negative Euclidean distance between the fixation location and the studied location, was significantly higher for location hits than for guess trials, and higher for high-precision trials than for low-precision trials. These findings suggest that eye fixations are associated with both retrieval success and the fidelity of the retrieved information.

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Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.05/PP18

Topic: I.07. Long-Term Memory

Support: Purdue University MRI Pilot Grant
Indiana CTSI Core Pilot Grant

Title: Motivated information seeking and learning during naturalistic web browsing

Authors: *H. SU, C. KNIGHT, P. LIU, C. XU, H. LEE;
Purdue Univ., West Lafayette, IN

Abstract: Intrinsically motivated information seeking plays a crucial role in real-world learning and knowledge acquisition, yet its neural underpinnings remain largely unexplored in naturalistic settings. To address this gap, we conducted a novel fMRI study using an unconstrained web browsing paradigm, in which participants freely explored real-world web content and later verbally recalled their browsing experiences. We focused on the natural, moment-to-moment fluctuations in two independent dimensions of intrinsic motivation underlying information seeking: liking (enjoyment of the content) and wanting (the desire to reduce uncertainty).

Participants retrospectively rated these motivational dimensions while watching screen recordings of their own web browsing sessions. Behaviorally, both higher liking and wanting were associated with fewer browsing actions that led to content switching (e.g., typing, moving the mouse), with liking showing a stronger negative relationship than wanting. Neurally, the two motivational dimensions engaged distinct brain regions during web browsing. Higher liking was linked to decreased activation in the anterior insula and cingulate cortices, while higher wanting was associated with greater activation in the anterior temporal lobe and hippocampus, when liking was low. Liking and wanting also interacted in influencing memory formation. Higher liking predicted successful recall of browsing events, regardless of wanting levels. Conversely, higher wanting predicted better recall only when liking was low, likely reflecting the mnemonic benefits of unexpectedly enjoyable content (i.e., low wanting but high liking). During free recall, event-specific neural activation patterns from the browsing session were reactivated within the default mode network, with stronger reactivation observed for high-liking events. Wanting, by contrast, showed no significant effect on reactivation. Together, these findings highlight the distinct roles of the motivational dimensions of liking and wanting in shaping memory formation and neural activity during naturalistic information seeking.

Disclosures: H. Su: None. **C. Knight:** None. **P. Liu:** None. **C. Xu:** None. **H. Lee:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.06/PP19

Topic: I.07. Long-Term Memory

Support: IBS-R015-D1
24-BR-03-04
Fourth Stage of Brain Korea 21 Project

Title: Neural Signatures of Spontaneous Thought Transitions

Authors: *K. HEO[1,2], D. KWON[3,2], W. SHIM[4,3,2];
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Abstract: Continuous narratives can be organized into discrete events as they unfold over time. Prior research has shown that the boundaries of these events, which reflect transitions in narrative context, elicit neural responses in the default mode network and hippocampus during movie watching or story listening. However, it remains unclear how the brain organizes narratives when they are generated internally, rather than constructed in response to external stimuli. To examine how continuously evolving internal thoughts are represented, we conducted

an fMRI study in which participants verbalized their thoughts, either spontaneously or following predefined topics. To characterize thought transitions, participants identified moments of topic shifts in their speech transcripts, and we quantified semantic change between consecutive sentences using distances between sentence embeddings. We identified brain regions that responded to the end of each sentence in participants' speech and examined how their neural responses related to distinct aspects of thought transition. Our results revealed a functional dissociation among brain regions within the default mode network and frontoparietal network. The para-cingulate network (PCN) closely tracked topic transitions identified by participants, whereas the posterior medial cortex (PMC) responded to semantic distance between sentences, indicating that these regions are involved in detecting shifts in situational context and encoding distinct semantic content, respectively. The right intraparietal sulcus (rIPS) was selectively engaged only when the task explicitly required transitions between predefined topics during speaking, suggesting its role in cognitive control. These patterns were observed not only during spontaneous speech involving self-generated transitions, but also during passive listening, where transitions were externally determined by the stimulus. In contrast, hippocampal activation was not associated with these types of transitions, but rather was engaged at event boundaries during episodic recall, including movie recall and autobiographical narratives. During such recall, hippocampal activity increased with both the intensity of episodic memory and the length of the recalled speech. These findings suggest that transitions in thought recruit multiple cognitive processes that are supported by distinct neural systems within the default mode and frontoparietal networks.

Disclosures: K. Heo: None. **D. Kwon:** None. **W. Shim:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.07/PP20

Topic: I.07. Long-Term Memory

Support: ZIA NS03144

Title: Single-trial population dynamics in the anterior temporal lobe exhibit discrete states during episodic memory retrieval

Authors: *R. KIRKPATRICK[1], S. K. INATI[1], K. A. ZAGHLOUL[2];
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Abstract: The neural mechanisms underlying the episodic memory retrieval process have been a topic of intense study. One influential theory of this process is known as sequential sampling theory where samples of memory evidence are continuously aggregated until a response threshold is crossed corresponding to a memory retrieval. Our data challenges this theory and suggests that the process of episodic memory retrieval may involve oscillations between discrete

on-states and off-states. We obtained subdural neural recordings from the anterior temporal lobe of focal epilepsy patients who completed a paired associates memory task concurrent with the recordings. We found that the presence of these discrete states predicted memory performance in our task. In addition, we show that both spectral power deflections and changes to across-trial phase consistency influence the presence of these states. Our findings elucidate potential neural mechanisms for how episodic memory retrieval is performed.

Disclosures: R. Kirkpatrick: None. **S.K. Inati:** None. **K.A. Zaghloul:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.08/QQ1

Topic: I.07. Long-Term Memory

Title: Spatial-temporal dynamics of alpha, theta, and gamma activity during visual-spatial memory encoding and retrieval

Authors: *S. D. SLOTNICK;
Psychology and Neurosci., Boston Col., Chestnut Hill, MA

Abstract: The temporal resolution of ERPs is a major advantage of this technique over other cognitive neuroscience methods; however, this technique is blind to neural activity in specific frequency bands that are known to be associated with different cognitive functions. In the present study, 128-channel EEG time-frequency analysis was employed to investigate the spatial-temporal dynamics of visual-spatial memory. During encoding, abstract shapes were presented to the left or right of fixation. During retrieval, old and new shapes were presented at fixation, and participants classified each shape as previously on the “left”, previously on the “right”, or “new”. A time-frequency analysis of spatial memory activity was conducted separately at retrieval and at encoding, and then activity was compared between retrieval and encoding, with all results corrected for multiple comparisons. To focus the analysis, a two-step procedure was conducted. First, in electrodes O1 and O2 that reflect visual sensory activity, spatial memory hits were compared to spatial memory misses and significant activity differences were identified in the time-frequency plot (ranging from 0 to 3000 ms and 0 to 60 Hz). Second, memory-related activity was evaluated over the entire scalp for each of these sensory time-frequency activations to identify potential associated memory-control regions. During retrieval, in visual sensory regions, differential memory activity was observed in the alpha band (~1900-2000 ms) and the gamma band (~1400-2300 ms). In other brain regions, there was concomitant gamma band activity over left frontal and parietal electrodes in the later time period (~2200-2300 ms), which may reflect shape visualization and post-retrieval monitoring. During encoding, in visual sensory regions, differential memory activity was similarly observed in the gamma band (~1200-2300 ms). In other brain regions, the same pattern of results was observed as with retrieval. A comparison of spatial memory hits during retrieval and subsequent memory hits during encoding

revealed differential visual sensory activity in the theta band within an early time period (~0-280 ms) and a later time period (~1500-2200 ms). In other brain regions, there was widespread differential theta activity during both periods. Notably, during retrieval in the early time period (even 0-50 ms), theta activity in visual sensory regions corresponded to bilateral peripheral visual stimulation (despite the central cue), which may reflect preparation for a subsequent memory matching process. The present results underscore the importance of time-frequency analysis in understanding the neural mechanisms of memory.

Disclosures: S.D. Slotnick: None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.09/QQ2

Topic: I.07. Long-Term Memory

Title: Multi-modal memory dataset: high-density fMRI sampling of human memory

Authors: *I. CHHABRA[1], F. ZOU[2], J. SEEWALD[3], C. BALDASSANO[4], J. CHEN[3], J. HUTCHINSON[1];
[1]Dept. of Psychology, Univ. of Oregon, Eugene, OR; [2]Dept. of Cognitive and Psychological Sci., Brown Univ., Providence, RI; [3]Dept. of Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD; [4]Dept. of Psychology, Columbia Univ., New York, NY

Abstract: Dense sampling using functional magnetic resonance imaging (fMRI), in which many sessions of data are collected for a limited number of participants, allows unique insight and extensive options for traditional and developing analytic techniques. This approach has been used fruitfully in the domain of visual perception and is quickly being employed in other cognitive domains. Here, we present a densely sampled fMRI dataset focusing on human audiovisual long-term memory: the Multi-Modal Memory Dataset (MMMData). MMMData features up to 30 sessions per participant (n=3), including high-resolution structural and diffusion scans, audio, visual, and motoric functional localizers, and 25 sessions of cued and free recall. Across 15 cued recall sessions, each individual studied 1000 spoken word-image pairs and following a short (minutes) or long (days) delay was subsequently cued to retrieve pairmates. Participants additionally participated in 10 movie and free recall sessions where they watched short videos and, following short or long delays, attempted to recall each video's content aloud, speaking freely from memory. Repetition of stimuli was systematically varied (with word-image pairs occurring once, 3 times, 3 times in a sequence, or 42 times—3 times per session—and movies occurring once or 10 times). We analyzed data from 15 completed fMRI sessions across all participants using 2AFC recognition task. Accuracy on a 2-AFC test for associative memory suggested that participants were able to remember image-word pairs (overall accuracy = 88.3%, sd = 5.9%). Further, memory was influenced by both item repetition (83.8%, sd = 9.2% correct for single presentation; 88.8%, sd = 10.9% correct for those repeated 3 times; and 89%, sd =

9.6% for those seen 3 times each session) and study-test delay (94.2%, sd = 5.0% for within-session delays; 80.2%, sd = 7.9% for across-session delays). We present a series of results from cued and free recall showing the dataset's potential for capturing core aspects of memory in trial-based and naturalistic settings, with sensitivity to fundamental dimensions of memory including delay and repetition. These results aim to highlight the potential of high-density sampling for human memory as well as preview a dataset slated for public release in the coming years. This resource offers the research community a unique opportunity to explore how the brain implements the richness and persistence of human memory. It opens new avenues for understanding how memories evolve over time, and how fundamental mechanisms of memory relate across trial-based and naturalistic settings, advancing our understanding of consolidation, learning, and forgetting.

Disclosures: I. Chhabra: None. **F. Zou:** None. **J. Seewald:** None. **C. Baldassano:** None. **J. Chen:** None. **J. Hutchinson:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.10/QQ3

Topic: I.07. Long-Term Memory

Title: Investigating memory retrieval and perceptual processing with steady-state visual evoked potentials

Authors: *R. JACKSON[1], T. SAMESHIMA[1], U. MAYR[2], J. HUTCHINSON[3];
[2]Psychology, [3]Dept. of Psychology, [1]Univ. of Oregon, Eugene, OR

Abstract: Episodic memory retrieval and perception interact in complex ways. The two processes can act in service of competing goals (guiding action based on either information presently available versus relevant information from the past), but also potentially engage overlapping neural substrates across perceptual processing and the recollection of perceptual details. Further, memory and perception often occur in rapid succession, such as when a perceptual cue triggers a related memory. Here, we sought to better understand this complex dynamic by using EEG and assessing when and to what degree the brain processes ongoing stimulation during remembering. Specifically, we recorded Steady-State Visual Evoked Potentials (SSVEPs) elicited by flickering visual stimuli during an episodic retrieval task. Participants encoded object-location associations paired with spoken word cues and later retrieved location information based on word cues while viewing 8 Hz and 12 Hz flickers at unique, corresponding locations. This allowed us to track perceptual processing in real time during remembering both broadly (i.e., overall response to flicker) and more narrowly (i.e., response to flicker frequency at a remembered location). To isolate the effects of memory retrieval, we included a control condition in which participants also saw flickers but responded to directional cues ("leftward" or "rightward") without demands on memory. In memory and

control conditions, SSVEP amplitudes increased following cue onset; however, this increase was significantly attenuated in the memory retrieval condition. Specifically, SSVEP amplitude was broadly suppressed between approximately 900-1100 ms post-cue ($p < .05$), suggesting that memory retrieval reduces perceptual processing during this critical period. Notably, such suppression was not sensitive to the remembered location. These findings support the hypothesis that cognitive resources are broadly reallocated away from sensory processing during memory retrieval. Together, our results provide new insight into how the brain might dynamically balance internally driven processes such as memory with ongoing perceptual input.

Disclosures: R. Jackson: None. **T. Sameshima:** None. **U. Mayr:** None. **J. Hutchinson:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

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Program #/Poster #: PSTR472.11/QQ4

Topic: I.07. Long-Term Memory

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Title: Neural Mechanisms Underlying Misinformation-induced False Recall Shared Across Individuals

Authors: *X. SHAO, B. ZHU;
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Abstract: Misinformation can lead to false memories for some people. Previous studies have shown that people have a shared neural representation of true recall after watching the same movie clips (Chen et al., 2017; Lee & Chen, 2022; Patai & Spiers, 2017). However, it is unclear whether different people have similar neural representations when they falsely recall the same event. Here, we used fMRI to record 43 participants' brain activity during all four stages of a modified misinformation paradigm: encoding of the original events, first free recall, encoding of the post-event misinformation, and second free recall of the original events. Behavioral results showed that misinformation increased false memories in free recall and that there were shared false memories across individuals. To investigate neural mechanisms of individual and shared false recall, intra- and inter-subject similarity of neural activity patterns between encoding and retrieval were used to measure individual and shared neural reinstatements of misinformation. Individual reinstatement of misinformation in the lateral temporal cortex was associated with individual false recall, whereas shared reinstatement of misinformation in the posterior medial cortex was associated with shared false recall. In addition, when different people reported the

same false recall, they showed shared representations in the prefrontal cortex during recall. Finally, there was no observed decline in either the individual or shared neural reinstatement of the original event information in the temporoparietal and frontal cortices. It suggests that memory traces of the original events remained constant after exposure to misinformation, which is consistent with the retrieval interference model of false memory. Together, our findings reveal the individual and shared neural representations underlying the misinformation effect in free recall of real-life events.

Disclosures: X. Shao: None. **B. Zhu:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.12/QQ5

Topic: I.07. Long-Term Memory

Title: Mind's eye memory: The effects of aphantasia on long-term memory

Authors: *A. SCHMIDT[1], S. R. ASHBY[2];
[1]Brigham Young Univ., PROVO, UT; [2]Psychology, Brigham Young Univ., Provo, UT

Abstract: Recent findings in psychology regarding visual imagery and inner speech suggest that such experiences previously considered ubiquitous may vary across individuals. These individual differences can vary widely, with some individuals reporting a complete absence of visual imagery (i.e., aphantasia) or inner speech (i.e., anendophasia). These differences present a unique opportunity to examine the role internal phenomenal experience plays in cognitive functions like memory. Episodic memory retrieval is typically accompanied by visual or auditory imagery, which is closely linked to autonoetic consciousness. Dual-coding theory posits that episodic details are encoded both visually and verbally thereby enhancing retrieval. This is reflected in the concreteness effect, where words referring to imageable, concrete objects (e.g., dog, apple, tree) are more easily remembered than abstract concepts (e.g., lie, love, injustice). To examine how variation in internal imagery influences memory, we conducted an fMRI study in which participants completed a recognition memory task for faces and words (categorized as concrete or abstract). Participants were grouped using the Internal Representations Questionnaire, with those scoring below 3.5 on the visualization subscale classified as low visualizers. Preliminary results suggest group differences in neural activation during memory retrieval. Compared to low-visualizers, controls show greater activation for concrete words in the insular cortex, angular gyrus, and the left visual word form area of the occipital fusiform cortex—regions associated with visual imagery and lexical processing. When comparing concrete vs. abstract words, similar regions were differentially engaged, including the lateral occipital cortex and the angular gyrus. Together, these early findings suggest that individuals with intact mental visual imagery may engage visual mental simulation during memory retrieval and highlight how subjective internal experiences can shape the neural mechanisms supporting memory.

Disclosures: A. Schmidt: None. **S.R. Ashby:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.13/QQ6

Topic: I.07. Long-Term Memory

Support: State of New York

Title: Unique Age-Related Alterations in Integrative versus Discriminative Memory Retrieval: An Eye-Tracking Study

Authors: *I. VALOUMAS[1], T. BROWN[2], M. R. DULAS[1];
[1]Psychology, Binghamton Univ., Binghamton, NY; [2]Binghamton Univ., Johnson City, NY

Abstract: Older Adults show relational memory deficits tied to changes in prefrontal and hippocampal processes. These deficits may be particularly pronounced when organizing information across episodes: integrating shared information or discriminating between similar, but distinct events. Imaging evidence suggests integration and discrimination are supported by unique hippocampal and prefrontal sub-regions, potentially subject to distinguishable age-related alterations. Eye-tracking may be a useful tool in understanding the full impact of age on these processes. Not only has eye-tracking been shown to index hippocampal involvement in memory retrieval, but it can provide novel insight into how aging impacts integrative versus discriminative memory retrieval processes as they unfold over time. The present study investigated the impact of aging on memory-driven attention during integrative vs. discriminative retrieval. Participants first studied scenes and learned unique people (workers) belonged at each location during the day vs. at night. The pair of workers for each scene were never shown together. After being tested on the direct worker-scene associations, participants then completed Discriminative and Integrative tests of memory (order counterbalanced). In the Discriminative test, participants were shown scenes at specific times of day and had to pick which of three people worked at each location at that specific time, including discriminating between that location's two studied workers. In the Integrative test, participants were shown a studied worker and had to identify which of three people also worked at that person's studied scene, despite never seeing them together. Older adults exhibited impairments across all memory tests, with exacerbated deficits for the across-episode tests. Eye-tracking results showed that both groups demonstrated similarly fast disproportionate viewing to the correct person in the Discriminative test, though this effect was weaker for older adults. In the Integrative test, older adults showed disproportionate viewing to the target face that was weaker and slower relative to young adults. Thus, while both discriminative and integrative memory retrieval show disproportionate age-related deficits in performance, eye-tracking data suggest such changes are tied to unique alterations in how these processes guide memory decisions. In sum, aging does not

impact all across-episode memory processes in the same way, suggesting distinct alterations in their neural correlates.

Disclosures: I. Valoumas: None. **T. Brown:** None. **M.R. Dulas:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.14/QQ7

Topic: I.07. Long-Term Memory

Title: Age-related declines in high-resolution item and spatial memory: The role of eye movements

Authors: *T. BROWN[1], I. VALOUMAS[2], M. R. DULAS[3];
[1]Binghamton Univ., Johnson City, NY; [3]Psychology, [2]Binghamton Univ., Binghamton, NY

Abstract: Older adults exhibit deficits in both item specificity and spatial memory relative to younger adults, yet the interaction between these measures of memory resolution remains unclear. Notably, high resolution item and spatial memory rely on the hippocampus, which is known to decline with age. Eye-tracking may offer insight into the potential trade-offs between item and spatial memory resolution across the lifespan, as hippocampal changes may drive shifts in information sampling during encoding. To investigate this, we employed eye-tracking during a novel spatial reconstruction task with young and older adults. On each trial, participants studied a spatial array of six objects, which were either all real world objects or all abstract shapes. After a 4 second delay, participants were presented with the six originally studied items interspersed with their mirrored counterpart. Their task was to reconstruct the studied array by selecting the correct items (rejecting mirrored lures) and placing each in its original location. Results showed that both groups had poorer item and spatial memory for abstract compared to real world objects. Further, older adults were significantly less accurate at selecting the correct item orientation and showed greater spatial misplacement regardless of stimulus type. However, age-related spatial memory deficits were particularly exacerbated for abstract objects. Study phase eye-tracking data in young adults revealed that the number of fixations to each stimulus predicted better memory performance across stimulus types for both item and spatial memory. In older adults, item fixations also predicted item memory performance for both stimulus types, though this effect was weaker than in young adults. Conversely, item fixations predicted spatial memory in older adults for abstract shapes, but not real world objects. Thus, increased fixations to individual items generally benefited both item and spatial memory resolution, though these correlations were weaker in older adults. Thus, older adults performed significantly worse than young adults, and showed weaker correlations between fixations and performance, suggesting a connection between allocation of attention at encoding and subsequent memory. Unlike item fixations, the between-item transitions did not strongly predict subsequent memory in either group suggesting that orderliness, rather than the amount, of transitions may be a key influence on memory

resolution. Overall, these findings highlight that age-related differences in high-resolution, hippocampally-mediated memory tasks may depend, at least in part on changes in viewing patterns during encoding.

Disclosures: T. Brown: None. **I. Valoumas:** None. **M.R. Dulas:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

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Program #/Poster #: PSTR472.15/QQ8

Topic: I.07. Long-Term Memory

Support: NIH Grant U01NS123128

Title: Decoding specific memory retrieval from human neural recordings

Authors: *S. L. DUNN[1], J. J. SAKON[1], Y. DING[2], C. DUAN[2], Y. ZHANG[2], A. DATTA[1], C. CHAN[1], A. AKBAR[1], J. I. BERGER[3], A. E. RHONE[3], C. M. GARCIA[3], K. V. NOURSKI[3], H. KAWASAKI[3], M. A. HOWARD, III[3], V. ROYCHOWDHURY[2], I. FRIED[1];
[1]Neurosurg., [2]Electrical and Computer Engin., UCLA, Los Angeles, CA; [3]Neurosurg., Univ. of Iowa, Iowa City, IA

Abstract: We possess episodic memory to store and retrieve one-time experiences. The ability to decode internal concepts (i.e., thoughts) from electrophysiological recordings of humans retrieving such unique experiences has not been demonstrated. Human single unit recordings have revealed neurons in the medial temporal lobe (MTL) that show selectivity to the semantic features of a stimulus, i.e. its meaning, invariant to sensory features or modality. These "concept" neurons may also support memory retrieval as they increase in firing rate seconds before participants verbally recall their selected concepts. While decoding of individual concepts is possible using such concept neurons, with our current technologies identification of these neurons often requires a targeted and extensive search. This makes them impractical targets for interventional therapies, particularly any that aim to act upon memory of new experiences. Here, we report the development of a transformer neural network model, trained on neural voltage spikes from intracranial microwires recorded across several regions as individuals viewed a single naturalistic audiovisual episode. Applying the trained models to neural data recorded as participants verbally recalled the episode, both before and after sleep, we successfully predicted concept retrieval seconds before concepts were spoken. Brain regions differentially contributed to memory decoding before and after sleep: models trained using only MTL spikes significantly decoded concepts before but not after sleep, while models trained using only frontal cortex spikes decoded concepts after but not before sleep. Models using traditional linear decoding methods, however, failed to decode concepts, suggesting a systems-wide distribution of information across neural populations that transforms over wake/sleep cycles. The success of our

approach for decoding internal states suggests a path towards brain-computer interfaces that ameliorate episodic memory dysfunction by targeting specific memories.

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Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: PSTR472.16/QQ9

Topic: I.07. Long-Term Memory

Support: RS-2023-00217361
RS-2022-NR070240

Title: Spatial Context and Past Experiences Build Spatial Memory

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[1]Dept. of Biomed. Engin., Sungkyunkwan Univ., Suwon, Korea, Republic of; [2]Dept. of Psychology, Sungkyunkwan Univ., Seoul, Korea, Republic of; [3]Ctr. for Neurosci. Imaging Research, Inst. for Basic Sci. (IBS), Suwon, Korea, Republic of

Abstract: Successful navigation relies on concrete spatial memory, which may be built upon either an egocentric reference frame or an allocentric reference frame. Egocentric reference frame encodes information relative to the navigator, whereas allocentric reference frame encodes static positions in a global reference frame. Although prior studies suggest that these two systems work in parallel, how they interact is yet difficult to discern from behaviors. Here, we set out to find their respective navigational advantages. Participants were asked to collect diamonds in a 5×5 maze either from a first-person (egocentric) or third-person (allocentric) perspective. During the training phase, walls were visible and physically present. In the test phase, however, the walls remained present but were rendered transparent, requiring participants to rely on their memory to avoid collisions. Participants completed the task more quickly and with fewer collisions when the spatial context remained consistent across phases (e.g. egocentric training phase is followed by an egocentric test phase). This suggest that participants learn and retrieve the spatial layout more efficiently in the congruent spatial contexts than incongruent ones (e.g. an egocentric training phase is followed by an allocentric test phase). We then investigated which memory component contributes to accurate retrieval by identifying an individual behavioral pattern called “Motif” for both training and test phases. This pattern enables us to trace back the most representative trajectory for each location based on past experiences. Motifs were also similar when participants were both trained and tested in the same spatial contexts. Our findings echo the notion that spatial memory is more easily retrieved in the same spatial context, and we

suggest that frequent visits to a certain location increase the likelihood of revisiting that location in the future, which strengthens spatial memory across both reference frames.

Disclosures: M. Jo: None. **M. Kang:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

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Program #/Poster #: PSTR472.17/QQ10

Topic: I.07. Long-Term Memory

Support: ERC-2021-STG, Grant 101043216, IN-MIND

Title: Neural basis of newborn verbal memory using HD-DOT

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Abstract: Memory plays a crucial role in learning and brain plasticity, yet its functioning at birth remains underexplored. The IN-MIND project aims to investigate early memory and language abilities, by looking at brain activity during verbal memory formation and the factors that modulate this capacity throughout infancy.The project integrates two neuroimaging methods, respiration acquisition, and video recordings to obtain a complete picture of infant brain activity during a resting state (RS) and when exposed to verbal auditory stimuli.The first aim is to identify specific areas of the brain responsible for verbal recognition, by measuring the brain's haemodynamic response. To do that, this study used a high density (HD) fNIRS/Diffuse optical tomography (DOT) Lumo (Gowerlabs, London UK) device with up to 2700 channels across the surface of the cortex, allowing for superior spatial specificity compared to traditional fNIRS systems. Ninety-eight newborns (mean gestational age (SD) = 39 weeks (1 week)) were tested in a 20 minute paradigm that consisted in a silent resting state (0-5 minutes), 8 blocks of encoding a single familiar pseudoword (5-10 min), a post-encoding silent resting state (10-15 min) and a test (15-20 min) splitting newborns into two groups. Group 1 was presented with 2 blocks of the familiar word and Group 2 with 2 blocks of a novel word. Significant differences in the mean change in oxyhaemoglobin (HbO) were found between the familiar v.s new word groups across different areas of the brain through blocks 9-16, signaling recognition after a 5-min interval. Stronger activation in response to novel words was first observed in the frontal and central regions during block 9, followed by increased activation in the left temporo-parietal areas during block 12. This temporal progression suggests a directional flow of information from frontal to posterior regions during word processing at birth. Preliminary coding of sleeping states has been completed and a validation against respiration data is in progress. Upcoming analyses will include HD-DOT and RS functional connectivity to investigate how sleep states modulate neural responses to word recognition at the individual level.

Disclosures: E. Visibelli: None. **G.A. Perkins:** None. **A. Fló:** None. **S. Benavides-Varela:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.18/QQ11

Topic: I.07. Long-Term Memory

Support: NIH Grant RO1AG082680

Title: Relationships between neural selectivity at encoding and retrieval-related reinstatement of face and scene information

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Abstract: A recent fMRI study reported a positive across-participants relationship between the strength of neural selectivity at encoding and the strength retrieval-related cortical reinstatement of face and scene information (as assessed with a multi-voxel metric). These findings suggest that the neural selectivity with which encoding events are processed or represented partially determines the strength of cortical reinstatement for the same events at retrieval. The current study further investigated this relationship and its generalizability using univariate metrics of selectivity and reinstatement. Forty young adults (18 to 27 years old, 20 female) underwent fMRI as they encoded words paired with images of faces or scenes. The subsequent scanned memory test required participants to identify whether or not a test word had been studied earlier and, for those words identified as studied, to indicate the associated image category (face or scene). Consistent with the previous study, source memory performance for faces was significantly greater than that for scenes. While the previous study had employed multi-voxel pattern similarity analysis to examine neural selectivity and reinstatement, here we computed univariate 'differentiation' and 'reinstatement' indices. These indices were estimated for 2 canonical face selective ROIs (fusiform and occipital face areas - FFA and OFA) and 2 canonical scene selective ROIs (parahippocampal and medial place areas - PPA and MPA). The indices were operationalized as the difference between the mean BOLD response of a given ROI's preferred and non-preferred image class, scaled by the pooled standard deviation of the single-trial beta estimates. Robust differentiation and reinstatement effects were identified in each ROI. Consistent with the previous report, differentiation and reinstatement effects were robustly positively correlated within each scene-selective ROI, providing evidence of the generalizability of these findings across different measures of these effects. In contrast, the analogous correlations were non-significant for the face-selective ROIs. Furthermore, differentiation indices correlated positively both within and across face- and scene-selective ROIs while reinstatement indices correlated positively within, but negatively across these ROIs. The latter

findings are novel and suggest a trade-off between the strength of reinstatement for face and scene information.

Disclosures: M.A. De Chastelaine: None. **S. Monier:** None. **A. Kidwai:** None. **M.D. Rugg:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.19/QQ12

Topic: I.07. Long-Term Memory

Support: NIH R01 AG082680

Title: Category-related neural selectivity and its association with memory performance as estimated by univariate and multi-voxel selectivity metrics

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Abstract: Previous studies have reported that neural selectivity for scenes in the parahippocampal place area (PPA) correlates positively with memory performance. These findings were reported for both univariate and multivoxel (pattern similarity) selectivity metrics. Here, during fMRI scanning, participants (N=41, ages 18-27, 21 female) viewed face and scene images paired with concrete words and were required to generate a scenario of the objects interacting with the paired image and to make a vividness response. In a subsequent test phase, participants indicated whether word cues were studied or unstudied earlier. If "studied", participants indicated whether the word had been paired with a face or a scene. Two selectivity metrics were employed to assess neural selectivity during encoding, which were extracted from four category-selective *a priori* defined regions of interest (ROIs). These were the scene-selective left and right PPA and medial place area (MPA) and the face-selective left and right fusiform and occipital face area (FFA, OFA). The two selectivity metrics were the univariate 'differentiation index' (estimated as the difference in mean activity elicited by the preferred vs. the non-preferred categories, scaled by the pooled trial-wise standard deviation) and a pattern similarity metric (estimated by subtracting within- from between-category multivoxel similarity, as indexed by Fisher transformed Pearson correlations). In the face selective ROIs, effect sizes for the two metrics (assessed by the Cohen's d associated with one-sided t-tests) were comparable for the univariate and multi-voxel metrics. In the scene-selective ROIs, however, effect sizes were consistently greater for the univariate metric. Of importance, within each ROI,

the two metrics were robustly correlated across participants, albeit more so in the scene than the face-selective regions. Thus, the two metrics appear to be sensitive to a common factor underlying individual differences in category-related neural selectivity. In a partial replication of prior findings, after controlling for chronological age and measures of visual acuity and contrast sensitivity, the univariate selectivity metric derived from the left (but not the right) PPA demonstrated a trend towards an association with source memory performance ($p = .051$), and also demonstrated a reliable association with item memory performance ($r = .36$, $p = .022$). No associations with memory performance were evident for the pattern similarity metric. These findings add to the evidence that scene-selectivity in the PPA reflects a generic process that supports episodic memory encoding.

Disclosures: A. Aktas: None. **M.A. De Chastelaine:** None. **A. Kidwai:** None. **S. Monier:** None. **M.D. Rugg:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.20/QQ13

Topic: I.07. Long-Term Memory

Support: Merit Award I01CX002626
NIH/NINDS R01 NS124585

Title: Use of a retrograde memory news events test to characterize memory impairment in a veteran with history of traumatic brain injury and epilepsy

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Abstract: Background: Traumatic brain injury (TBI) and epilepsy can cause difficulty learning new information (anterograde amnesia, AA) and remembering information learned previously (retrograde amnesia, RA). Existing cognitive measures do not allow distinction of AA versus RA. News events tests hold promise for reliable quantification of memories across the adult lifespan, especially when there are multiple neurological insults. Methods: Case study of a 39-year-old male Veteran with history of mild TBI (3 IED blasts in one day) followed by epilepsy onset 6 years later. AA and RA were measured using retrograde memory news events test (RM-NET), which measures recall and recognition memory with 253 questions about transient news events that occurred between 1948 and 2021. Recall and recognition memory accuracy were measured in the Veteran, in adults with normal cognition (controls), pre-surgical epilepsy patients (no TBI), and mild TBI patients (no epilepsy) by asking about events that occurred

between 2021 to the time in which the participant was 15 years old. We hypothesized the Veteran would (1) exhibit impaired news event memory relative to control groups and (2) exhibit intact remote memory. These effects would be more pronounced for recall vs. recognition. Results: The Veteran exhibited poorer performance on the RM-NET relative to control groups, with recall more impaired than recognition. Compared to controls, the Veteran exhibited RA and AA surrounding his TBI and epilepsy onsets. Recognition memory was intact 6-8 years prior to TBI onset, whereas recall was impaired across all time periods. Compared to the epilepsy group, the Veteran exhibited AA surrounding his TBI onset and RA for information acquired 0-4 years previously for both recall and recognition memory. Compared to mTBI controls, the Veteran exhibited AA after TBI onset and 4 years of RA prior to TBI onset. Conclusions: The RM-NET provided an objective and tractable way of examining RA and AA in a patient who had a history of both TBI and epilepsy.

Disclosures: K.B.A. Nguyen: None. **J. Rosato:** None. **K. Westerman:** None. **A. Stasenko:** None. **C.R. McDonald:** None. **L. Delano-Wood:** None. **C.N. Smith:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

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Program #/Poster #: PSTR472.21/QQ14

Topic: I.07. Long-Term Memory

Support: VA Merit Award I01CX001375
UCSD ACTRI Pilot Grant 1031915

Title: Hippocampal and parahippocampal subregion volumes and their relationship to news event memory in older adults with normal cognition or mild cognitive impairment

Authors: *M. D. GOMEZ[1,2], J. Y. TSUI[1,3], C. W. TALLMAN[3], A. M. DAUGHERTY[6], J. K. LEUTGEB[4], C. N. SMITH[1,5,7];
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Abstract: Individuals with Mild Cognitive Impairment (MCI) are at risk for developing Alzheimer's disease (AD). According to existing tests, MCI patients exhibit extensive impairment in remembering the past (retrograde memory, RM) concurrent with only mild impairment in new learning (as assessed by traditional episodic memory tests, EM). This finding suggests that more sensitive RM tests could identify MCI closer to when subtle neural and cognitive changes begin, therefore improving earlier diagnosis and access to interventions. The transentorhinal cortex (perirhinal and entorhinal cortices), subiculum (SUB), and CA1 are the first regions in the medial temporal lobe (MTL) affected by tau pathology and volume loss in

those at risk for AD, whereas the dentate gyrus (DG) is most affected by normal aging. Cognitive tests that are related to the volumes of transentorhinal, CA1, and SUB will be useful for the early identification of AD risk. In older adults with either MCI (N=33) or normal cognition (NC) (N=34), we examined if a novel RM news events test (RM-NET) could significantly predict brain volumes of MTL subregions that decline in AD. The MCI group was significantly impaired on the RM-NET compared to the NC group. In the MCI group, the RM-NET significantly predicted SUB and rostral perirhinal (35/36r) volumes, with strong trends for CA1, DG, and entorhinal. These findings remained when a quality control vector was included in the analysis. The strength of the brain-behavior correlations for the SUB and 35/36r significantly decreased as memory age increased, suggesting recent time periods are more predictive than remote. By contrast, traditional EM tests significantly predicted volumes for the whole hippocampus, CA1, and DG, whereas traditional semantic memory (SM) tests significantly predicted volumes for the whole parahippocampal gyrus and 35/36r. No significant relationships between the RM-NET and MTL volumes known to decline in AD were identified in the NC group. The RM-NET was significantly related to volumes in regions known to decline in AD (SUB and perirhinal cortex), and it did not significantly predict DG. While both the RM-NET and traditional tests significantly predicted the volume of perirhinal cortex, the effect sizes (standardized beta coefficients) were much larger for the RM-NET than for traditional tests (RM-NET: 0.77, EM: 0.38, SM: 0.44). Performance on the RM-NET was associated with volumes of regions known to decline early in AD in those at risk for dementia, and the association was stronger than traditional tests of EM and SM. Thus, unlike traditional tests, lower performance on the RM-NET is more likely to indicate risk for AD than normal aging.

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Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.22/QQ15

Topic: I.07. Long-Term Memory

Support: NIH/NINDS R01 NS124585

Title: Retrograde memory for news events in epilepsy: examination of the temporal extent of retrograde amnesia

Authors: *J. ROSATO[1,4], A. STASENKO[2], E. KAESTNER[2], E. BRADY[5], D. L. DRANE[5], C. R. MCDONALD[2,4,3], C. N. SMITH[4,2,6];
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Abstract: Background: Individuals with epilepsy exhibit severe retrograde memory (RM) impairment according to clinical measures of personal episodic (autobiographical memory) and personal semantic memory. For personal semantic memory, only recent time periods are impaired and early adult and childhood memories are intact. Patients also exhibit severe impairment according to novel measures of semantic memory (e.g., news event memory, famous personalities), but the extent of retrograde amnesia has not yet been examined in presurgical patients. Methods: Using a novel test of news event memory (RM-NET), we obtained measures of recall and recognition memory accuracy in presurgical epilepsy patients (N=14, 38.5 years old) and controls (N=19, 38.3 years old) across the entire adult lifespan, separated into 3-5 year time periods. We compared mean accuracy on the RM-NET across the groups and estimated the extent of retrograde amnesia. Results: The epilepsy group exhibited significantly poorer mean recall and recognition memory accuracy for news events relative to controls. The epilepsy group exhibited poorer memory for news events across all nine 3-year time periods examined (27 years). The findings were similar when time periods were separated into those that happened before epilepsy onset (retrograde amnesia) and after epilepsy onset (anterograde amnesia). Conclusions: The RM-NET was sensitive to RM impairment in epilepsy. Similar to an earlier postsurgical study (Leeman et al., 2009), all time periods representing the adult lifespan were affected. Together, these findings suggest that the severe retrograde amnesia in epilepsy results from epilepsy itself and not from surgical treatment for epilepsy.

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Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.23/QQ16

Topic: I.07. Long-Term Memory

Support: VA Merit Award I01CX002626

Title: Creation of two equivalent versions of a news events test for repeated testing

Authors: *S. BARHATE[1,2], O. SHARLAI[2], C. N. SMITH[1,2];
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Abstract: Background: News events tests have been used to assess anterograde and retrograde memory in neurological groups (Alzheimer's disease, semantic dementia, epilepsy). In clinical studies/trials, it is useful to test patients twice (e.g., before and after an intervention) to assess the effect of an intervention on performance. However, repeated testing with the same measure can lead to practice effects. Methods: Our goal was to (1) create two equivalent versions of the published retrograde memory news events test (RM-NET; Cawley-Bennett et al., 2022), (2)

update the test to include news events from more recent years, and (3) split the updated time periods into equivalent versions. We examined recognition memory accuracy scores in 34 older adults with normal cognition that completed the RM-NET between 2018-2021, which contained 230 questions about news events that occurred between 1958-2017. For each question, we identified the topic (international, national, entertainment), and computed the mean accuracy score. Questions for events that happened prior to 1958 were eliminated as were questions that had a mean accuracy score below 25%. Finally, we examined whether test versions A and B were similar for older adults with normal cognition and were also similar for older adults with mild cognitive impairment (MCI). For each time period, the accuracy score from the whole test was compared to the accuracy scores for versions A and B. Results: Total accuracy scores for versions A (75.5±4.4% correct) and B (76.1±4.7% correct) were not significantly different from the accuracy scores from the entire test (74.6±3.0% correct). For each year or 3-year time periods (for the oldest questions) the accuracy scores for versions A (69-82% correct) and B (68-81% correct) were not significantly different from the entire test (69-81% correct). The same was true for the MCI group, which had 67.6±4.1% correct for version A, 62.5±5.1% correct for version B, and 64.8±3.1% correct for the entire test. For the year/3-year time periods, the MCI group exhibited similar ranges for version A (58-80% correct), version B (54-72% correct), and the entire test (59-70% correct). Measures of internal consistency (Cronbach's Alpha) were similar for formats A (0.86) and B (0.86) and were modestly lower than the entire test (0.93). The same was true for the MCI group (A: 0.80; B: 0.74; Entire Test: 0.86). To assess memory for events from 2018-2023, 39 new questions were created based on pilot testing of healthy adults. Conclusions: We created two similar versions of a news events test that can be used for testing participants on multiple occasions, reducing the impact of practice effects on performance.

Disclosures: S. Barhate: None. **O. Sharlai:** None. **C.N. Smith:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.24/QQ17

Topic: I.07. Long-Term Memory

Title: Cardiovascular Risks Contribute to Age-related Differences in fMRI activations in Visual Episodic Memory

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Abstract: The inverse relationship between aging and episodic memory is characterized by an inability to discriminate between highly similar items, termed pattern separation (Pishdadian et al., 2020). This relationship is indexed by lower activation in older adults in MTL and visual areas that help with item specific encoding. However, older adults' inability to modulate BOLD activation, may impact their nonspecific item memory performance and is related to their

increased cardiovascular risk. As one ages, the blood vessels may harden due to calcification, affecting the flow of oxygen to the brain and causing the heart to pump more blood into the arteries, thus increasing pulse pressure (Qin & Basak, 2020). Another factor of cardiovascular risk is reduced cardiorespiratory function (CRF) of the heart. The fluctuations in CRF and arterial stiffness have been analyzed previously by Qin & Basak (2022) using non-exercise estimate of VO_2 max and pulse pressure. In this event-related mnemonic similarity fMRI task, which requires subsequent discrimination of old targets from both similar lures and new lures, we investigated whether age-related difference in BOLD signal engaged during encoding is influenced by individual differences in CRF and arterial stiffness. We expect older adults to have lower success in this pattern separation task due to reduced recruitment of item-specific encoding regions. Our aim is to assess if this relationship is exaggerated for older adults with a higher cardiovascular risk and identify unique activation or suppression patterns of different regions related to memory performance.Several regions of interest were identified through age contrasts; BOLD activation patterns between memory performance (remember, misremember, and forgot) were correlated with the performance condition for these regions. Distinct age-related patterns of activation between memory performance of the left lateral occipital and temporal fusiform cortices, precuneus, and temporal pole reaching into the insular cortex in older adults were found to be correlated with cardiovascular risk factors. More specifically, age differences in pattern separation were represented by reduced engagement of the left lateral occipital/temporal fusiform cortex and a failure to modulate the suppression of the precuneus/PCC by older adults. Interestingly, older adults overactivated middle frontal gyrus, a central executive network hub, during this visual episodic memory task. But this overactivation was related to higher CRF, lower pulse pressure and lower BMI, implicating the importance of cardiovascular risks and cognitive control in episodic memory.

Disclosures: C. Basak: None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.25/QQ18

Topic: I.07. Long-Term Memory

Support: NSF Grant 2145172

Title: Probing temporal associations in cued recall for naturalistic events

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Abstract: Episodic memory involves retrieval of contextual information associated with past experiences. How does retrieved context support recall of temporally adjacent events? Prior studies using random (temporally unstructured) word lists have demonstrated a forward

advantage in cued recall, whereby a cued item more strongly facilitates recall of the subsequent item than the preceding item. However, events in real life have complex associations, for example, a given event usually contains more information about preceding events than subsequent ones, and experiences are typically marked by event boundaries.
Here, we investigate what determines whether temporally adjacent events could be associated in memory and whether such associations are time-symmetric, in a naturalistic setting. Participants watched 30-minute movies and were later cued with short clips from the film. For each cue, participants first rated its vividness, then recalled what happened either immediately before or after the clip. Cue clips were systematically sampled to vary in proximity to their scene's beginning or end boundary.
We replicated and extended previous findings that cued recall performance is lower with across-event cues than that with within-event cues, in both backward and forward directions. Notably, this boundary effect was present even in trials with high vividness ratings. While event boundaries caused temporal asymmetries in across-event cued recall, there was no evidence that cued recall performance in within-event trials was time asymmetric. These results suggest memory associations of naturalistic events exhibit different patterns from those of unstructured word lists, where event boundaries modulate the associations and there might not exist a forward asymmetry in cued recall.

Disclosures: X. Xu: None. **J.R. Manning:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.26/QQ19

Topic: I.07. Long-Term Memory

Support: NIH grant MH55687

Title: Cross-task decoding isolates distinct components of episodic memory and mental arithmetic

Authors: *R. DEHAAN[1], Y. EZZYAT[3], M. RANDAZZO[4], M. J. KAHANA[2];
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Abstract: Neuroscientists often use neural decoders to identify whether information relating to a behavioral task can be detected somewhere in the brain. However, decoding based on an individual task may reflect attentional or arousal processes that do not specifically relate to a particular cognitive function of interest. Alternatively, decoding could depend on neural activity generated by task-specific processes which would presumably disengage during unrelated tasks. Here we ask this question using data from 371 neurosurgical patients implanted with intracranial electrodes who performed a free recall task that has standard memory encoding and retrieval

phases with an intervening arithmetic distractor phase that, arguably, has nothing to do with the encoding of memory items. We train classifiers separately on neural activity from each of these phases to predict behavioral outcomes and ask whether these classifiers transfer to the other tasks. Encoding classifiers transfer to retrieval but not to arithmetic while arithmetic classifiers transfer to retrieval but not to encoding. Retrieval classifiers transfer to both encoding and arithmetic. These results suggest separate factors of neural activity, one factor underlying processes shared across encoding and retrieval and one shared across retrieval and arithmetic. Further, encoding-retrieval transfer performance robustly exceeds retrieval-arithmetic transfer, indicating a close relationship between these memory task phases in line with retrieved-context theories of memory. Decoding performance in these tasks thus does not merely reflect a single neural factor driven by attentional arousal signals. We propose this form of cross-task decoding as a method of identifying the factor structure of neural patterns underlying distinct forms of human cognition.

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Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.27/QQ20

Topic: I.07. Long-Term Memory

Support: NIH/NINDS ZIA NS003144

Title: Fidelity of neuronal spike sequences in the human anterior temporal lobe is related to successful memory formation

Authors: *E. JITENDRAN[1], J. ZHANG[2], J. H. WITTIG, Jr.[3], W. XIE[4], S. N. JACKSON[1], S. INATI[1], T. E. BEHRENS[5], K. A. ZAGHLOUL[3];
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Abstract: Bursts of spiking activity in the human anterior temporal lobe can organize into neuronal sequences in response to visual stimuli. These sequences may represent semantic information that is later replayed during successful memory retrieval. However, it is unclear how the extent of this representation - or “sequence fidelity” - may vary across task conditions. We recorded spiking activity from microelectrode array recordings (n=11) in the human anterior temporal lobe (ATL) of participants during a semantic categorization and recall task. Bursts and corresponding sequences were extracted from trial periods during the categorization phase of the task. We operationalized sequence fidelity as the similarity between individual held-out sequences and average “template” sequences from each of the four semantic categories. We found that neuronal sequences have significantly higher within-versus-across category fidelity -

in other words, higher similarity between sequences of the same category compared to those of different categories - when participants are actively encoding stimuli into memory, as evidenced by subsequent recall of those stimuli. This data suggests that the fidelity of neuronal sequences in the ATL may be modulated by successful memory formation.

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Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.28/RR1

Topic: I.07. Long-Term Memory

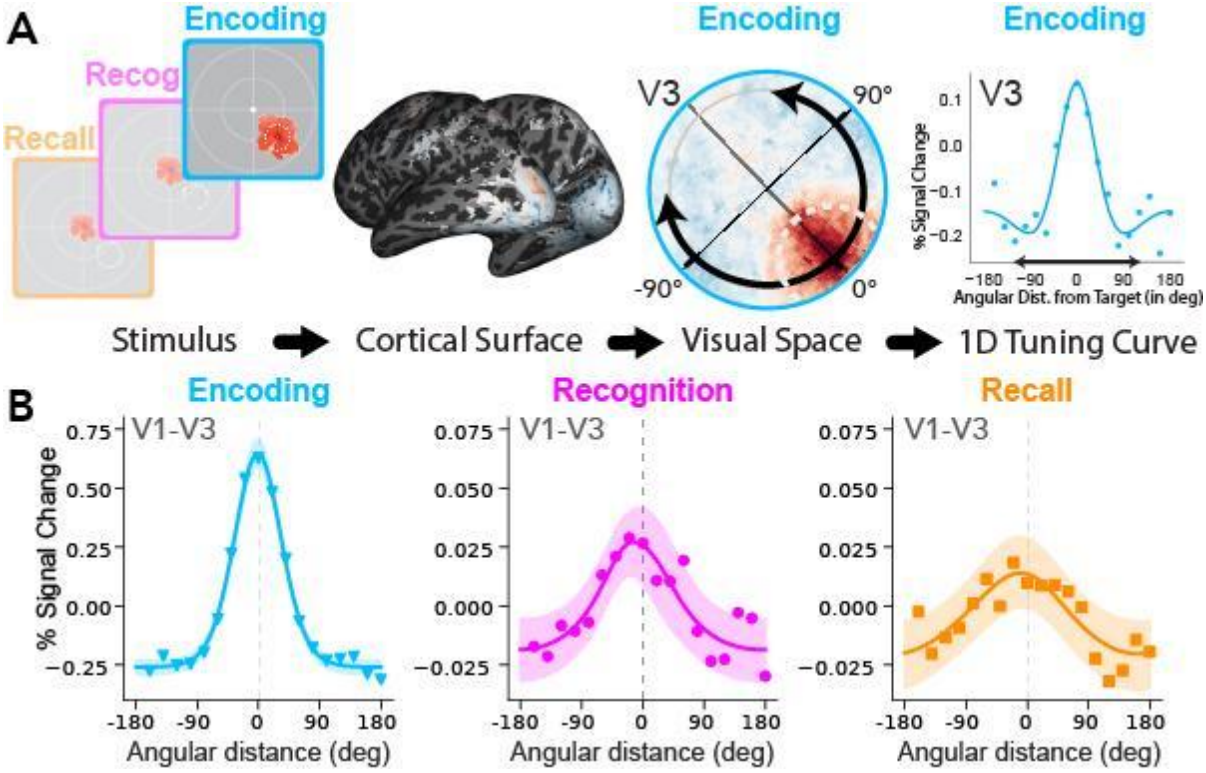
Support: NIH T90 DA059110
NIH R01 EY027401
NIH R01 EY033628
NIH F99 NS105223

Title: Early Visual Cortex Supports One-Shot Episodic Memory via Spatially Tuned Reactivation

Authors: *R. WOODRY[1], J. WINAWER[2], S. FAVILA[3];
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Abstract: A hallmark of episodic memory is the ability to retrieve details from a single experience. Classic models of episodic memory propose that retrieval relies on the reactivation of previous perceptual representations in sensory cortex, a phenomenon known as cortical reinstatement. However, support for this idea, particularly in early sensory areas, comes primarily from studies involving highly trained memories, leaving open the relevance of early sensory cortex for retrieval of single events. Here, we used fMRI and population receptive field modeling to test whether spatially tuned memory responses emerge in early visual cortex after a single encoding event in human adults. We scanned 20 subjects while testing them on their memory of peripheral objects seen only once. Subjects encountered 480 object images across three interleaved tasks: encoding, old/new recognition, and location recall. During encoding scans, peripheral objects appeared at one of four polar angles while subjects maintained central fixation and judged whether the object was bigger/smaller than a shoebox. During recognition scans, either the same objects or lures were presented centrally while subjects made old/new judgments. During location recall scans, subjects viewed old objects centrally and indicated the polar angle of the object at encoding. We observed spatially tuned responses in early visual cortex during both recognition and recall, even though spatial location was never explicitly probed during recognition. These responses were better tuned for successfully remembered

items, revealing a relationship between neural tuning in early visual cortex and behavioral memory performance, even after a single encoding event. Moreover, spatial tuning at encoding predicted subsequent memory: responses for subsequently remembered objects were stronger near the object location and suppressed elsewhere, relative to forgotten items. Our findings demonstrate that early visual cortex plays an important role in successful episodic memory after minimal experience.



Disclosures: R. Woodry: None. **J. Winawer:** None. **S. Favila:** None.

Poster

PSTR472: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.29/RR2

Topic: I.07. Long-Term Memory

Title: Distinct electrophysiological patterns associated with forward and backward transitions in episodic memory retrieval

Authors: R. M. GUTIERREZ, *J. D. JOHNSON;
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Abstract: Forming associations among stimuli, contexts, and time is a hallmark of encoding events and experiences into episodic memory. Moreover, these associations can subsequently play an important role in guiding strategies at the time of retrieval. While numerous studies have used a variety of approaches to characterize the neural signatures of episodic and associative memory, the neurocognitive processes involved in transitioning across information that was encoded at different points in time are less understood. Here, we sought to further understand how deliberation and search processes during retrieval proceed in a forward versus backward manner, with the specific goal of providing novel insights into the neural correlates of such processing. Scalp EEG was acquired from 24 human subjects who completed a series of encoding-retrieval cycles. Each cycle consisted of a list of about 8 successively presented words which was immediately followed by a cued-recall task. The recall task involved presentation of a studied word from a randomly selected position in the list along with arrows designating that subjects should deliberate about (for 5 seconds) and then report the two words that came next in the study list (forward) or the two words that preceded the cue (backward). Event-related potentials (ERPs) and oscillatory EEG activity from the deliberation period were used in conjunction with multivariate pattern analysis (MVPA) to train classifiers to distinguish the forward versus backward conditions. The primary results indicated that activity patterns reliably differed according to the direction of deliberation, providing novel evidence of dissociable processes contributing to cued recall. These findings are discussed in relation to time-based strategies, such as mental time travel, that are thought to guide successful episodic retrieval.

Disclosures: R.M. Gutierrez: None. **J.D. Johnson:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.01/Web Only

Topic: I.09. Spatial Navigation

Support: Departamento de ciencias de la salud

Title: Neuroinflammation without observable cognitive impairment: A spatiotemporal behavioral and neurohistological analysis of LPS administration in C57BL/6 mice

Authors: *P. TORRES GARCÍA[1], K. R. ALVA-ANDRADE[2], E. CORDERO-RAMIREZ[2], K. R. GUZMAN-RAMOS[2];
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Abstract: Lipopolysaccharide (LPS) administration is a widely used model for inducing neuroinflammation in rodents, commonly associated with cognitive dysfunction. However, methodological variability across studies makes results difficult to interpret. Differences in dosage, timing of behavioral assessments (often shortly after administration), and the sensitivity

of behavioral metrics contribute to confounding effects such as sickness behavior, transient hypolocomotion, and poor behavioral robustness. These factors may support the interpretation of cognitive impairment when none exists, or mask real deficits. In this study, we employed two LPS administration protocols in C57BL/6 male mice that differed in both dose and temporal pattern: one protocol involved five intraperitoneal (i.p.) injections of 500 μg/kg administered every 48 hours, while the second consisted of five daily injections, with the first three at 1000 μg/kg and the final two at 2000 μg/kg. Animals were evaluated using the Morris Water Maze task, with both conventional metrics and high-sensitivity spatiotemporal analyses. Specifically, we calculated spatial and path entropy indices and used Pathfinder to classify search strategies as hippocampal or non-hippocampal. Counterintuitively, neither protocol resulted in significant behavioral impairments. However, immunofluorescence analysis revealed robust glial activation, with increased GFAP and IBA-1 markers in the hippocampus, confirming the presence of neuroinflammation. These findings highlight a dissociation between neuroinflammation and observable cognitive dysfunction under the conditions tested. The absence of behavioral effects remarks the importance of the implementation of more robust analyses and differential roles of inflammatory processes in functional outcomes. Our results underscore the importance of combining more sensitive behavioral tools with biomarker validation to fully capture the complexity of neuroinflammation models. They also challenge the assumed direct and necessary link between brain inflammation and cognitive decline, encouraging a critical reevaluation of these models in preclinical research.

Disclosures: P. Torres García: None. **K.R. Alva-Andrade:** None. **E. Cordero-Ramirez:** None. **K.R. Guzman-Ramos:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.02/RR3

Topic: I.09. Spatial Navigation

Support: University of San Diego, College of Arts and Sciences

Title: Route selection impairment and neuroinflammation in a rodent model of Attention Deficit Hyperactivity Disorder (ADHD)

Authors: S. SKUBIC, M. KRAMER, A. MOFFATT, *J. B. HALES;
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Abstract: The ability to remember locations of objects and make spatial decisions is critical when navigating an environment. Such tasks, however, can be difficult for individuals with certain neurological conditions, such as Attention Deficit Hyperactivity Disorder (ADHD). Our lab has used the naturalistic spatial foraging task, known as the Traveling Salesperson Problem (TSP), to examine these processes in rodents. The TSP is an optimization task that requires

subjects to identify the shortest route of travel between a certain number of targets. Previous studies from our lab have found that rats with hippocampal or medial entorhinal cortex lesions were impaired on measures of spatial memory in the TSP task, but neither group showed impairments in measures of spatial decision-making. This study examined the performance of male and female Spontaneously Hypertensive Rats (SHR), the most widely used rodent model of ADHD, relative to their control model, Wistar Kyoto (WKY) rats, on the TSP task. Both rodent and human studies of ADHD have primarily used male subjects, resulting in females being understudied. This disproportionate focus on males has contributed to a lack of understanding of the symptoms and neurological mechanisms of ADHD in females, highlighting the need for studies that examine sex as a biological variable. Our behavioral findings suggest that both male and female SHRs have greater deficits in route selection compared to WKY rats. We also examined microglia expression as a marker of neuroinflammation in the prefrontal cortex, hippocampus, and medial entorhinal cortex in male and female SHR and WKY rats. Preliminary histological results suggest differential microglia expression and activation morphologies in male and female SHR and WKY rats within these defined brain regions of interest. This study expands on existing literature within ADHD-model rats by exploring their ability to effectively route optimize using a naturalistic task.

Disclosures: S. Skubic: None. **M. Kramer:** None. **A. Moffatt:** None. **J.B. Hales:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.03/RR4

Topic: I.09. Spatial Navigation

Support: National Research Foundation of Korea

Title: Astrocytic modulation in the CA1 dorsal hippocampus influences spatial memory performance in mice

Authors: *P. CHAEEUN[1], S. PARK[1,2], Y. HUH[3,4], J. CHO[1];
[1]Dept. of Brain and Cognitive Sci., Ewha Womans Univ., Seoul, Korea, Republic of; [2]Brain Link Creative Res. Section, Electronics and Telecommunications Res. Inst. (ETRI), Daejeon, Korea, Republic of; [3]Catholic Kwandong Univ., Incheon, Korea, Republic of; [4]Dept. of Med. Science, Col. of Med., Catholic Kwandong Univ., Gangneung-si, Korea, Republic of

Abstract: Astrocytes are increasingly recognized as active modulators of synaptic transmission and neural circuit dynamics, extending beyond their traditionally ascribed role as passive support cells. Emerging studies have highlighted their involvement in higher cognitive functions, including learning and memory like spatial memory. Recent findings suggest that astrocytic calcium signals are temporally coordinated with neuronal firing during memory-related behaviors, indicating a possible contribution to information processing. However, the extent to

which astrocytic activity directly influences hippocampus-dependent spatial memory remains incompletely understood. Given the central role of the hippocampal CA1 region in spatial information encoding, we examined the impact of astrocytic modulation in the dorsal hippocampus on spatial learning and memory performance with DREADD-based chemogenetic tools.Behaviors of mice that received pAAV-GFAP-Gq-DREADD (activation), pAAV-GFAP-Gi-DREADD (inhibition), or pAAV-GFAP104-mCherry (control) virus injections into the CA1 dorsal hippocampus were compared. Open Field Test (OFT) showed no difference in locomotion among groups. A significant difference in the discrimination index was observed between the astrocyte-inhibited (Gi) group and the control group in the object location test (OLT). In the Dry Water Maze, Gi mice failed to meet the learning criterion (latency <20s) even after 8 days of training, while the control and Gq groups successfully learned the task. Reversal test of the dry water maze further revealed impairment in learning flexibility of the Gi group. However, no significant group differences were observed in contextual fear conditioning or extinction.Our findings demonstrate that chemogenetic inhibition of astrocytes in the hippocampal CA1 region specifically impairs hippocampus-dependent spatial learning and memory tasks. These results provide evidence that astrocytic activity in the dorsal hippocampus influences spatial memory encoding and learning, thereby advancing our understanding of glial involvement in cognitive function.

Disclosures: P. Chaeeun: None. **S. Park:** None. **Y. Huh:** None. **J. Cho:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.04/RR5

Topic: I.09. Spatial Navigation

Support: Horizon 2020 ICT (https://cordis.europa.eu/project/id/101016787, DEEPER)
Chan Zuckerberg Advancing Imaging through Collaborative Projects, 2023-2024

Title: Encoding of spatial information in astrocytic calcium dynamics during naturalistic spatial navigation revealed by miniaturized two-photon microscope recordings in the mouse hippocampus

Authors: *S. CURRELI[1], A. SATTIN[2], L. MADDALENA[2], G. LETTI[2], T. FELLIN[2];
[1]Optical Approaches to Brain Function Lab., [2]Optical Approaches to Brain Function, Inst. Italiano di Tecnologia, Genova, Italy

Abstract: Recent findings in awake head-fixed mice during virtual spatial navigation show that astrocytic calcium signals in the CA1 hippocampal area encode spatial information. Information encoded in astrocytic calcium dynamics was observed to be complementary and synergistic to

that encoded in the spike output of neighboring CA1 neurons[1]. However, these findings relied on head-restrained animals navigating in a virtual environment. Such experimental conditions prevent the engagement of the vestibular system and employ sensory stimuli of lower complexity compared to those present in naturalistic spatial navigation[2]. Here, we tested the hypothesis that astrocytic calcium dynamics encode spatial information during freely moving spatial navigation in a real bidimensional arena. To this aim, we used the MINI2P[3] technology and performed high-resolution two-photon recordings of calcium dynamics from hippocampal CA1 astrocytes labeled with GCaMP6f in freely moving mice. Signals from astrocytic somata, proximal processes, and perivascular endfeet were tracked while animals were engaged in behavioral sequences occurring during open field spatial navigation. Using multiple regression and machine learning approaches, we found that astrocytic cellular sub-compartments encoded significant information about the animal position in the real bidimensional arena and that the position of the animal could be effectively decoded from recorded astrocytic calcium dynamics. Altogether, these results open a new window on the encoding properties of astrocytic subcellular compartments during complex naturalistic behavior.

Bibliorgaphy:
1. Curreli, S., Bonato, J., Romanzi, S., Panzeri, S. & Fellin, T. Complementary encoding of spatial information in hippocampal astrocytes. PLoS Biol 20, e3001530 (2022).
2. Minderer, M., Harvey, C.D., Donato F., Moser, E.I. Neuroscience: Virtual reality explored. Nature 533, 324-325 (2016).
3. Zong, W., et al. Large-scale two-photon calcium imaging in freely moving mice. Cell 185, 1240-1256 e1230 (2022).

Disclosures: S. Curreli: None. **A. Sattin:** None. **L. Maddalena:** None. **G. Letti:** None. **T. Fellin:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.05/RR6

Topic: I.09. Spatial Navigation

Support: Brain Research Foundation Seed Grant BRFSG-2021- AQ2 11

Title: Persistent Impact of Prior Experience on Spatial Learning

Authors: *M. P. AWH[1], K. W. LATIMER[2], N. ZHOU[4], Z. LEVERONI[3], A. POON[1], J. Y. YU[1];
[2]Neurobio., [3]Psychology, [1]Univ. of Chicago, Chicago, IL; [4]The Univ. of Chicago, Chicago, IL

Abstract: Learning to solve a new problem involves identifying the operating rules, which can be accelerated if known rules generalize in the new context. We ask how prior experience affects learning a new rule that is distinct from known rules. Specifically, we manipulated the number of

spatial navigation tasks rats had previously learned before measuring their learning in a novel task. In this initial training phase (Phase 1), rats either trained on one spatial navigation task (non-switching group) or alternated between two tasks (switching group). In Phase 2, all rats learned a novel task, which differed from Phase 1 tasks in spatial layout and navigation rule. Although Phase 2 absolute performance did not differ by group, we found experience-dependent differences in exploration patterns, as well as differences in the types of errors. In early stages of exploration, the switching group exhibited a greater tendency to switch between straight and turning trajectories. During stable performance, the switching group exhibited greater sensitivity to recent actions during an alternation task, implying more effective use of working memory. By contrast, the non-switching group was more likely to return to a home base when required, suggesting greater reliance on reference location memory. To characterize these observations, we modeled choice sequences using a distance-dependent Chinese Restaurant Process, including a time constant τ that determined how influential past choices were on the next choice and a parameter C that determined the influence of only the most recent choice. Bayesian posterior estimates showed the switching group has a significantly longer τ and a larger C, suggesting a greater sensitivity to recent history. A second model generated choice sequences in the new task with a second-order Markov chain that used transition matrices trained on sequences in Phase 1 or a uniform random distribution. This model failed to replicate Phase 2 behavior, indicating that simple rule or strategy switching does not explain the observed difference. Both early and late differences are consistent with the animals adopting unique experience-dependent memory strategies. Our results indicate that prior experience shapes learning strategies and continues to influence behavior throughout novel contexts.

Disclosures: M.P. Awh: None. **K.W. Latimer:** None. **N. Zhou:** None. **Z. Leveroni:** None. **A. Poon:** None. **J.Y. Yu:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.06/RR7

Topic: I.09. Spatial Navigation

Title: Assessment and Classification of Idiosyncratic Behavioral Sequences in Rodent Navigation

Authors: *M. G. SEGAL[1], D. A. HAMILTON[2];
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Abstract: Navigation is essential to survival, allowing organisms to reach resources and evade danger. Exactly what is learned during navigation remains a topic of intense study and debate. Recent studies suggest that individual rodents learn to execute similar paths from trial to trial in the Morris Water Task (MWT) from distinct release points, while paths between different release

points are dissimilar at levels comparable to differences between rats. To assess whether idiosyncratic behavioral sequences are characteristic of rodent spatial learning in the hidden-platform MWT, we utilized supervised machine learning classification via long short-term memory neural networks (LSTM) to identify individual rats based on swim path characteristics. Moment-to-moment position (head-tracked), path entropy, heading error, and velocity time series were analyzed to assess idiosyncrasies in spatial and kinematic behavioral constituents. LSTMs were utilized due to their strengths in objectively capturing sequential patterns. Fifteen cognitively healthy adult male Long-Evans rats were trained in the MWT for five days, experiencing fifteen trials from each of four release points. Independent classification iterations (N=100) were conducted on datasets with valid labeling and randomly identity-scrambled datasets for comparison. Independent sample t-tests between the valid and scrambled data were used to evaluate the predictive validity of behavioral sequences and revealed that classification accuracy was significantly greater compared to identity-scrambled datasets for all behavioral measures ($p < 0.001$). ANOVA detected significant differences in classification accuracy between behavioral measures; Tukey HSD post-hoc comparisons revealed head-tracked position provided greater accuracy over other measures ($p < 0.001$). Mean classification performance on head-tracked coordinates was 512% greater than chance, establishing it as the most effective behavioral characteristic for identification of individuals rats in the sample. These outcomes support the notion that rodents express idiosyncratic behavioral sequences during navigation in the MWT and implicates behavioral sequences a key element of what is learned in the MWT. The outcomes observed here may also have implications for gaining a greater understanding of which behaviors are most salient in achieving place navigation as well as how unique neurobiological function is reflected in behavior.

Disclosures: M.G. Segal: None. **D.A. Hamilton:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.07/RR8

Topic: I.09. Spatial Navigation

Support: HHMI

Title: Mouse behavior exhibits hierarchical structure during spontaneous exploration of complex environments

Authors: T. MA[1], A. M. HERMUNDSTAD[2], ***J. VOIGTS**[3];
[1]Computation and Theory, [2]Janelia Res. Campus, Ashburn, VA; [3]HHMI Janelia Res. Campus, ashburn, VA

Abstract: In natural settings, animals must navigate richly structured sensory surroundings and rapidly adapt to changes in these surroundings. While many studies have

explored navigation in mazes and open arenas, relatively little is known about how animals navigate in naturalistic terrain that is too complex to directly memorize and lacks clearly defined routes. Here, we probe the structure of mouse behavior in a complex, reconfigurable 3D arena in darkness and without explicit reinforcement. Mice quickly converge on a set of running and jumping paths through the arena. We developed new algorithms to partition this behavior into a set of motifs based on re-occurring path segments; this enabled us to describe long paths as hierarchical compositions of shorter sub-paths. Over days, mice construct long repeated paths from shorter ones and occasionally reconfigure parts of their path repertoire e.g. by discovering shortcuts. We then introduced a local perturbation to the arena that interacted with existing composite paths. This led to a rapid emergence of new motifs that elicited non-local changes in behavior. Together, these results suggest that mice navigate complex environments by learning a sparse set of discrete paths and provide a lens for studying complex, long-timescale behavior by quantifying its compositional structure.

Disclosures: T. Ma: None. **A.M. Hermundstad:** None. **J. Voigts:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.08/RR9

Topic: I.09. Spatial Navigation

Title: Do animals go as far as they can, or as far as they have to?

Authors: *M. ELBON[1], S. HERCULANO-HOUZEL[2];
[1]Psychology, [2]Dept. of Psychology, Vanderbilt Univ., Nashville, TN

Abstract: An animal's "home range" is the surface area where it can normally be found over a given time. Larger animals have larger home ranges, which may result from a need for more energy, from the ability to cover longer distances per unit time, or both. Whatever determines the size of an animal's home range, representing that space might constitute an advantage that imposes selective pressure for a commensurate number of hippocampal neurons across species. In that case, a requisite finding is a positive and universal correlation between home range and number of hippocampal neurons. We compiled a dataset of home ranges for 342 mammalian species, and compared home range against known body mass, metabolic rates, cortical neuron counts, and hippocampal neuron counts. We show that the number of hippocampal neurons is not a universal predictor of home range: in particular, primates have smaller home ranges, whereas aquatic carnivores have far larger home ranges, than predicted for their numbers of hippocampal neurons. Our findings show that having a larger home range does not require more hippocampal neurons, and suggest that primates have a higher discriminatory ability when mentally representing their home range - or "spatial representational resolution"-, whereas aquatic carnivores have reduced spatial resolution, whilst obviously capable of navigating their

environment. Interestingly, we find that neither body mass nor energy expenditure explains home range universally, which begs the question: Do animals go as far as they *can*, or as far as they *have to*?

Disclosures: M. Elbon: None. **S. Herculano-Houzel:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.09/RR10

Topic: I.09. Spatial Navigation

Title: Operant conditioning of the micro glassfish Danionella cerebrum and priapus in open field tanks

Authors: *A. STUART[1,2], K. HENDERSON[1], C. MORROW[1], A. RAVAN[1], K. M. BRANSON[1], V. JAYARAMAN[1];
[1]Janelia Res. Campus, HHMI, Ashburn, VA; [2]Johns Hopkins Univ., Baltimore, MD

Abstract: Much of our understanding of the mechanistic basis of spatial navigation has come from neural recordings in selected brain regions thought to underlie the relevant computations. Performing such recordings during behavior has revealed specialized neural representations across many animals, including grid, place, and head direction cells. However, it has been harder to construct a more complete picture of how networks of neurons with such properties ultimately enable goal-directed navigation. In exciting recent developments, such representations have been observed in the transparent larval zebrafish, which permits whole-brain recordings. Unfortunately, larval zebrafish (7-9 days post fertilization) perform poorly in many associative learning tasks despite having functional visual and motor systems at that age, which may make it challenging to link these representations to flexibility in behavior. A different genus of fish, Danionella, which retain larva-like transparency throughout their lifetimes, offers the possibility of studying navigation at both the neural and behavioral levels in adults. In early steps towards such a goal, we show that adult micro glassfish Danionella (90+ day old) learn to use conditioned non-directional sensory cues to inform motor output and navigate efficiently for reward in an open tank, across multiple behavioral paradigms. Over five days of training, Danionella cerebrum increased the length of consecutive successful trials within a day from 7 to 25, consistent with sensitivity to recent outcomes and undirected cues. A larger species, Danionella priapus, performs 75-100 total trials within a two hour training session, after becoming task proficient. Future work will take advantage of the transparency of adult Danionella to perform functional calcium imaging in order to understand how navigational representations are built and combined with contextual sensory cues over the course of learning to produce goal-directed navigational strategies.

Disclosures: A. Stuart: None. **K. Henderson:** None. **C. Morrow:** None. **A. Ravan:** None. **K.M. Branson:** None. **V. Jayaraman:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.10/RR11

Topic: I.09. Spatial Navigation

Support: DFG Grant 505659964

Title: A Mnemonic Goal Proximity Map in the Dopamine-Ventral Striatum System

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Dept. of Fundamental Neurosci., Univ. of Lausanne, Lausanne, Switzerland

Abstract: Accumulating evidence suggests that animals, such as rodents and humans, can construct an internal cognitive map in the brain to navigate to remembered goals in the environment. This ability is thought to be supported by neural representations of an animal's current position in the hippocampus and the entorhinal cortex, as well as those of future goals in the orbitofrontal cortex. However, goals are not always fixed - animals often need to switch between multiple targets within the same environment. Whether the brain retains past navigation experiences and, if so, how these goal location memories are mapped in neural circuits is still unclear. The midbrain dopamine-striatum system has long been implicated in decision-making, particularly in evaluating sensory cues relative to expected rewards. Here, we hypothesize that this system may also play a key role in associating values with spatial positions. To test this hypothesis, we recorded neuronal activity in the nucleus accumbens (NAc) - a key structure of the ventral striatum - while rats performed a goal-directed navigation task. We found that neuronal spiking increased as the animals approached a reward location and adapted flexibly when the goal position changed. Using support vector regression, we discovered that NAc activity reliably estimated the proportional distance between the animal's current location and ongoing target relative to the total journey length. Moreover, following goal switches, NAc neurons encoded proximity not only to the animal's current target but also to previously visited goals traversed during navigation. Estimation of previous goals was observed regardless of the animal's destination, indicating the NAc representation of goal memory rather than decision. Finally, to identify input sources supporting the NAc's goal coding, we silenced neuronal activity in the hippocampus (HPC) or the medial entorhinal cortex (MEC), or inhibited dopamine (DA) release in the NAc. We found that the inhibition of HPC or MEC had no effect on the animals' navigation ability or the NAc's goal proximity coding. In contrast, DA release inhibition impaired the animal's ability to navigate to a fixed goal and to revisit remembered goals from previous journeys. Taken together, these findings suggest that the dopamine-ventral striatum system constructs a map of remembered goals, tracking proximity to valuable locations for memory-guided navigation independently of the hippocampus and entorhinal cortex.

Disclosures: N. Takakuwa: None. **H.T. Ito:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.11/RR12

Topic: I.09. Spatial Navigation

Support: University of San Diego, College of Arts and Sciences

Title: Examining the role of the medial prefrontal cortex and sex-based differences in spatial navigation in rats performing the traveling salesperson problem

Authors: *L. KAZANJIAN[1], A. EHRLICH[1], J. SPAULDING[1], M. TAVARES[2], R. BLASER[1], J. B. HALES[1];
[1]Neuroscience, Cognition, and Behavior, Univ. of San Diego, San Diego, CA; [2]Univ. of California San Diego, San Diego, CA

Abstract: Cognitive impairments, including memory loss, disrupted spatial navigation, and poor executive function, are devastating features of many neurological conditions. Effective research into the causes and treatments of such disorders requires knowledge of the neurological mechanisms that underlie these cognitive processes. Our lab used the naturalistic spatial foraging task, known as the Traveling Salesperson Problem (TSP), to examine these processes in rodents. The TSP is an optimization task that requires subjects to identify the shortest route to travel between a certain number of targets. Previous studies from our lab have found that rats with hippocampal lesions or medial entorhinal cortex lesions were impaired on measures of spatial memory in the TSP task, but neither group showed impairments in measures of spatial decision-making. Given that the medial prefrontal cortex (mPFC) is involved in decision-making and other higher-level processes and that it receives projections from the hippocampus and medial entorhinal cortex, our lab investigated the effect of mPFC lesions on rodent performance on the TSP. Our study also included both male and female rats in order to directly examine sex as a biological variable. Historically, animal studies have predominantly focused on males, with the justification that female hormone fluctuations increase data variability. This focus has resulted in research procedures that are optimized for males. For studies involving lesions, established rat brain atlases only provide detailed neuroanatomical analyses for the male rat brain, limiting our understanding of female rat brain anatomy and localization. Our study found an interaction between mPFC lesions and sex in TSP performance, with mPFC-lesioned males, but not females, choosing a less optimal path between targets. Our histological results also suggest a possible difference in lesion extent between lesioned males and females, highlighting the need for increased neuroanatomical examination of the female rat brain. A consequence of widespread underrepresentation of female animals in research can be seen in the inadequate evaluation, diagnosis, and treatment of various medical conditions within biologically female patients, since

current systems are still optimized for male patients. This study expands on existing literature for the interaction of different brain regions with performance on the TSP.

Disclosures: L. Kazanjian: None. **A. Ehrlich:** None. **J. Spaulding:** None. **M. Tavares:** None. **R. Blaser:** None. **J.B. Hales:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

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Program #/Poster #: PSTR473.12/RR13

Topic: I.09. Spatial Navigation

Support: NIH Grant U01NS126046
NIH Grant U24NS11367

Title: Recording Hippocampal Spiking Activities from Rats Performing a Dynamical Environment Navigation Task with Polymer Microelectrode Arrays

Authors: *Z. JIN[1], H. XU[1], Z. LU[1], X. ZHANG[1], Y. GAO[1], K. SCHOLTEN[2], J. LIANG[1], E. MENG[1,3], D. SONG[1,4];
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Abstract: Understanding the neural basis of learning and memory remains a central challenge in neuroscience. Long-term synaptic plasticity (LTSP) is thought to support these processes, yet its role during naturalistic navigation is poorly understood. A key limitation is the rapid, often one-shot formation of hippocampal place fields, which constrains data collection. To overcome this, we developed an experimental-modeling framework to infer LTSP from endogenous spiking activity recorded during a Dynamical Environment Navigation (DEN) task. In the DEN task, rats explore a circular arena partitioned into four quadrants with distinct wall cues. Removable dividers are sequentially removed and reinserted to gradually expose new spatial contexts, allowing systematic examination of neural dynamics under environmental reconfiguration. We chronically implanted 64-channel conformal polymer microelectrode arrays (pMEAs), tailored to the hippocampal curvature, to record from the dentate gyrus, CA3, and CA1 (n = 15 rats, ≥5 sessions each). Behavioral analysis showed increased average speed and area coverage during progressive exposure. Speed rose after divider removal and decreased after reinsertion, consistent with exploratory responses to novel configurations. Over 300 single units were isolated and classified into pyramidal neurons and interneurons based on waveform shape, autocorrelograms, and firing statistics. Interneuron activity was more tightly correlated with locomotion speed. UMAP projections revealed greater neural drift during exposure phases, with pyramidal neurons remapping in novel zones while remaining stable in familiar regions. Place field analyses revealed diverse dynamics: some fields were unstable; others remained spatially stable but changed in firing rate; and some remapped near divider boundaries or expanded with

increasing environmental scale. Certain fields emerged only after prior exposure, suggesting that hippocampal coding is influenced by both environmental geometry and experiential history. These findings highlight the adaptive nature of hippocampal representations and suggest a role for LTSP in mediating spatial learning during navigation. Future work will integrate a computational model of hippocampal input-output transformations to test whether observed changes in neural dynamics and spatial representations can be explained by LTSP.

Disclosures: Z. Jin: None. **H. Xu:** None. **Z. Lu:** None. **X. Zhang:** None. **Y. Gao:** None. **K. Scholten:** None. **J. Liang:** None. **E. Meng:** None. **D. Song:** None.

Poster

PSTR473: Animal Navigation

Location: SDCC Halls B-H

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Topic: I.09. Spatial Navigation

Support: NIH Grant 1R01NS104897-01
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NIH Grant 5R01NS104897-04
NIH Grant 5R01NS104897-05

Title: Wirefree miniscope calcium imaging in 3D staircase

Authors: *S. Z. WANG[1], Q. YE[1], C. HAYS[1], X. XU[3,2], D. A. NITZ[4,2];
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Abstract: The hippocampal CA1 region plays a critical role in memory encoding, temporal processing, and spatial navigation, yet its function in three-dimensional (3D) environments remains underexplored. In this study, we employ a wire-free calcium imaging miniscope to record neural activity in the dorsal CA1 of freely behaving mice navigating a custom-designed 3D staircase. By pairing neural recordings with behavioral tracking from dual orthogonal cameras, we reconstruct the animals' trajectories and correlate spatial behavior with neuronal dynamics. Using DeepLabCut for behavioral pose estimation and SCOUT (Single-Cell spatiOtemporal longitUdinal Tracking) for neuron identity registration across sessions, we build a comprehensive dataset linking position and directionality to CA1 activity. Further analysis includes CEBRA (Consistent EmBeddings of high-dimensional Recordings using Auxiliary variables) to uncover the latent topological and temporal structure of population-level dynamics. This project offers new insights into the neural coding of 3D navigation and advances the use of untethered imaging and AI-driven analysis in neuroscience.

Disclosures: S.Z. Wang: None. **Q. Ye:** None. **C. Hays:** None. **X. Xu:** None. **D.A. Nitz:** None.

Poster

PSTR473: Animal Navigation

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Program #/Poster #: PSTR473.14/RR15

Topic: I.09. Spatial Navigation

Title: Neural representation across 3D multiple curved surfaces: distinct roles of RSC and MEC

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Abstract: Animals live in three-dimensional (3D) environments, and even for ground-dwelling animals like humans and mice, precise navigation on multiple 3D surfaces is crucial. However, the mechanisms supporting stable directional and spatial representations on 3D surfaces remain poorly understood. In this study, we developed an experimental paradigm in which mice freely navigate a cylindrical structure composed of a top platform and a continuous curved surface (cylindrical side). The neuron activity in the retrosplenial cortex (RSC) and medial entorhinal cortex (MEC) were collected using miniature two-photon imaging when mice freely explored in this experimental paradigm. In the RSC, we found that numerous neurons followed the dual-axis (DA) rule, dynamically adjusting their preferred firing directions (PFDs) along the cylindrical side while maintaining coherent tuning on the top platform, thus exhibiting global directional tuning, a phenomenon not reported in the RSC previously. Besides DA cells, a neuron population maintained stable directional tuning along the cylindrical surface, independent of visual input and primarily driven by gravitational cues, named tangent-plane (TP) cells, were found in both the RSC and MEC. Using generalized linear models (GLM), we revealed distinct coding mechanisms between DA and TP cells: DA cells integrated both head rotation within the tangent plane and body-axis rotation relative to gravity, whereas TP cells solely coded head rotation within the tangent plane. Furthermore, DA cells preserved the relative phase of their PFDs, while TP cells reorganized their directional tuning through transitions between 3D and 2D environments, suggesting that these cell types were formed through distinct mechanisms. For spatial coding, the MEC showed superior encoding than RSC, with greater precision in the horizontal dimension, while the grid-like firing patterns were disrupted on the curved surface. Together, our results suggest that DA cells support multi-surface integrative coding, whereas TP and spatial cells reflect localized encoding. The coexistence of complementary coding strategies across brain regions enables flexible and robust directional and spatial navigation in complex 3D environments.

Disclosures: X. zhang: None. **X. Yuan:** None. **Z. Wang:** None. **C. miao:** None.

Poster

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Program #/Poster #: PSTR473.15/RR16

Topic: I.09. Spatial Navigation

Support: Wellcome Trust
European Union's Horizon 2020 (101022757)

Title: Spatial navigation engages a distributed brainwide neural representation

Authors: *E. H. VAN BEEST, B. TERRY, K. D. HARRIS, M. CARANDINI;
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Abstract: Introduction. Navigation is a complex, goal-directed behavior that requires the brain to flexibly integrate sensory input, reward, motor control, and internal spatial representations. In the brain, signals related to navigation have been typically found in the hippocampal formation, where 'place' and 'grid' cells encode position, and in retrosplenial and parietal cortex. More recently, spatial signals have been observed even in visual and olfactory cortices, hinting at a brain-wide representation. To test whether spatial representations are distributed and distinct from other navigation-related processes such as motion, sensation, and reward, we recorded activity across multiple brain regions during spatial behavior in a virtual corridor.
Methods. We used Neuropixels probes to record from >18k neurons across cortex, hippocampus, thalamus, striatum, and midbrain in head-fixed mice navigating a virtual corridor with sensory-identical halves. Landmarks were of variable contrast. Some trials included auditory cues, and wheel gain varied to decouple physical and virtual position. We trained a Bayesian decoder to predict position, and linear encoding models to predict how each neuron's firing rate depends on spatial and non-spatial variables (stimuli, speed, reward).
Results. In 152/153 sessions, we decoded position significantly above chance, regardless of which regions were recorded. The distribution of decoding errors was bimodal, with a main peak at 0 cm (veridical position) and a secondary peak at 40 cm, the distance between sensory identical locations. Across regions, 69 ± 9% of neurons were fit with >1% of explainable variance explained by encoding models. Non-spatial variables such as running speed (57 ± 10% of neurons) or visual contrast (17 ± 10%) significantly contributed to variance explained across the brain. Crucially, spatial predictors significantly improved variance explained in 16 ± 5% of neurons, exceeding chance in somatosensory, motor, and retrosplenial cortex, striatum, midbrain, some thalamic nuclei, hippocampus, and visual regions anterior, rostrolateral, primary, and posteromedial. The dependence of neurons on sensory and spatial predictors in the task significantly correlated with their tuning to sensory stimuli outside the task, indicating that the corridor recruited sensory responsive neurons.
Conclusions. During navigation, many neurons across the brain encode combinations of spatial and non-spatial information. These findings support a distributed representation of space across brain regions, including subcortical structures.

Disclosures: E.H. van Beest: None. **B. Terry:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

PSTR473: Animal Navigation

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Program #/Poster #: PSTR473.16/RR17

Topic: I.09. Spatial Navigation

Support: BRAIN Initiative grants RF1NS113287 and RF1NS126044

Title: Longitudinal Cortical Dynamics of Active Spatial Navigation

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Abstract: Spatial navigation is a fundamental behavior essential for survival, and interrogation of the neuronal dynamics simultaneously during spatial navigation tasks in a physical environment has been challenging. Previously, we developed a robotic cranial exoskeleton capable of supporting the weight of neural recording hardware orders of magnitude heavier and larger than a mouse while still allowing mice to move through a physical space (Hope et al. Nature Methods 2024). In this study, we utilized the cranial exoskeleton equipped with a wide-field neural imaging macroscope to record single-cell calcium activity over 30mm2 of the dorsal cortex while the mice navigate a physical Figure-8 maze arena (n = 6 mice, 12 to 14 recording sessions in each mouse across 47 days). Neural recordings were obtained across the visual, somatosensory, retrospenial, motor and association cortices. In total, we recorded an average of 12,409 cells within each mouse, most tracked across multiple sessions. Principal component analysis revealed that cortical population dynamics create a neural representation mirroring the physical maze structure, with task-relevant transformations that bring reward zones closer together in this latent space. At the single-cell level, we observed regional heterogeneity with visual and retrosplenial cortices showed significantly higher spatial tuning (37% and 35% of cells, respectively) compared to somatosensory and motor regions (22% and 25%). Linear decoders achieved high accuracy (0.89 ± 0.16 R2) in predicting mouse position from population activity both within and across sessions, with patterns of a slow representational drift appearing when decoding across days. Characterizing the temporal evolution of single-cell place-tuning across multiple sessions, we find that neural encodings are less stable in earlier sessions (0.75 ± 0.25 mean R2 in session 1), but that a subset of neurons gradually shift towards a more stable representation of space over time as the mice gain familiarity with the environment (0.90 ± 0.15 mean R2 in subsequent sessions). Furthermore, we observed a consistent decrease in spatial tuning during the first lap (-0.11 ± 0.19 R2) of each session, followed by rapid recovery by the second lap ($p << 0.05$, one-sample t-test), even after familiarization. These results reveal distinct mechanisms for maintaining stable spatial representations despite ongoing neural variability, and identify two timescales of representational change: a slow inter-session drift and a rapid intra-session adaptation that compensates for session-to-session variability.

Disclosures: R. Peters: None. **J. Hope:** None. **M. Feldkamp:** None. **T. Beckerle:** None. **S.B. Kodandaramaiah:** None.

Poster

PSTR473: Animal Navigation

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Program #/Poster #: PSTR473.17/RR18

Topic: I.09. Spatial Navigation

Support: Alexander Von Humboldt

Title: A Unique Somatosensory System for Touch navigation

Authors: *W. LUO[1], S. CHAKRABARTI[2], G. R. LEWIN[3];
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Abstract: Naked mole-rats (Heterocephalus glaber) are one of the most incredible creatures in the animal kingdom. They are a unique eusocial rodent species with extraordinary longevity and able to communicate with each other with versatile colony-specific dialects and can even survive under extreme hypoxia by switching to fructose as a fuel. Their subterranean burrows are large and complex with multiple branching tunnels, which can spread more than 3km, but mole-rats orientate themselves and navigate without reliance on visual cues. However, the underlying mechanisms used by these animals to navigate have not yet been studied. Our results suggest that naked mole-rats utilize their densely innervated body hairs as tactile navigational tools. Behavioral experiment indicates that the deflection of these hairs as they move down narrow tunnels aids in accurate navigation. Additionally, mechanoreceptors innervating these hairs are tuned to certain deflection angles, probably providing directional information feedback. Moreover, these receptors can also fire continuously for minutes in response to static displacement, potentially providing information on time travelled as the hairs remain bent by tunnel walls during movement. Collectively, our findings illuminate the sophisticated tactile-based navigation system employed by naked mole-rats.

Disclosures: W. Luo: None. **S. Chakrabarti:** None. **G.R. Lewin:** None.

Poster

PSTR473: Animal Navigation

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Program #/Poster #: PSTR473.18/SS1

Topic: I.09. Spatial Navigation

Support: Jane Coffin Childs Memorial Fund
HHMI

Title: Activity in the vestibular nucleus during REM sleep resembles that during active freely moving exploration

Authors: *C. PURANDARE[1], G. BOUVIER[2], M. SCANZIANI[3];
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Abstract: During rapid eye movement (REM) sleep our brain generates vivid mental simulations which we call dreams. Despite being isolated from the external world, and motor execution blocked by atonia, this simulated activity of the sleeping brain is often perceptibly indifferent from awake experience. This makes REM sleep a natural behavioral state suitable for the study of mental simulations. Are sensory areas active during REM in the same way they are during wakefulness? We decided to address this question in the vestibular nucleus of the mouse, a brainstem structure that receives primary sensory input from the vestibular organ and whose activity in the awake animals reports head movements.We performed chronic extracellular recordings from the vestibular nucleus with linear probes in unrestrained mice during both wakefulness and sleep. The head movements of the animal were monitored with inertial measurements units affixed to the head and with a top view camera. The vast majority (~70%) of vestibular nucleus neurons were modulated by head movements in either clockwise or counterclockwise direction along the azimuth. The largest fraction responded similarly to movements of the head in either direction and, in most of these neurons, the firing rates increased with head velocity. In a smaller fraction of neurons, the firing rates increased with increasing head velocities in one direction and decreased with increasing head velocities in the opposite direction. A neural decoder trained on the spiking activity of these neurons could decode head velocity above chance levels.During REM sleep neurons in the vestibular nucleus remained active, and the pairwise correlations of their activity resembled that observed in the awake animal. Interestingly, the decoder trained during wakefulness reported head velocities that were often non-zero during REM sleep, despite the immobility of the sleeping animal's head.Our work shows that the vestibular nucleus neurons encode speed and direction of actively performed head movements. Furthermore, we show that population activity during REM sleep resembles that observed during awake head movements. Given its central position to broadcast vestibular activity throughout the brain, this nucleus might play a role in coordinating brain-wide activity during REM sleep.

Disclosures: C. Purandare: None. **G. Bouvier:** None. **M. Scanziani:** None.

Poster

PSTR473: Animal Navigation

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Program #/Poster #: PSTR473.19/SS2

Topic: I.09. Spatial Navigation

Support: UCSF Discovery Fellowship
HHMI

Title: Dynamics of the collicular code for directional turns during navigation

Authors: *C. WILHITE[1], L. M. FRANK[2], M. SCANZIANI[3];
[1]UCSF, SAN FRANCISCO, CA; [2]Departments of Physiol. and Psyciatry, UC San Francisco, San Francisco, CA; [3]Univ. of California, San Francisco, San Francisco, CA

Abstract: Changes in movement direction, like left and right turns, are fundamental building blocks of an animal's behavior as it navigates through its environment. How the superior colliculus (SC), a midbrain structure involved in stimulus triggered orienting movements, encodes changes in movement direction during internally driven behaviors like navigation is not fully understood. Here we recorded from populations of SC neurons as mice navigated a Y-maze. We discovered that a large fraction of neurons not only fired more as the animal turned in one specific direction at the choice point (left or right turn neurons) but, even during straight segments, their activity was modulated by the ongoing left-right head-body oscillation characteristic of locomotion. Interestingly, neurons with opposite turn direction selectivity fired at opposite phases of the head-body oscillation. Furthermore, we discovered that the activity of turn neurons was modulated by hippocampal representations of spatial trajectories that sweep ahead of the animal and orient towards possible left or right future paths. For a given trajectory, turn neurons fired more during trials that contained hippocampal sweeps in their preferred turn direction compared to trials that contained sweeps in their non-preferred turn direction. Together, our results reveal a code for internally driven turns in the SC during navigation that is rhythmically coupled to locomotion and modulated by hippocampal representations of possible future paths.

Disclosures: C. Wilhite: None. **L.M. Frank:** None. **M. Scanziani:** None.

Poster

PSTR473: Animal Navigation

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Program #/Poster #: PSTR473.20/SS3

Topic: I.09. Spatial Navigation

Support: Howard Huges Medical Institute
Human Frontier Science Program

Title: Using visual feedback to walk straight - the contribution of the mammalian visual cortex

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Abstract: Visual feedback is used to guide many motor actions, even ones as simple as walking in a straight line. During locomotion, visual feedback informs course-corrections that maintain heading, but the circuits through which this is achieved in the mammalian brain are unknown. We developed a closed-loop assay to reliably evoke visually guided course-corrections (VGC) in freely locomoting mice. We found that in mice, corrective turns are selectively triggered by the eye experiencing a temporo-nasal shift of the visual environment. Lesioning the visual cortex of one hemisphere mirrored the effect of occluding the contralateral eye. This result indicates that the visual cortices of each hemisphere use visual feedback to trigger course corrections in opposite directions. We show that visually guided course-corrections depend on projections from visual cortex to the ipsilateral zona incerta, a subthalamic nucleus that inhibits the motor output layers of the ipsilateral superior colliculus. Indeed, not only do neurons in the zona incerta respond to visual stimuli in a manner that depends on visual cortex, but blocking synaptic transmission from cortico-recipient zona incerta neurons prevented course-corrective turns. Our study reveals that mice use visual feedback to maintain through an ongoing competition between the left and right visual cortices and identifies a neural circuit from the visual periphery to the motor centers underlying this innate behavior.

Disclosures: G. Atlan: None. **M. Scanziani:** None.

Poster

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Topic: I.09. Spatial Navigation

Support: NIH Fellowship 1F31EY033661-01

Title: From vision to navigation: tecto-cortical control of place field reorganization in the hippocampus

Authors: *J. M. BRENNER[1], S. RUEDIGER[2], C. WILHITE[3], Y. SENZAI[4], M. SCANZIANI[5], R. BELTRAMO[6];
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Abstract: Vision is fundamental to how animals navigate their environment, yet the neural pathways that convey visual inputs to the spatial navigation system remain poorly understood. Lateral higher visual cortical areas (LHVAs) are situated at the crossroads between the superior

colliculus, from which they receive visual information via the tecto-pulvinar pathway, and the hippocampus, where spatial information is represented in maps of place fields. To determine the impact of the tecto-pulvinar-LHVA pathway on these hippocampal representations of space, we trained animals to traverse a linear track with reward locations at each end and alternated blocks of trials under ambient illumination with blocks in near-total darkness (<100 R*/rod/s). Following training, recordings from CA1 during trials in ambient light revealed stable place fields that tiled the track, as expected. Interestingly, shifting to near-total darkness led to a drastic spatial rearrangement of place fields, yielding a new yet stable sequence tiling the track. The original arrangement of place fields was reinstated upon returning to light, after which the rearranged map could be retrieved by returning to darkness. The targeted surgical ablation of LHVAs abolished this rearrangement; that is, the maps in light became identical to the maps in darkness. Chronically silencing the tecto-pulvinar pathway with the conditional expression of tetanus toxin light chain produced a nearly identical effect. In contrast, surgical ablation of the primary visual cortex had little effect on rearrangements of light and dark maps. Thus, LHVAs and the tecto-pulvinar pathway are essential for dynamically updating CA1 spatial representations based on visual input.

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Poster

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Program #/Poster #: PSTR473.22/SS5

Topic: I.09. Spatial Navigation

Support: Simons Collaboration on the Global Brain SCGB 543015
Simons Collaboration on the Global Brain SCGB 543025

Title: Cognition Without Cortex: Rapid Learning, Generalization, and Long-Term Memory in Acortical Mice

Authors: *J. ZHENG[1,1], K. SADORF[2], Z. TURAN[1], M. MEISTER[1];
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Abstract: In humans, the neocortex and hippocampus are central to memory, learning, and cognitive flexibility. To test whether these structures are similarly essential for rodent cognition, we studied an “acortical” mouse mutant born without the dorsal forebrain, lacking hippocampus and most of the neocortex. We tested these mice in two maze tasks: a complex binary-choice labyrinth and a massively reconfigurable arena called the Manhattan Maze. We probed four phases of learning across increasing timescales: exploration leading to reward discovery, rapid learning of an optimal route, long-term memory of the same environment, and generalization to novel mazes. Surprisingly, acortical mice were impaired only during the early exploration phase

but retained other learning capacities. Despite delayed discovery of the reward location in the maze (~3× slower than controls), they exhibited one-shot learning of a short route to the reward, comparable to normal mice. They also rapidly obtained rewards when revisiting the same maze configurations after weeks-long and even months-long gaps. After learning the first maze, they solved new configurations more efficiently, generalizing across both acyclic and cyclic graph structures. Together, these results show that the absence of cortex and hippocampus slows the initial phase of exploration leading to a solution, but does not interfere with rapid exploitation of that solution, long-term memory, or generalization across similar tasks in the long run. We highlight the potential of subcortical circuits to support complex spatial cognition in mice, and suggest a more limited and specific role for the mouse hippocampus in the process of learning.

Disclosures: J. Zheng: None. **K. Sadorf:** None. **Z. Turan:** None. **M. Meister:** None.

Poster

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Topic: I.09. Spatial Navigation

Support: NIH Grant NS121918
Simons Fdn 543015
NIH Grant NS111477

Title: Rodent hippocampus accelerates learning of a cognitive map, but is dispensable while using the map

Authors: *J. WU, C. LOIS, M. MEISTER;
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Abstract: The hippocampus is known to support spatial learning and memory, but its distinct roles during different learning phases remain under debate. While previous studies have demonstrated hippocampal involvement in encoding and retrieval of spatial information, it is unclear whether this engagement is strictly required once an internal representation of space has formed. To directly test this, we observed mice that navigated a complex labyrinth with hidden rewards, and perturbed their hippocampus by chemogenetic silencing in different phases. On first exposure to the labyrinth, control mice begin to explore it more and more efficiently, until they cover the entire environment (20-40 min). That leads to discovery of a hidden reward location. After just ~10 rewards they learn the shortest route to that location. Silencing hippocampus greatly delayed discovery of the reward (by a factor of ~3). The mice traveled in futile repetitive loops that prevented them from efficiently exploring the environment. However, once the reward location was discovered, the animals again learned to exploit it quickly by the shortest route. A third group of mice was first allowed to explore the labyrinth with an intact hippocampus, but with no rewards present. During a subsequent rewarded phase we silenced hippocampus. These

pre-exposed animals efficiently discovered and navigated to the reward location, performing comparably to controls. These results reveal a temporal dissociation in hippocampal function: While the hippocampus assists in the exploratory behavior that builds a cognitive map, it becomes dispensable for reward-guided navigation once that map is acquired.

Disclosures: J. Wu: None. **C. Lois:** None. **M. Meister:** None.

Poster

PSTR474: Observation, Simulation, and Manipulation of Human Brain Through Optical, Pharmacological, and AI Tools

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.01/SS7

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant 5R01NS126282-03

Title: Cortical measurements from acute phase magnetic resonance imaging (MRI) predict post-traumatic epilepsy (PTE)

Authors: *D. JIN[1], B. B. AYVAZ[1], J. WHEELOCK[1], J. APPLETON[2], J. LI[3,4], B. OMAY[2], B. EDLOW[3], B. WESTOVER[5], E. GILMORE[1], J. KIM[1];
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Abstract: PTE is the onset of unprovoked seizures after the 7-day acute phase of traumatic brain injury (TBI). While PTE-related epileptogenesis is believed to involve disruption of the cortex, the quantitative relationship between cortical measurements and PTE is unclear. By leveraging acute phase clinical MRIs to obtain these measurements, we aim to assess their utility in PTE prediction. We retrospectively identified 38 PTE and 93 non-PTE adult TBI patients without prior seizure history. Acute phase T1w images were processed with FreeSurfer v7.4.1 SAMSEG and recon-all to get thickness, thickness standard deviation, and volume measurements for 34 cortical regions in each hemisphere. Lesion masks were made using ScribblePrompt-UNet v0.1.0 to correct for lesions in FreeSurfer processing. 3 sets of MRI features were made: (1) "individual" features created by combining FreeSurfer measurements (averaging thicknesses, pooling standard deviations, summing volumes) across hemispheres, (2) "supergroup" features created by combining individual features by broad anatomic location (4 lobes + insular and cingulate cortices), and (3) "grouped-significant" features created by only including individual features significant ($p<0.05$) in univariate Cox regression when combining by broad location. Univariate Cox regression and multivariate regularized Cox regression with 5-fold cross validation were used to assess PTE prediction. PTE patients had lower volumes of the cingulate cortex and lower volumes and thicknesses of the insular cortex and temporal lobe ($p<0.05$). In univariate analysis, lower thicknesses, greater thickness standard deviations, and lower volumes

predicted PTE ($p<0.05$), with the frontal and temporal lobes being the most commonly involved. In multivariate analysis, grouped-significant features performed better than individual and supergroup features (avg testing c-indices: 0.70, 0.67, 0.63). When using grouped-significant features of a specific measurement type, volumes performed better than thicknesses and similar to thickness standard deviations (avg testing c-indices: 0.65, 0.64, 0.65). In summary, combined measurements of significant cortical regions obtained from acute phase MRI can predict PTE, where lower thicknesses and volumes and greater thickness standard deviations, especially in the frontal and temporal lobes, are associated with increased risk of PTE-related epileptogenesis. This suggests that destruction of certain tissues in the cortex may be central to PTE, with experimental studies needed to determine causative mechanisms. These results can inform TBI management and help hypothesize modes of PTE development.

Disclosures: D. Jin: None. **B.B. Ayvaz:** None. **J. Wheelock:** None. **J. Appleton:** None. **J. Li:** None. **B. Omay:** None. **B. Edlow:** None. **B. Westover:** None. **E. gilmore:** None. **J. Kim:** None.

Poster

PSTR474: Observation, Simulation, and Manipulation of Human Brain Through Optical, Pharmacological, and AI Tools

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.02/SS8

Topic: H.04. Emotion

Title: Psilocybin Disrupts Post Stimulus Suppression of Neural Variability in Human Visual Cortex

Authors: *N. H. HELLER[1], M. K. DOSS[2], G. LOFLAND[3], F. S. BARRETT[3];
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Abstract: Background: Serotonergic psychedelics may disrupt the brain's ability to regulate neural variability, but the temporal dynamics and computational consequences of this disruption remain unclear. We explored the mean-variance relationship in human EEG responses to emotional visual stimuli under placebo and psilocybin across distinct ERP windows. Methods: Participants (N = 18) completed two EEG sessions under placebo and psilocybin in a randomized, double-blind, within-subjects design. Stimuli were emotionally evocative images, presented centrally for 3 seconds at 12° visual angle. Only trials with clean EEG from -500 to +500 ms relative to stimulus onset were analyzed. EEG data were epoched, baseline-corrected, and cleaned using ICA. For each drug condition, we computed trial-wise mean amplitude, across-trial variance (ATV), percent change from baseline variance (%ΔATV), and across-subject correlation between mean amplitude and ATV within ERP-defined windows. Using cluster-corrected paired t-tests comparing post-stimulus placebo and psilocybin time courses, early (74-146 ms: $t = 4.65$, $p = 0.0002$) and late (182-273 ms: $t = -4.95$, $p = 0.0001$) ERP

windows were defined. Results: ATV did not differ significantly between conditions, but %ΔATV diverged. Under placebo, %ΔATV peaked at ~20% during the early window ($t = 2.95$, $p = 0.013$) and returned to baseline. No significant clusters were observed in the late window. The observed suppression of variability shortly after stimulus onset in the placebo condition is consistent with quenching via dynamic gain control. Under psilocybin, %ΔATV rose immediately after stimulus onset, peaked similarly in the early window ($t = 4.85$, $p = 0.002$), but remained elevated throughout the late window (182-273 ms: $t = 3.85$, $p = 0.003$), where it was significantly greater than placebo ($t = 2.46$, $p = 0.025$). Elevated %ΔATV persisted across most of the 0-500 ms window ($t = 3.62$, $p = .007$), indicating sustained disruption of variability suppression. Finally, under placebo, ERP amplitude and %ΔATV were significantly correlated across subjects in both early ($r = -0.53$, $p = 0.026$) and late ($r = 0.65$, $p = 0.006$) windows, indicating that individuals with larger evoked responses also exhibited greater trial-to-trial variability. Under psilocybin, this relationship was transiently present at the start of the early window ($r = -0.56$, $p = 0.017$), but abolished in the late window (no significant clusters), suggesting a late-emerging, subject-specific decoupling of signal and noise. Conclusion: Psilocybin may induce a breakdown in the typical relationship between evoked response magnitude and neural variability.

Disclosures: N.H. Heller: None. **M.K. Doss:** None. **G. Lofland:** None. **F.S. Barrett:** F. Consulting Fees (e.g., advisory boards); Mindstate Design Labs LLC, WavePaths, Ltd, Gilgamesh PharmaceuJcals, Inc..

Poster

PSTR474: Observation, Simulation, and Manipulation of Human Brain Through Optical, Pharmacological, and AI Tools

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.03/SS9

Topic: I.04. Executive Functions

Title: Validity of a smartphone-based finger tapping task for neurodegenerative disorders

Authors: *Z. LI[1], M. SANDERSON-CIMINO[2], M. O'CONNOR[2], A. SADARANGANI[1], J. D. DOWNER[3], R. FREGLY[1], J. TAYLOR[2], A. WISE[6], E. PAOLILLO[1], H. W. HEUER[1], L. FORSBERG[7], B. BOEVE[7], C. SEAMAN[4], A. L. BOXER[8], A. M. STAFFARONI[5]; [1]UCSF, San Francisco, CA; [2]UCSF, San Francsico, CA; [3]Neurol., [4]Epidemiology & Biostatistics, UCSF, San Francisco, CA; [5]UCSF, Half Moon Bay, CA; [6]Univ. of California, Davis, Davis, CA; [7]Mayo Clin., Rochester, MN; [8]Howard Hughes Med. Inst., Dept Biochem, New York, NY

Abstract: Motor disturbances are a clinically relevant feature of many neurological and neurodegenerative syndromes. Digital health technologies for motor assessment could provide a scalable repeatable approach to improve diagnosis and monitoring, especially outside the clinic setting. The ALLFTD Mobile App's smartphone-based finger-tapping test (mApp-FTT) is one

such alternative to traditional in-person testing. In this study, we assessed the validity of the iPhone mApp-FTT in 47 participants (mean age = 67.3 ± 9.4), diagnosed with behavioral variant frontotemporal dementia (n=17), primary progressive aphasia (n=13), mild cognitive and/or behavioral impairment (n=4), progressive supranuclear palsy (n=1), corticobasal syndrome (n=4), Alzheimer's disease syndrome (n=2), clinically normal (n=3), or other non-neurodegenerative syndromes (n=3). The mApp-FTT requires participants to tap for 20 seconds on each of two trials: one with dominant and one with non-dominant hand, if possible. Performance for each hand is summarized as total taps. Participants also completed a gold-standard manual FTT (score: total taps) and a clinician-administered measure of disease severity with motor syndromes (Progressive Supranuclear Palsy Rating Scale; PSPRS). All tasks were completed in person. A subset (n=42) completed finger tapping in the presence of a neurologist, and their performance was classified as normal or abnormal. Pearson and Spearman correlation analyses were conducted to evaluate the associations between tapping metrics and clinical measures. Linear regression models were used to examine differences in total taps by neurological exam finger tapping classification, adjusting for age and sex. Total taps on the smartphone and manual finger tapping tasks were highly correlated for the dominant ($r = 0.71$, 95% CI [0.51, 0.83], $p<0.001$) and non-dominant hands ($r=0.59$, 95% CI [0.36,0.76], $p<0.001$). Patients with finger-tapping impairment during the neurological exam performed significantly worse on the mApp-FTT ($B=-25.45$, 95% CI [-45.31, -5.59], $p<0.05$). Total taps on the mApp-FTT were also associated with total score on the PSPRS ($\rho = -0.64$, 95% CI [-0.80, -0.39], $p < 0.001$). Collectively, these findings support the validity of the digital mApp-FTT, suggesting it may be a promising tool for assessing motor function in neurogenerative conditions. Results should be replicated in larger samples. Future directions include studying the validity of mApp-FTT data collected remotely.

Disclosures: Z. Li: None. **M. Sanderson-cimino:** None. **M. O'Connor:** None. **A. Sadarangani:** None. **J.D. Downer:** None. **R. Fregly:** None. **J. Taylor:** None. **A. Wise:** None. **E. Paolillo:** 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.; received research support from the NIA/NIH and the Alzheimer's Association.. **H.W. Heuer:** None. **L. Forsberg:** None. **B. Boeve:** 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.; received research support from the EIP Pharma, the Transposon, the Cognition Therapeutics, and the Rainwater Charitable Foundation.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); He has received publishing royalties from a publication relating to health care.. **C. Seaman:** None. **A.L. Boxer:** 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.; received research support from the NIA/NIH, the Bluefield Project to Cure FTD, the GHR Foundation and the Rainwater Charitable Foundation.. F. Consulting Fees (e.g., advisory boards); He has provided consultation to Alector, Alexion, Arrowhead, Arvinas, Eli Lilly, Janssen, Merck, Neurocrine, Novartis, Oligomerix, Ono, Oscotec, Switch and Transposon.. Other; He is a scientific cofounder of Neurovanda Therapeutics. **A.M. Staffaroni:** 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.; received research support from the NIA/NIH, the Bluefield Project to Cure FTD, and the Association for Frontotemporal Degeneration.. F. Consulting Fees (e.g., advisory boards); He has provided consultation to Alector, Aviado Bio, Cervomed, Prevail Therapeutics/Eli Lilly, Passage Bio, Takeda, and Vesper Bio.. Other; He received licensing fees for the ALLFTD Mobile App Finger Tapping Task.

Poster

PSTR474: Observation, Simulation, and Manipulation of Human Brain Through Optical, Pharmacological, and AI Tools

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.04/SS10

Topic: J.07. Data Analysis and Statistics

Title: Enhancing clinical trial data extraction using GPT-4, Claude 3.5, and Llama 3.1 in Parkinson's disease research

Authors: *E. CLINTON[1], R. J. YOUNG[1], A. M. MATTHEWS[1], Z. A. RILEY[2], B. POSTON[1]; [1]Univ. of Nevada, Las Vegas, Las Vegas, NV; [2]Indiana University- Indianapolis, Indianapolis, IN

Abstract: The purpose was to evaluate the effectiveness of three advanced Large Language Models (LLMs), specifically GPT-4, Claude 3.5 Sonnet, and Llama 3.1 70B, in extracting clinical trial data involving Parkinson's disease (PD) and transcranial direct current stimulation (tDCS). We developed an automated pipeline utilizing ClinicalTrials.gov's API, where identical trial information formatted in structured JSON schemas was analyzed by each model. Agreement among models was quantified using Cohen's kappa for categorical data and intraclass correlation coefficients (ICC) for continuous data. The analysis identified 64 relevant PD trials involving tDCS, significantly exceeding traditional keyword search yields (28-56 trials). The models demonstrated strong agreement for straightforward attributes such as brain stimulation presence ($\kappa = 0.60$), non-invasive classification ($\kappa = 0.61$), and perfect concordance for stimulation intensity (ICC = 1.00). However, agreement decreased for complex data points such as secondary anatomical targets ($\kappa = 0.61$) and treatment duration (ICC = 0.35). Each LLM exhibited unique strengths: GPT-4 excelled in interpreting complex protocols, Claude 3.5 in extracting precise numerical data, and Llama 3.1 in straightforward classifications. In addition, a consensus-based method incorporating cross-verification and manual review was used to improve data integrity. Overall, the data demonstrated the utility of multiple LLMs in enhancing clinical trial data extraction, particularly for clearly defined parameters, while underscoring the continued importance of human oversight for complex elements. These findings suggest that LLMs provide a promising way for researchers to automate the work intensive processes of traditional review methods such as key word searches and manual data extraction.

Disclosures: E. Clinton: None. **R.J. Young:** A. Employment/Salary (full or part-time): UnitedHealth Group Inc.. **A.M. Matthews:** None. **Z.A. Riley:** None. **B. Poston:** None.

Poster

PSTR474: Observation, Simulation, and Manipulation of Human Brain Through Optical, Pharmacological, and AI Tools

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.05/SS11

Topic: D.04. Brain Injury and Trauma

Title: A nonparametric analysis of fNIRS signals recorded during a visual prediction task

Authors: *K. HOSAKA, H. YOSHIDA, T. KOHAMA;
Grad. Sch. of Biology-Oriented Sci. and Technol., Kindai Univ., Kinokawa / Wakayama, Japan

Abstract: Higher brain dysfunction is an abnormality in cognitive function caused mainly by acquired brain damage. One of the aftereffects of this impairment is the attention dysfunction. In local cities where transportation is scarce, this disorder hinders reintegration into society, and efficient rehabilitation is required to improve driving skills. This impairment can make it difficult for people in local cities, who rely on cars for transportation, to reintegrate into society, as they have a limited ability to drive safely. Therefore, efficient rehabilitation is required to improve driving skills. Experts in the rehabilitation field hypothesize that enhanced predictive function and attentional control lead to improved driving skills, and enhancing activity in brain regions associated with predictive function may shorten the recovery process of driving-related brain function. In this study, we measured brain activity during a visual task using non-invasive and low-constraint functional near-infrared spectroscopy (fNIRS) to develop an efficient rehabilitation method for driving skills. We set up tasks with and without information to predict the target's position and evaluated the differences in the fNIRS signals measured during both tasks. Nine male and female participants in their 20s participated in this experiment. Typical pre-processing methods used in previous studies, such as hemodynamic separation (Yamada et al., 2012) and bandpass filters, were applied to the measured fNIRS signals to obtain the difference between the predictive and non-predictive tasks. According to Endsley's situational awareness model (Endsley, 1995), information processing in the brain during a prediction task involves a stepwise transition from understanding to predicting a situation. Based on this model, we classified the states during the experiments. We then employed an extension of Singh et al.'s (2008) nonparametric statistical method to identify the significant differences between the two tasks at each time point. We selected the channels in which the prediction task was dominant for each participant and mapped the probe position to the corresponding Brodmann area using the NIRS-SPM. The results showed that the brain regions commonly identified as predominant in the prediction task in most participants were Brodmann areas 9 and 10, which are known to be involved in situational judgment and prediction and are consistent with previous findings. These results confirm the validity of the analytical methods used in this study.

Disclosures: K. Hosaka: None. **H. Yoshida:** None. **T. Kohama:** None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.01/SS12

Topic: J.02. Systems Biology and Bioinformatics

Support: NIH Grant U01NS126054

Title: Calcium and RNA multiplexed activity imaging (CaRMA) 2.0: an integrated platform for functional and transcriptomic profiling

Authors: *W. CHEN[1], H. YANG[2], M. LEE[1], H. SURI[1], I. HOSSAIN[1], A. LUKASHEV[1], S. XU[3], M. CUI[4], S. M. STERNSON[1];
[1]UCSD, San Diego, CA; [2]Yale Univ., New Haven, CT; [3]Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai, China; [4]Purdue Univ., West Lafayette, IN

Abstract: Our understanding of how neuronal activity patterns relate to underlying gene expression profiles remains limited. To address this challenge, we previously developed the Calcium and RNA Multiplexed Activity (CaRMA) imaging platform (Xu et al., *Science*, 2020). Here, we present CaRMA 2.0—an enhanced version that integrates two-photon (2P) imaging system with a customized Expansion-Assisted Iterative Fluorescence In Situ Hybridization (EASI-FISH) pipeline (Wang et al., *Cell*, 2022). CaRMA 2.0 employs a custom aberration-corrected objective paired with a custom-designed gradient-index (GRIN) lens, enabling greatly enhanced *in vivo* imaging quality. We have applied CaRMA 2.0 in the lateral hypothalamus. The EASI-FISH protocol allows robust detection of over 27 transcripts within 300-µm-thick brain sections, effectively encompassing the full imaged volume, streamlining and simplifying the original CaRMA imaging workflow. To facilitate spatial correspondence between *in vivo* functional recordings and *ex vivo* gene expression data, we developed a registration pipeline leveraging open-source tools such as Suite2p and BigWarp (FIJI), substantially reducing the manual effort required for region-of-interest (ROI) alignment and annotation. In summary, CaRMA 2.0 provides a scalable, high-resolution framework for linking neuronal activity to molecular identity at the single-cell level, offering a powerful toolset to accelerate discovery in systems neuroscience.

Disclosures: W. Chen: None. **H. Yang:** None. **M. Lee:** None. **H. Suri:** None. **I. Hossain:** None. **A. Lukashev:** None. **S. Xu:** None. **M. Cui:** None. **S.M. Sternson:** None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.02/TT1

Topic: J.02. Systems Biology and Bioinformatics

Title: Integrated Spatial RNA and Protein Profiling in Glioblastoma Reveals Tumor-Neuron Interactions with Xenium in situ

Authors: *W. STAUFFER, T. ZHANG, S. DADHWAL, C. CHRISTOPHERSON, S. PATHARE, H. CHANG, J. HENSEL, C. ESPENEL, V. GONZALEZ MUNOZ;
10x Genomics, Pleasanton, CA

Abstract: Integrated spatial RNA and protein profiling offers a deeper biological understanding of complex tissue architecture and cellular interactions. In glioblastoma (GBM), a highly heterogeneous brain tumor with intricate neuronal crosstalk, such multiomic analysis is particularly critical. GBM is defined not only by diverse tumor subpopulations, but also by its interactions with surrounding neuronal networks—features that are often obscured in single-modality approaches.
Here, we present a method for simultaneous RNA and protein detection using the Xenium In Situ platform, applied to human FFPE glioblastoma samples. This dual-modality assay revealed distinct spatial patterns of RNA and protein expression across tumor regions, highlighting subpopulations that would not have been identified through RNA profiling alone. The integration of protein detection allowed us to map tumor cells embedded within neuronal networks and, importantly, to characterize the corresponding gene expression in these protein-defined regions. These findings demonstrate the power of spatial multiomics in dissecting the cellular and molecular complexity of GBM. By capturing both transcriptomic and proteomic signals within intact tissue, the Xenium platform reveals discordant RNA-protein expression patterns and previously undetected tumor-neuron interactions. When combined with high-resolution post-Xenium H&E imaging, this approach provides a robust framework for studying disease mechanisms in the brain and development of multiomic strategies for characterizing aggressive tumors like glioblastoma.

Disclosures: W. Stauffer: A. Employment/Salary (full or part-time): 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **T. Zhang:** A. Employment/Salary (full or part-time): 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **S. Dadhwal:** A. Employment/Salary (full or part-time): 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **C. Christopherson:** A. Employment/Salary (full or part-time): 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **S. Pathare:** A. Employment/Salary (full or part-time): 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **H. Chang:** A. Employment/Salary (full or part-time): 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **J. Hensel:** A.

Employment/Salary (full or part-time): 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **C. Espenel:** A. Employment/Salary (full or part-time): 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics. **V. Gonzalez Munoz:** A. Employment/Salary (full or part-time): 10x Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10x Genomics.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.03/TT2

Topic: J.02. Systems Biology and Bioinformatics

Support: NIH T-R01
HHMI

Title: Song Nuclei-specific Regulatory Elements Revealed by the Zebra Finch Associated Resource Visualization (ZARVis) Project

Authors: *C. LEE[1], M. H. DAVENPORT[2], C. JOHNSON[1], L. CANTIN[3], C. GILBERT[1], E. D. JARVIS[1];
[1]Rockefeller Univ., New York, NY; [2]Rockefeller Univ., New York City, NY; [3]The Rockefeller Univ., New York, NY

Abstract: Finches' beaks gave Darwin a key insight into the evolution of physical form, and now their brains are providing important clues into the evolution of learned behavior. Zebra finch song learning is produced by four forebrain subregions known as song nuclei (Area X, LMAN, HVC, and RA), which exhibit specialized gene expression patterns compared to adjacent non-vocal brain regions. While many specialized transcripts are known, the cis-regulatory mechanisms underlying these specializations remain largely unexplored, because songbird genome annotations have lacked regulatory element information and have relied primarily on transcription start site (TSS) annotations. In this study, we systematically identified regulatory elements in the zebra finch reference genome (GCF_003957565.2, bTaeGut1.4.pri) by analyzing multi-omics datasets from adult male tissues, including blood, liver, testis, ovary, and brain, encompassing both song nuclei and neighboring non-vocal regions, benchmarking the ENCODE and nf-core frameworks. We validated TSSs in the NCBI RefSeq annotation for promoter assignments using bulk and single-nucleus transcriptome data (RNA-seq, Iso-seq, snRNA-seq), identified regulatory element candidates using DNA methylation (Bisulfite-seq, 5mC HiFi methylation) and chromatin accessibility data (ATAC-seq), and classified these elements as active (H3K27ac, H3K4me3) or repressive (H3K27me3, H3K9me3) based on histone modification profiles. From a comparative genomics perspective, we further explored the

evolutionary origins of these regulatory regions using reference-free, genome-wide CACTUS alignments across 20 avian genomes generated by the Vertebrate Genomes Project. Although some raw sequencing data are not yet publicly available, all key findings—including the identified promoters, enhancers, and repressors with their read coverage, peak and dip signals, and evolutionary dynamics across birds—have been visualized in a publicly accessible UCSC track hub (https://genome.ucsc.edu/s/clee03/ZARVis). This resource lays a foundation for dissecting the cis-regulatory architecture of vocal learning in songbirds and broadens our understanding of brain region-specific regulatory landscapes in evolutionary neuroscience.

Disclosures: C. Lee: None. **M.H. Davenport:** None. **C. Johnson:** None. **L. Cantin:** None. **C. Gilbert:** None. **E.D. Jarvis:** None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.04/TT3

Topic: J.02. Systems Biology and Bioinformatics

Support: Eric and Wendy Schmidt AI in STEM Postdoc Fellowship
R35 GM119850
ACES Innovation Fund

Title: Predicting the effects of genomic variation on cell-cell communication

Authors: *C. M. AAMODT[1], A. MUOTRI[2], K. PIERCE[3], E. COURCHESNE[4], N. LEWIS[1]; [1]Pediatrics, [2]Pediatrics/Cellular Mol. Med., [3]Neurosciences, UC San Diego, La Jolla, CA; [4]Neurosciences, Univ. California San Diego, La Jolla, CA

Abstract: Cell-cell communication is central to complex polygenic phenotypes, but tools for analysis are lacking. Previously our group developed a tool called Tensor:Cell2Cell that models cell-cell communication from single-cell RNA-seq data. Here we expand on this tool by coupling machine learning with tensor decomposition to predict how single nucleotide variants impact cell-cell communication. The tool scans our curated list of variants known and predicted to impact ligand and receptor post-translational modifications and identifies the most salient sets of mutations predicted to impact specific cell types. We demonstrate its utility by applying this tool to autism diagnosis and brain size in donor-derived brain organoids and test for differential enrichment of predicted patterns in genome wide association study summary statistics. This work has the potential to transform our ability to understand the mechanistic basis of complex disorders and efficiently identify the genetic basis of individual traits for precision health.

Disclosures: C.M. Aamodt: None. **A. Muotri:** None. **K. Pierce:** None. **E. Courchesne:** None. **N. Lewis:** None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.05/TT4

Topic: J.02. Systems Biology and Bioinformatics

Support: Parkinson's Foundation Center Grant PF-RC-936279

Title: A Metacell-Integrated Network Framework Reveals Cell-Type-Specific Drivers of Parkinson's Disease

Authors: *L. CHU[1], G. YU[1], X. ZHOU[2], M. WANG[2], Z. YUE[3], B. ZHANG[2];
[2]Genet. and Genomic Sci., [3]Neurol. and Neurosci., [1]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Identifying single cell specific key regulators in Parkinson's Disease (PD) remains challenging due to cellular complexity and technical noise in single-cell RNA sequencing (scRNA-seq). Network-based approaches offer a powerful framework to model gene regulation, but sparsity in scRNA-seq data limits their effectiveness. Here, we introduce a novel metacell-based framework that integrates gene co-expression and causal network analysis in single-nucleus RNA-seq (snRNA-seq) data to overcome these limitations using our previously cohort of 23 idiopathic PD and 9 healthy controls. Our method improves correlation estimates and enables robust detection of key driver genes at cell-type resolution. We recover known disease-associated genes (e.g *UCHL1, NSF*) and identify novel candidates, many of which are not captured by Genome Wide Association Study or understudied in the literature, highlighting new potential targets. Notably, we observe consistent network candidate such as *STMN2* from our bulk RNAseq based network analysis. The added resolution of snRNA-seq also reveals distinct regulatory driver profiles and molecular subnetworks in vulnerable and/or susceptible neuronal and glial subtypes. This framework enables the discovery of both known and novel disease drivers, providing a foundation for future hypothesis-driven studies and therapeutic development for PD.

Disclosures: L. Chu: None. **G. Yu:** None. **X. Zhou:** None. **M. Wang:** None. **Z. Yue:** None. **B. Zhang:** None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.06/TT5

Topic: J.02. Systems Biology and Bioinformatics

Support: AUC Graduate Research Support Grant

Title: Gut and oral microbial signatures of Schizophrenia and Bipolar disorders in Egyptian cohort

Authors: *R. KHALEL, K. RAMADAN ALI ABDELAAL, A. MOUSTAFA;
The American Univ. in Cairo, Cairo, Egypt

Abstract: Recent evidence highlights the gut and oral microbiota as potential modulators of brain function through the oral-gut-brain axis, with associations observed between microbial dysbiosis and the pathophysiology of neuropsychiatric disorders such as schizophrenia (SZ) and bipolar disorder (BD). While dysbiosis has been linked to inflammation and neurotransmitter imbalances commonly found in these conditions, our study focuses on investigating these microbial alterations as correlational biomarkers rather than implying a causal relationship. Notably, previous research has largely centered on Western populations, leaving critical gaps in our understanding of how regional microbiome patterns may differ, particularly in underrepresented areas like the Middle East and North Africa. We present, to the best of our knowledge, the first study on an Egyptian cohort to investigate oral and gut microbiome alterations in SZ and BD. Saliva and stool samples were collected from 120 patients (60 SZ, 60 BD) and 30 matched healthy controls following rigorous inclusion and exclusion criteria, including DSM-5 diagnosis, age 15-65, and exclusion of comorbid psychiatric or gastrointestinal conditions. Samples underwent DNA extraction and 16S rRNA gene sequencing. The results of our differential abundance analyses show clear microbial dysbiosis in both gut and oral microbiomes associated with SZ and BD, with significant differences in community structure and diversity metrics compared to controls. Importantly, the Egyptian cohort formed distinct clusters when compared with international publicly available datasets collected through a secondary analysis pipeline, revealing unique microbial community configurations not observed in global populations. This divergence demonstrates the value of regional representation in psychiatric microbiome research. Our study provides foundational data from an understudied MENA population and offers new insights into microbial signatures potentially relevant to diagnosis and therapy. By integrating region-specific microbiome data with broader global analyses, we aim to contribute to the development of more personalized and effective neuropsychiatric diagnostics and interventions.

Disclosures: R. Khalel: None. **K. Ramadan Ali AbdElaal:** None. **A. Moustafa:** None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.07/TT6

Topic: J.02. Systems Biology and Bioinformatics

Support: DFG

Title: Deep Learning Integration of Multi-Omics Data to Understand Shared Mechanisms in Parkinsons Disease and Inflammatory Bowel Disease.

Authors: *P. GUPTA;
Univ. Clin. Erlangen, Germany, Erlangen, Germany

Abstract: Converging evidence suggests mechanistic overlap between Parkinsons disease (PD) and inflammatory bowel disease (IBD) through immune and metabolic dysregulation. We will develop a deep learning framework to integrate transcriptomic, metabolomic, and proteomic data from PD and IBD cohorts. The model will use autoencoders and attention mechanisms to extract joint low-dimensional representations, enabling robust disease classification and pathway analysis. We will compare performance against traditional integration methods and models trained on individual omics modalities to evaluate the added value of multi-omics integration. We anticipate the identification of shared alterations in amino acid metabolism, mitochondrial dysfunction, and pro-inflammatory signaling. This work will assess the utility of deep learning-based integration for uncovering convergent biological signatures across neurodegenerative and gastrointestinal disorders.

Disclosures: P. Gupta: None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.08/TT7

Topic: J.02. Systems Biology and Bioinformatics

Support: Sex Differences Collaboration, Simons Foundation Autism Research Initiative (734069)
WashU IDDRC NIH P50HD103525
Diabetes Research Center NIH P30 Dk020579
Institute of Clinical and Translational Sciences/NCATS CTSA award UL1 TR002345
Siteman Cancer Center/NCI CCSG Grant P30 CA091842

Title: Utilizing metabolomics to investigate sex variation across early human neurodevelopment

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Abstract: Biological sex influences development from conception, with the combination of sex chromosomes in early embryogenesis setting the framework for sex specification. While genetics

drive sex differentiation during the initial weeks in utero, by week fourteen, gonads have differentiated and are producing hormones like testosterone and estrogen. In particular, pre- and postnatal testosterone surges in males are thought to induce masculinization of brain regions like the hypothalamus and amygdala. However, evidence of this “mini puberty” in humans has primarily been found in saliva and blood, with limited information on how increased testosterone in males affects downstream metabolic and genetic pathways. To better understand the impact of early sex hormones on neurodevelopment, we analyzed human samples from both pre-natal and post-natal periods using LC-MS and a combination of other -omics methods. Our results provide the first brain-specific evidence of the male testosterone surge in utero, along with the influence on downstream metabolomic and genomic pathways. Additionally, we have characterized the molecular landscape of the early brain before and after birth, identifying potential key metabolites at different sensitive periods of neurodevelopment. Overall, our findings offer some of the first comprehensive metabolomic profiles of the early human brain, highlighting potentially functional impacts with relevance to health and disease.

Disclosures: **S.M. Chaturvedi:** A. Employment/Salary (full or part-time): Co-Chair, Sex and Gender Health Collaborative, American Medical Women Association. **E. Jones:** None. **K. Hennick:** None. **J. Kim:** None. **H. Margulies:** None. **M. Son:** None. **N. Marrus:** None. **J.D. Dougherty:** None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.09/TT8

Topic: J.02. Systems Biology and Bioinformatics

Support: U01MH130907

Title: Bridging function and transcriptomics: Cell types and function in the mouse visual cortex

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Abstract: A major goal in neuroscience is to understand how the diverse transcriptomic identities of neurons give rise to their specific functional roles within brain circuits. While we can now categorize neurons based on their molecular makeup, how these distinct cell types contribute to complex processes like sensory processing and learning remains largely unknown. Our research directly addresses this gap by investigating the fine-grained relationship between neuronal identity and in vivo activity in the mouse primary visual cortex (V1). We utilized multiplane two-photon calcium imaging in vivo to record neuronal responses. We then employed

two post-hoc methods to analyze gene expression at single-cell resolution: Hybridization Chain Reaction (HCR) mFISH in thick-tissue samples and the Xenium spatial transcriptomics platform in thin-tissue sections. Using these two methods, we were able to identify a wide array of cell types, including various subclasses and further hierarchical subdivisions. Furthermore, we were able to compare the populations of cell types and variability in gene expression identified using each method. We co-registered these molecularly defined cell populations with their functional activity recorded in vivo using two-photon calcium imaging. This allows us to directly examine how specific transcriptomically defined cells respond to visual stimuli and participate in neural activity during behavioral tasks. By making this direct link, our work aims to illuminate the fundamental contributions of diverse cell types to cortical computations. Ultimately, our goal is to enhance our understanding of how cell types influence brain function, providing a critical framework for future investigations into the mechanisms of neural circuits.

Disclosures: H. Schryver: None. **O. Zobeiri:** None. **M. Davis:** None. **J. Kim:** None. **C. Berry:** None. **S. McCulloch:** None. **A. Williford:** None. **S.R. Olsen:** None. **P.A. Groblewski:** None. **M.E. Garrett:** None. **A. Arkhipov:** None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

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Program #/Poster #: PSTR475.10/TT9

Topic: J.02. Systems Biology and Bioinformatics

Support: NIH R01 NS134722
NIH R01 NS135763

Title: Long term in vivo imaging of transplanted human ipsc-derived neural precursor cells

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Abstract: Stem cell transplantation therapies are emerging as some of the most promising methods for treating an array of neurological and neurodegenerative disorders where the primary cause of pathology is cell death. human Neural Precursor Cells (hNPCs) that are derived from human induced Pluripotent Stem Cells (hiPSCs) to replace neuronal loss are among the most promising of these approaches. For targeted stem cell therapies to be successful, programmed hNPCs must undergo a complex and dynamic set of processes *in vivo* after transplantation, including proliferation, migration, and integration into the existing circuit. The ability to track the changes that hNPCs undergo once in the neocortex, *in vivo* over the lifetime of the animal, will provide key insights into the mechanisms governing transplant integration, as well as the functional impact that transplants have on existing circuits. To address this challenge, I transplanted GFP (LV-CMV-GFP) labeled hNPCs and prepatterned human Neurons (hNeurons) reprogrammed from 2 individuals (M = 34 y.o, F = 51 y.o) into adult SCID mice in the primary

visual cortex (R.C: -4mm, M/L: 2.5 mm, D/L = 200-400 um, N=6 animals). Long term imaging of engrafted hNPCs at intervals between 24 hours and 1 week/animal (N=15 sessions/animal) allowed us to visualize these changes at the level of individual NPCs and neurites. I aligned raw Z-stack data across imaging sessions using a rigid body transform of the original image into a rotated and translated image by maximizing the correlation between the image and the image taken in the previous session . I observed substantial plasticity across imaging sessions, including observing cell migration, cell division, and neurite extensions and retractions Furthermore, when I imaged individual neurites (N=15) over multiple days, I tracked extension and retraction events of over multiple days, revealing the complex structural dynamics that engrafted cells undergo. Taken together, these data suggest that a critical feature for evaluation of the success of transplantation as a therapy is understanding the dynamics of individual transplants; The multi-photon long term imaging method presented offers one powerful way to address this question.

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Poster

PSTR475: Systems Biology and Multiomics Approaches

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Topic: J.02. Systems Biology and Bioinformatics

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R01AG082185
K08MH122911
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BX004189
R01AG065582

Title: Evolutionary tradeoffs in complement component 4 haplotypes

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Abstract: Background/Aims: The major histocompatibility complex (MHC) locus is vital to immune function and harbors the strongest genetic association with schizophrenia. Within MHC, complement component 4 (C4), central to synaptic pruning, supports the “excessive pruning” hypothesis of schizophrenia. We examined distinct C4 haplotypes across the phenome, revealing possible evolutionary tradeoffs. Using the Million Veteran Program (MVP) and United Kingdom Biobank cohorts, we imputed C4 haplotypes in over 900,000 individuals of European and

African ancestry to assess genetic implications and the influence of C4 copy number.
Methods: C4 haplotypes were imputed using Beagle and the Kamitaki et al. (2020) reference panel. Phenome-wide association studies (PheWAS) were performed for haplotypes meeting the threshold of ≥2 occurrences in ≥0.5% of quality-controlled samples per ancestry. We evaluated aggregated z-scores across 18 curated phenotypic categories using two-sample t-tests with FDR correction. Correlation analyses were conducted to compare results across ancestries.
Results: In Europeans, multiple C4 haplotypes showed strong tradeoffs among phenotypic categories. The common C4 BS haplotype is associated with higher musculoskeletal disease risk but lower mental disorder risk ($q \sim 6.57 \times 10^{-9}$). Additional tradeoffs appeared between circulatory and digestive disorders ($q \sim 6.55 \times 10^{-8}$) and endocrine/metabolic vs. digestive disorders ($q \sim 1.77 \times 10^{-6}$). The C4 AL-BS and C4 AL-BS-BS haplotypes displayed distinct associations, notably in the digestive and circulatory systems. We also note high consistency of C4 associations across biobanks. Among African-ancestry individuals, haplotype frequency was markedly different and tradeoffs were less pronounced, though C4 BL-BL showed significant linkage with chronic obstructive asthma.
Conclusions: C4 haplotypes are strongly linked to diverse traits and exhibit notable evolutionary tradeoffs across phenotypic categories. These findings highlight the multifaceted influence of C4 variation on phenotypic diversity, offering key insights into its complex role in genetic risk.

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Poster

PSTR475: Systems Biology and Multiomics Approaches

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Program #/Poster #: PSTR475.12/TT11

Topic: J.02. Systems Biology and Bioinformatics

Support: U01 MH106882-01

Title: Elevated somatic LINE-1 retrotransposition in hippocampal neurons

Authors: *M. CUOCO[1,2], M. WANG[1], I. GALLINA[3], D. R. WEINBERGER[4], J. A. ERWIN[4], E. A. MUKAMEL[5], A. C. PAQUOLA[6], F. H. GAGE[1];
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Abstract: Long interspersed nuclear element-1 (LINE-1 or L1) retrotransposons are mobile genetic elements capable of copying themselves within the genome. Although L1 activity is largely suppressed in most somatic tissues, low-level retrotransposition occurs in human neurons, generating somatic mosaic insertions that can affect neuronal function and contribute to

neurological disorders.To systematically chart this activity, we applied Somatic L1-Associated Variant sequencing (SLAV-seq) to 4,028 single neurons isolated from post-mortem prefrontal-cortex and hippocampal tissue from 37 donors. Leveraging a new peak-calling algorithm that isolates authentic insertion signals from flanking genome amplification artifacts, we nominated 26,856 region-specific peaks as candidate somatic L1 insertions. PCR validation of 15 randomly selected candidates confirmed 12, and—crucially—these candidates displayed endonuclease (EN) target-site motif enrichment that closely matched known non-reference L1 insertions, further supporting their authenticity. The burden of candidate somatic insertions per cell followed a negative-binomial distribution: 733 neurons contained none, whereas progressively fewer cells carried higher loads. Furthermore, insertion counts were independent of library size, total peaks called, and sensitivity to detect known non-reference insertions, indicating minimal technical bias. Mixed-effects modelling additionally revealed a significant enrichment of candidate insertions in hippocampal neurons relative to prefrontal cortex, a pattern driven by a subset of donors who showed pronounced region-specific differences. Collectively, our findings expose substantial donor- and region-dependent heterogeneity in somatic L1 retrotransposition within the human brain. Future efforts that model somatic insertions in vitro with functional genomics will be pivotal for pinpointing the molecular consequences of these insertions and clarifying their roles in neuronal physiology and disease.

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Poster

PSTR475: Systems Biology and Multiomics Approaches

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Program #/Poster #: PSTR475.13/TT12

Topic: J.02. Systems Biology and Bioinformatics

Title: Cross species enhancer codes across neural cell types

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Abstract: Understanding how enhancers drive gene expression in specific neural cell types is fundamental for neuroscience, disease research, and the development of gene therapies. These enhancers are often cloned into AAV viral vectors to achieve targeted expression in desired cell types. Identifying such enhancers is therefore critical for enabling downstream applications. Single-cell ATAC-seq (scATAC-seq) is a high-throughput method that captures chromatin accessibility in individual cells, providing a powerful way to prioritize open chromatin regions that may function as enhancers. However, in complex brain regions like the cortex and basal

ganglia, identifying cell-type-specific enhancers based solely on chromatin accessibility is challenging due to overlapping signals and cellular heterogeneity. This highlights the need to decode enhancer function directly from the underlying DNA sequence.
DNA sequence-to-function machine learning models, as implemented within the CREsted (Cis Regulatory Element Sequence Training, Explanation and Design) framework, are well-suited for this task, as they enable the quantification of sequence feature contributions, motif identification, and the learning of regulatory patterns specific to individual cell types. Using CREsted, we can uncover functional enhancer codes across species, supporting both cross-species generalization and novel regulatory element discovery. By training neural networks on well-annotated cell types in the primary motor cortex, we successfully identified cell type-specific motifs and regulatory codes, which also helped us interpret false positive (Type 1) and false negative (Type 2) errors in enhancer selection. Additionally, we detected both shared and divergent transcription factor motif patterns across cell types and these insights are particularly valuable for the rational design of synthetic enhancers. Building on this foundation, we are now extending our analyses to the basal ganglia, aiming to characterize enhancer codes across multiple cell types and species to reveal both conserved and divergent regulatory logic.

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Poster

PSTR475: Systems Biology and Multiomics Approaches

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Topic: J.02. Systems Biology and Bioinformatics

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Title: Molecular and spatial analysis of ganglion cells on retinal flatmounts: diversity, topography, and perivascularity

Authors: *K. NIMKAR[1], M. ZHAO[2], T. GARRETT[3], Y. WANG[2], F. CAVAL-HOLME[4], A. T. EHRLICH[5], A. R. KRIEGSTEIN[6], M. H. DO[4], Y. HU[7], B. SIVYER[8], X. DUAN[2], K. SHEKHAR[1];
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Abstract: Retinal ganglion cells (RGCs) are feature detectors and the output neurons from the eye to the brain. Transcriptomic studies categorize RGCs into roughly 45 types, with these types showing good correspondence with morphological and functional properties. It is not comprehensively understood how RGC types are spatially distributed on the wholemount retinal surface, nor how local microenvironments may influence function or disease. To address these gaps, we combined imaging-based spatial transcriptomics (MERFISH) and histology on thin flatmount retinal sections. We mapped the somata distributions of all RGC types through image segmentation and stitching. At a global scale, we found most types exhibited non-uniform distributions, suggesting the retina is adapted to sample visual space non-uniformly. Via local neighborhood analysis, we identified seven perivascular RGC types located near blood vessels. These include members of direction-selective RGC (DSGC) and intrinsically photosensitive RGC (ipRGC) subclasses. Finally, we showed that under an elevated intraocular pressure model of glaucoma, surviving RGCs are enriched near the vasculature. In particular, we found perivascular DSGCs and M1 ipRGCs appear to have cell-extrinsic neuroprotection independent of the mTOR pathway. Together, our work provides a comprehensive spatial atlas of RGC types and links microenvironment context to differential vulnerability in neurodegeneration.

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Poster

PSTR475: Systems Biology and Multiomics Approaches

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Program #/Poster #: PSTR475.15/TT14

Topic: J.02. Systems Biology and Bioinformatics

Support: 25-BR-02-01
RS-2024-00431492

Title: Unveiling the proteomic landscape of meningeal fibroblasts: a foundational study for therapeutic targeting in neurological conditions

Authors: *B. HA[1], J.-Y. HEO[1], Y.-J. JANG[1], J. LEE[2], S.-J. JEONG[1];
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Abstract: The membranous meninges, a protective tissue for the brain and spinal cord, consist of diverse cellular components, including fibroblasts, immune cells, hematopoietic cells, and lymphatic vasculature. These layers are fundamental for neuroprotection and orchestrate brain development during embryogenesis. Within the meninges, meningeal fibroblasts (MFs), originating from mesodermal and neural crest embryonic precursors, constitute the dominant cellular population. MFs contribute critically to neuronal migration and cortical morphogenesis through their production of extracellular matrix components, laminins, and integrins, which functionally interact with neuroepithelial and radial glial cells. Despite recent insights, a thorough understanding of MFs' precise roles in central nervous system homeostasis and their pathogenic contributions to neurodegenerative and neurodevelopmental disorders remains incomplete. This knowledge gap underlines the imperative for comprehensive investigations into human MFs to evaluate their viability as therapeutic targets for neurological pathologies. Our current study established MFs cultures derived from the spinal and cerebral dura mater of patients presenting with 6 distinct neurological conditions. We subsequently conducted a comprehensive, label-free, quantitative mass spectrometry-based proteomic analysis. Proteomic analysis revealed unique protein expression profiles between spinal- and cranial-derived MFs, but a significant proportion of identified proteins overlapped in components of cell projection, microtubule cytoskeleton, focal adhesion, cilium, and centrosome. Functional network analysis, utilizing ClueGO/CluPedia, further elucidated distinct functional protein interactions in each disease-specific context. Collectively, the findings from this exploratory study are anticipated to catalyze subsequent cellular and molecular investigations, thereby advancing our mechanistic understanding of this rare meningeal disorder.

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Poster

PSTR475: Systems Biology and Multiomics Approaches

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Program #/Poster #: PSTR475.16/TT15

Topic: J.02. Systems Biology and Bioinformatics

Support: 3OT2OD032619-01S3

Title: Sparc data repository: impact of curation by humans and machines on the quality of metadata

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Abstract: The SPARC (Stimulating Peripheral Activity to Relieve Conditions, RRID:SCR_017041) data repository hosts high-quality data that is highly curated using both human effort and machine-based tooling to ensure quality and completeness of both data and metadata. SPARC datasets can be quite large, and many are multimodal with many techniques represented, such as electrophysiology, microscopy, gene expression, and anatomical and computational models. Datasets can be composed of tens of thousands of small files presenting a challenge in organizing these and any one file can be very large, presenting a challenge in working with individual documents. We were interested in finding out if the process of curation improves the quality of metadata, data and eventual impact of these complex datasets. To address this question, we took advantage of the Pennsieve data platform, which provides the data repository infrastructure for SPARC. Pennsieve is a multi-tenant platform that also hosts data submitted by individual researchers, independent of SPARC. Thus, we compared curated data from SPARC against uncurated data of similar size and complexity hosted on Pennsieve. All datasets are published using a DOI which requires that metadata be deposited in DataCite. These metadata are more complete for datasets in SPARC compared to Pennsieve, with a higher % of author information 94% vs 50%, “describedby” links to other documents such as papers 30% vs 0%, and contacts 100% vs 60%). SPARC datasets adhere to a BIDs-like standard, the SPARC data structure (SDS, RRID:SCR_027028) for file organization; they are structured by investigators with human curator oversight, and using a tool, SODA (RRID:SCR_018996), that helps investigators to structure data on their personal machines, create metadata, upload datasets, and create file manifests which are later used to determine if all files were uploaded. Once uploaded, the dataset is checked using the SDS data format verification pipelines, which detect issues with SDS structure, incomplete metadata and matching of files with subjects, samples and other metadata files. Curators assist data submitters throughout the entire process from initial account curation, to structuring the data to final publication. In the future we will check metadata completeness based on the validation pipeline error report and we will monitor the download metrics and citations of datasets to determine if higher quality of data is indeed used more frequently.

Disclosures: **A. Bandrowski:** A. Employment/Salary (full or part-time): SciCrunch Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch Inc. **A. Pilko:** None. **B. Patel:** None. **J.B. Wagenaar:** None. **J.S. Grethe:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch Inc.. **T. Gillespie:** None. **J. Boline:** A. Employment/Salary (full or part-time): Informed Minds, Inc. **M.E. Martone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc..

Poster

PSTR475: Systems Biology and Multiomics Approaches

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Program #/Poster #: PSTR475.17/TT16

Topic: J.02. Systems Biology and Bioinformatics

Support: 75N97021P00135

Title: A survey of the “dark genome” as defined by an informatics approach, is less likely to be associated with research tools, highlighting higher value protein targets for the study of disease

Authors: *A. E. BANDROWSKI[1], D. DEUTSCH[2], A. PARKER[2];
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Abstract: The dark genome, as defined by those genes that are understudied (Opera, 2024) have been defined to some extent by the Illuminating the Druggable Genome, IDG project (RRID:SCR_016924), which elucidates the identification of understudied genes by detecting the amount of data associated with each gene has been encapsulated into a software package. One goal of this project is to detect genes that are likely to be important for precision medicine but are currently understudied. The KOMP project (RRID:SCR_005571) aims to knock out 8500 genes from mice, to deliver these mice to the research community and to create a highly valuable genotype / phenotype dataset. We do not know how well the presence of a knock out animal, the presence of data as defined by the IDG project, or the availability of tools like antibodies and plasmids impact the attention of researchers on specific genes.
First we wanted to enhance our understanding of the dark genome. We downloaded the list of mouse genes and a list of manuscripts associated with mouse genes from the NCBI gene (RRID:SCR_002473). After the compilation of the full list of mouse genes, we queried the scicrunch.org Application Programming Interface, API, to determine which antibodies, plasmids and mice were available for scientists to use for which genes. We will present the data in a histogram where gaps in research tools will be highlighted and genes that seem to have significant associated tooling will be shown as a set of genes that should be able to be explored. Areas in which few papers exist, but tools are available will be highlighted.
We explore correlations between the dark genome definitions and show areas that do not match. We also explore different gene categories represented in the IDG database in an attempt to find dark genes which are promisingly related to an otherwise well-studied family. The output is a survey of key data about the less studied genes that are likely to be interesting targets for the study of disease.
Oprea, T.I. Exploring the dark genome: implications for precision medicine. Mamm Genome 30, 192-200 (2019). https://doi.org/10.1007/s00335-019-09809-0

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Poster

PSTR475: Systems Biology and Multiomics Approaches

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Program #/Poster #: PSTR475.19/TT18

Topic: J.02. Systems Biology and Bioinformatics

Title: High-plex spatial proteomics for neuroscience identifies single-cell and spatial niches in neurodegenerative cortical tissues

Authors: *D. JIMENEZ SANCHEZ[1], L. SCHUETZ[2], M. INGALLS[1], F. SVARA[2], A. NORTHCUTT[1], O. BRAUBACH[1];
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Abstract: Spatial proteomics has revolutionized our understanding of tissue biology and is poised to transform neuroscience. To this end, robust workflows are required to (1) generate spatial proteomic data for neuronal tissues and (2) analyze these data to yield single-cell level insights, including the spatial relationships of individual cells to extracellular aggregates -also named spatial niches or spatial neighborhoods. We present a quantitative multiplex immunofluorescence approach to study brain tissues using the CellScape™ Precise Spatial Multiplexing platform. Tissues are mounted on standard microscope slides and then enclosed in microfluidic chambers for immediate use or long-term storage. Staining and imaging are then conducted automatically, on-instrument, and in real-time. With the facilitation of cell profiling and spatial analysis in mind, we developed an antibody panel consisting of neuronal, glial, vascular, and cellular architecture markers for use in human and mouse tissue samples. Computational analysis of multiplex imaging data in brain tissue is particularly challenging due to the complex and diverse morphologies of neurons and glia. Precise cell segmentation is required to capture fine cellular arborizations to ensure that multiplexed marker signals are mapped correctly to individual cells. Furthermore, diverse cellular and extracellular aggregates characterize neural tissue structure in tissue affected by a number of neurodegenerative disorders. To address these challenges, we utilize Ariadne.ai's SPATIAL™ platform, which enables the precise segmentation of brain cells, including markers such as IBA1, NeuN and GFAP. The platform supports the detection and pathological classification of protein aggregates, integrating both cellular and extracellular information to map tissue microstructure and discover spatial biomarkers associated with both disease and normal function.

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Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.20/UU1

Topic: J.02. Systems Biology and Bioinformatics

Title: Recent Advances In Molecular Mechanisms of MicroRNAs in Pathogenesis of Glioblastoma: A Narrative Review

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Abstract: OBJECTIVE: To understand how molecular and epigenetic factors drive progression and therapy resistance in Glioblastoma and summarize relevant findings from recent literature. BACKGROUND: Glioblastoma (GBM) is the most common and fatal form of brain cancer. Despite advancements in treatments, the average survival is 12 to 15 months. This dire prognosis is largely due to its recurrence rates, tumor invasiveness, and resistance to standard therapies, highlighting the need for a deeper understanding of the molecular physiology that drives GBM. Micro(mi)RNAs have emerged in cancer research as crucial regulators that play vital roles in tumor onset, growth, and resistance to therapy in GBM. DESIGN/METHODS: Systematic retrieval of information using specific keywords was performed on PubMed, Embase, and Google Scholar. To study recent advances, only articles from 2019 to 2024 were included, duplicates were removed, and articles not related to the title were excluded. Relevant data from appropriate studies were entered into a database and used in this article. RESULTS: miRNAs interact with key signaling pathways, epigenetic modifiers, and circRNAs to regulate tumor growth, invasion, and resistance. Genetic and epigenetic changes, such as DNA methylation, MGMT hypermethylation, p53 transactivation, and mutations in EGFR and PDGFR, along with signaling pathways like Notch, Hedgehog, Wnt/β-catenin, PI3K/Akt/mTOR, and immune-related epigenetic modifications, all influence GBM progression. This review discusses clinical trials targeting these mechanisms, their future implications, and identifies potential biomarkers and therapeutic targets, such as miR-21-5p and miR-34a, which show promise in restoring gene regulation and sensitizing tumors to treatment in preclinical models. CONCLUSIONS: The heterogeneity of GBM tumors and their ability to develop resistance highlight the need for further research. The potential for novel therapeutic strategies, particularly in miRNA-targeting and immune modulation, provides a promising frontier in the management of this challenging tumor.

Disclosures: S. Patnala: None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.21/UU2

Topic: J.02. Systems Biology and Bioinformatics

Support: This work was supported by NIH Common Fund award 3OT2OD030541 from the Office of the Director through the Stimulating Peripheral Activity to Relieve Conditions program (SPARC Project, RRID:SCR 017041)

Title: Sckan: a semantic knowledgebase for modeling and exploring multiscale neural connectivity of the autonomic nervous system

Authors: F. T. IMAM[1], T. GILLESPIE[1], I. ZIOGAS[3], M. C. SURLES-ZEIGLER[1], B. DE BONO[4], I. OZYURT[1], D. DEL PIANO[5], G. IDILI[5], J. BOLINE[6], S. TAPPAN[7], *J. S. GRETHE[2], M. E. MARTONE[1];
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Abstract: As part of the NIH Common Fund's Stimulating Peripheral Activity to Relieve Conditions (SPARC) program, we developed SCKAN, the SPARC Connectivity Knowledgebase of the Autonomic Nervous System (ANS), to enhance understanding of ANS connectivity for bioelectronic medicine. It is a highly curated, dynamic knowledgebase designed to systematically capture, organize, and formalize evidence-based connectivity information across multiple scales.
Built using the Neuron Phenotype Ontology (NPO), SCKAN models connectivity at the neuron population level, where each population is defined by shared phenotypic properties of neural pathways rather than specific cell types. SCKAN is continually enhanced with knowledge extracted from open-access literature sources via an NLP-supported pipeline and integrated through a rigorous curation process. Central to curation is the SCKAN Composer, a web-based tool that replaces error-prone manual approaches with a tractable pipeline for constructing, validating, and formalizing connectivity statements with detailed phenotypic specificity and provenance for expert review. SCKAN currently includes 467 neuron populations across major ANS and sensory-motor pathways, covering major mammalian end organs.
SCKAN is a powerful resource for populating, reasoning over, and querying connectivity across multiple scales. While accessible through SPARC's interactive connectivity maps (https://sparc.science/apps/maps), the complexity of neural pathways in SCKAN cannot be fully accessed through a single interface. To address this, we developed a suite of tools for different user communities. These include: SCKAN Explorer for curators to rapidly verify SCKAN contents; Simple SCKAN, a query-friendly layer of SCKAN for developers; and the SCKANNER interface for advanced visualization and summarization for researchers. To achieve a versatile interface for SCKAN, we developed SCKAN NLI, an AI-based interface powered by large language models. Using Retrieval-Augmented Generation (RAG), it synthesizes accurate, relevant responses from SCKAN data. SCKAN NLI supports natural language queries with varying granularities for pathway summarization, diagram generation, and deeper insights. It now includes features for tracing sympathetic and parasympathetic innervations to specific organs and identifying pre- and post-ganglionic synaptic connections.
This poster highlights the maturation of SCKAN and recent updates to its tools, which collectively support discovery, validation, and visualization of neural pathways, advancing research in neuromodulation therapies and broader biomedical applications.

Disclosures: F.T. Imam: None. **T. Gillespie:** None. **I. Ziogas:** None. **M.C. Surles-Zeigler:** None. **B. de Bono:** None. **I. Ozyurt:** None. **D. Del Piano:** None. **G. Idili:** None. **J. Boline:** None. **S. Tappan:** None. **J.S. Grethe:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds);

SciCrunch Inc. **M.E. Martone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch Inc..

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.22/UU3

Topic: J.02. Systems Biology and Bioinformatics

Support: 1U19MH114830-01

Title: Conserved and Divergent Neuronal Identities in the Medulla and Spinal Cord of the Mouse CNS

Authors: *J. XIE[1], Y. GAO[1], K. JIN[4], C. LEE[5], M. HOOPER[1], T. CARDENAS[1], T. CASPER[7], A. CHAKKA[2], R. CHAKRABARTY[1], M. CLARK[1], R. FERRER[1], J. GOLDY[6], J. GUZMAN[1], K. JAMES[1], M. JUNGERT[1], R. A. MCCUE[3], E. PHILLIPS[1], A. RUIZ[2], A. TORKELSON[1], N. DEE[7], K. SMITH[1], H. ZENG[7], Z. YAO[7], C. VAN VELTHOVEN[1];
[2]Mol. Biol., [3]Tissue Processing, [1]Allen Inst., Seattle, WA; [4]Mol. Genet., [5]Modeling Analysis and Theory, [6]BiCore, Allen Inst. For Brain Sci., Seattle, WA; [7]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Understanding the organization and diversity of cell types across the central nervous system (CNS) is essential for uncovering principles of neural function. Here, we present a comprehensive analysis of conserved and divergent cell type signatures in the caudal medulla and spinal cord of the adult mouse (P56). Our dataset includes 205,815 nuclei collected from the caudal medulla and spinal cord, and data were generated using the 10x Genomics v3 and 10x Genomics Multiome platforms. Through integration with multiple published studies (502,737 nuclei), we identified a core set of conserved neuronal and non-neuronal high-resolution cell types shared across these regions, including molecularly distinct subclasses of neuronal and non-neuronal cells, as well as region-specific specializations that reflect their distinct physiological roles. For example, excitatory and inhibitory cell types found in dorsal or ventral regions of spinal cord are also present in the caudal medulla and show similar dorsal/ventral spatial patterns across the regions. Well-defined Chat-positive neurons present in the spinal cord are also observed in the caudal medulla. Cross-region comparisons revealed shared transcriptional programs, signaling modules, and gene regulatory networks that likely contribute to the maintenance of conserved cell identities and circuit features. Despite broad conservation, each region also exhibited unique gene expression and chromatin accessibility profiles reflecting local functional specialization. To place the identified cell types in a spatial context and assess their relative abundance, we used the Molecular Cartography spatial transcriptomics platform with a panel of 100 genes. Collectively, this work provides a foundational reference for understanding cellular composition and molecular architecture in the brain stem and spinal cord regions of the mouse CNS.

Disclosures: J. Xie: None. **Y. Gao:** None. **K. Jin:** None. **C. Lee:** None. **M. Hooper:** None. **T. Cardenas:** None. **T. Casper:** None. **A. Chakka:** None. **R. Chakrabarty:** None. **M. Clark:** None. **R. Ferrer:** None. **J. Goldy:** None. **J. Guzman:** None. **K. James:** None. **M. Jungert:** None. **R.A. McCue:** None. **E. Phillips:** None. **A. Ruiz:** None. **A. Torkelson:** None. **N. Dee:** None. **K. Smith:** None. **H. Zeng:** Other; H.Z. is on the scientific advisory board of MapLight Therapeutics, Inc.. **Z. Yao:** None. **C. van Velthoven:** None.

Poster

PSTR475: Systems Biology and Multiomics Approaches

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.23/UU4

Topic: J.02. Systems Biology and Bioinformatics

Support: Howard Hughes Medical Institute
Rockefeller University

Title: Gene regulation of the vocal learning song circuit via three-dimensional genomic organization

Authors: *C. A. JOHNSON, M. H. DAVENPORT, L. CANTIN, C. LEE, E. D. JARVIS; Rockefeller Univ., New York, NY

Abstract: Vocal learning in Australian zebra finches (Taeniopygia castanotis) is produced by four discrete regions of the forebrain. Transcriptome analyses of these brain regions-called song nuclei-have revealed several thousand genes with specialized expression compared to surrounding non-song tissue. Further epigenetic analysis revealed differential open chromatin in the song nuclei compared to surrounding regions. Despite ample data describing the specialized expression of these vocal-learning-associated (VLA) genes, the cis-regulatory mechanisms remain largely unknown. Here, we combine measurements of chromatin accessibility and DNA-DNA interactions to quantify specialization in the 3D cis-regulatory environment of song nuclei compared to non-song controls. We find that promoter-bound DNA-DNA contacts overlap with differential open chromatin peaks and active transcription regions in a tissue-specific manner. We then combine these data with single-nucleus RNA measurements of expression specialization to reconstruct the song-specific promoter-enhancer connections regulating specialized genes. This work serves as a proof-of-concept that intrachromosomal contacts can, in part, explain the specialized expression of VLA genes.

Disclosures: C.A. Johnson: None. **M.H. Davenport:** None. **L. Cantin:** None. **C. Lee:** None. **E.D. Jarvis:** None.

Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.01/UU5

Topic: J.04. Physiological Methods

Title: Personalized brain network mapping reveals thermosensory pathways as novel DBS targets in refractory chronic pain.

Authors: *P. D. MCGEOCH[1,2], Y. HUANG[2], N. KABOODVAND[1], T. LIU[1], B. REID[1], A. CHIBUKHCHYAN[1], K. PATRON[1], L. YAMADA[3], A. FOGARTY[1], C. ROLLE[1], J. PARK[4], M. POLAT[2], A. G. RAMAYYA[1], P. NUYUJUKIAN[5,2,6,7,8], K. DEISSEROTH[9,10,11], V. BUCH[2,7]; [2]Neurosurg., [1]Stanford Univ., Palo Alto, CA; [3]Electrical Engin., Stanford Univ., Stanford, CA; [4]Palo Alto, Stanford Univ., Palo Alto, CA; [5]Bioengineering, Stanford Univ., Stanford, CA; [6]Electrical Engin., [7]Human Neural Circuitry (HNC) Program, [8]Wu Tsai Neurosciences, Stanford Univ., Palo Alto, CA; [9]Human Neural Circuitry (HNC) Program, Stanford Univ., Stanford, CA; [10]Bioengineering, [11]Psychiatry, Stanford Univ., Palo Alto, CA

Abstract: Deep brain stimulation (DBS) for treatment-refractory chronic pain syndromes holds significant promise. However, clinical trial outcomes in this area have been confounded by heterogeneous target selection and inclusion of patients with a broad range of diagnoses. As part of an innovative clinical care protocol in the setting of our Human Neural Circuitry Program, we carried out multisite intracranial stereo-EEG mapping of the pain network in a 43-year-old female patient with treatment-resistant bilateral anesthesia dolorosa (AD). Her facial pain, which was worse on the left, had developed as a complication of treatment for bilateral trigeminal neuralgia. Stimulating through the sEEG electrodes revealed multiple therapeutic nodes across nociceptive, affective, and notably, thermosensory pathways. Among these, the posterior portion of the ventral medial nucleus (VMpo) - a pain- and temperature-specific relay in the thalamus - and its cortical projection target in the dorsal posterior insula (dpIns), were identified as novel and highly effective targets for pain modulation. Acute stimulation of these sites reliably reduced pain intensity and, in the case of the dpIns, subjective unpleasantness. Guided by these observations, and informed by electrophysiological biomarkers and functional connectivity, we implanted four DBS leads to capture the following targets: right VMpo/periventricular gray (PVG); right dpIns; right anterior cingulate cortex; and left VMpo/PVG. Stimulation via these DBS leads allowed sustained and substantial pain relief, as well as improved thermal pain thresholds, as assessed by quantitative sensory testing, at 12-month follow-up. This suggests that targeting of thermosensory pathways, specifically, VMpo and dpIns, could be a novel, effective and durable means of treating AD, and possibly other related pain syndromes. We observed that turning off the left VMpo/PVG lead exacerbated pain in the left face, while turning it back on reduced left pain. This effect was reproducible, and right VMpo/PVG stimulation similarly relieved ipsilateral pain. Hemispheric imbalance in temperature perception is thought to contribute to the pathogenesis of central post-stroke pain (CPSP), and may explain reports of “analgesic” second strokes in the contralateral hemisphere reducing pain. Similar mechanisms may also be involved in AD. Together, these data suggest a role for bilateral, rather than conventional contralateral, DBS in refractory pain syndromes, and illustrate an approach to

invasive functional brain mapping to discover definitive treatments across the broad spectrum of neuropsychiatric diseases.

Disclosures: P.D. McGeoch: None. **Y. Huang:** None. **N. kaboodvand:** None. **T. Liu:** None. **B. Reid:** None. **A. Chibukhchyan:** None. **K. Patron:** None. **L. Yamada:** None. **A. Fogarty:** None. **C. Rolle:** None. **J. Park:** None. **M. Polat:** None. **A.G. Ramayya:** None. **P. Nuyujukian:** None. **K. Deisseroth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics, Cargo Therapeutics. F. Consulting Fees (e.g., advisory boards); Allen Institute, Modulight, RedTree. **V. Buch:** None.

Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.02/UU6

Topic: J.04. Physiological Methods

Support: Gatsby Foundation
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Title: Ketamine increases hippocampal theta oscillations and alters hippocampal-cortical phase locking

Authors: *E. SOLOMON[1,2], T. LIU[2,3], I. KAUVAR[2], S. VESUNA[1,2], A. CHIBUKHCHYAN[2], P. MUKUNDA[2], L. YAMADA[2,3], A. FOGARTY[2,3], P. NUYUJUKIAN[3,4,5,2,6], C. I. RODRIGUEZ[1,2], V. BUCH[4,2], K. DEISSEROTH[1,7,2,3];
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Abstract: The NMDA receptor antagonist ketamine induces profound changes in sensory experience and cognition, including dissociation, alterations in spatial awareness, perceptual disturbances, and amnesia. Prior animal work found that ketamine affects hippocampal electrophysiology, altering properties of the endogenous oscillations that organize cellular activity during memory and navigation tasks. However, it is not known whether ketamine exerts similar effects in humans and whether it alters the hippocampal-neocortical dialogue. Here, we recorded intracranial EEG (iEEG) from neurosurgical patients while giving IV ketamine to assess for changes in hippocampal oscillations and cortical connectivity. We recruited 19 neurosurgical patients with indwelling electrodes and recorded neural activity while they

received IV infusions of ketamine (0.5mg/kg) over a 40-minute interval. iEEG signals were analyzed using oscillation-detection algorithms to understand the neural response to ketamine across the theta (3-8Hz), alpha (9-13Hz), beta (15-25Hz), and gamma (30-55Hz) bands. Phase analyses were conducted to assess connectivity between the hippocampus and cortex, with a focus on how ketamine might change the global structure of hippocampal-cortical networks. Relative to pre-infusion baseline, ketamine significantly increased the occurrence of hippocampal theta oscillations (t-test, $T(17)=4.78$, $p<0.001$) and decreased beta ($T(17)=-4.27$, $p<0.001$), but caused no significant change in the rate of alpha or gamma oscillations. Phase locking was broadly increased between the cortex and medial temporal lobe ($z=5.3$, $p<0.01$, nonparametric), implicating the medial temporal lobe complex as a hub of ketamine-induced theta connectivity. However, while phase locking was increased overall, we further observed a phase shift between the hippocampus and a frontoparietal network that suggested a change in the relative timing of oscillations between regions. These results suggest ketamine may exert effects on spatial awareness and episodic memory through alterations in the fundamental rhythms that organize hippocampal-neocortical information processing.

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Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.03/UU7

Topic: J.04. Physiological Methods

Support: Stanford Neurochoice Initiative
HHMI
Duhamel Addiction Medicine

Title: Insular input to accumbens induces avoidance behavior in rats and is associated with trait-like risk avoidance in humans

Authors: *L. MORTAZAVI[1], F. GORE[2], Y. YAN[3], M. HERNANDEZ[2], A. DADIOTIS[4], B. D. KNUTSON[5], K. DEISSEROTH[6];
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Abstract: Identifying reliable neurophenotypes for psychistric symptoms has long been a central aim of neuroscience and neuroimaging research, but remains a significant challenge. Here, we aim to assess the convergence of candidate neurophenotypes across structural and functional imaging modalities in humans and to validate causal involvement of the relevant pathway in motivated behavior in rodent models. Specifically, we test whether anterior insula (AIns) activity during risky choice is associated with AIns activity during loss anticipation -previously shown to prospectively predict risk for relapse in stimulant users, and whether these functional measures relate to the structural coherence of the AIns-Nucleus Accumbens (NAcc) white-matter tract and to real-life measures of risk taking of humans. In a multimodal MRI study of healthy adults (N=53, 24 females, 26.6±6.4 years old), we find that activity of AIns during pre-choice phase of gambles is highly correlated with AIns activity during loss anticipation (R=0.47, p=.0003) and this association is specific to loss but not gain anticipation. Coherence of the AIns-NAcc white-matter tract as measured by diffusion MRI was in fact associated with activity of AIns during gambles (R=0.30, p=.022) and during loss anticipation (R=0.30, p=.023), consistent with a route of influence on motivation and behavior. Validating a real-life indication of this pathway in risky choice, we find that individuals with higher AIns activity during both tasks tend to have lower cumulative debt (gambles: β=-3.23, p=.001; loss anticipation: β=-3.76, p=.0002) - an effect that explains variance in debt above and beyond financial, demographic, and behavioral measures. To test whether activity in the AIns-NAcc pathway causally modulates motivated behavior, we first characterized this pathway in rat models anatomically by combining diffusion MRI with viral tracing and light sheet microscopy, and next characterized its properties functionally with optogenetics. After validating the existence of a tract between AIns-NAcc in rats, we found that optogenetic stimulation of the AIns input to NAcc induces place aversion in a real-time place preference assay (t(16)=2.01, p=.03) and inhibits feeding approach in a novelty suppressed feeding task (latency: t(18)=2.09, p=.026; feeding time: t(18)=-2.34, p=.016). These findings suggest a causal role for the AIns-NAcc tract in avoidance motivation. Together, this evidence supports the stability and trait-like measurement quality of the AIns tract in humans, and offer a translational path for developing interventions aimed at conserved mechanisms of dysregulated motivation.

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Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.04/UU8

Topic: J.04. Physiological Methods

Support: P50DA042012
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AE Foundation
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Title: Synchronizing Invasive Neural Recording, Fast Behavioral Readouts, and IV Medication Administration in the Inpatient Hospital Setting: Clinical Protocol Design in the Human Neural Circuitry (HNC) Program

Authors: T. LIU[1,8], **I. KAUVAR**[1,8,9], S. VESUNA[2,8], A. CHIBUKHCHYAN[1,8], L. YAMADA[3,8,4], A. FOGARTY[5,8,4,6], E. SOLOMON[5,8], E. CHOI[4,8], P. MUKUNDA[2], D. GIL-HERNANDEZ[2,8], K. PATRON[1,8], A. MITRA[2,8], P. VAN ROESSEL[2,8], B. D. HEIFETS[7,8], *C. I. RODRIGUEZ[5,10,8], V. BUCH[4,8], P. NUYUJUKIAN[1,4,3,8], K. DEISSEROTH[1,2,11,8];
[1]Bioengineering, [2]Psychiatry and Behavioral Sci., [3]Electrical Engin., [4]Neurosurg., [6]Neurol. and Neurolog. Sci., [7]Anesthesiol., [5]Stanford Univ., Stanford, CA; [8]Human Neural Circuitry Program, Stanford, CA; [9]Grad. Sch. of Educ., Stanford, CA; [10]Veteran Affairs Palo Alto Hlth. Care Syst., Palo Alto, CA; [11]Howard Hughes Med. Inst., Stanford, CA

Abstract: While substantial opportunity exists for deep insights into human brain function with intracranially-implanted human participants, careful clinical protocol design is essential for safely, ethically, and effectively achieving this goal. To investigate the principles underlying the emergence of lasting emotional states from brief sensory input, we integrated subjective verbal reporting, deep brain-wide electrophysiological measurement, fast and repeatable behavioral readout, and medication-based intervention in adults implanted with intracranial recording electrodes. Here we present the design, safety, and initial scientific outcomes from the first stage of this work, during which we integrated 40 min 0.5 mg/kg continuous ketamine infusions with precise behavioral perturbations in human participants with intracranial stereo-electroencephalography recordings. This research platform enabled insights via the synchronization of behavioral and neural measures across multiple time scales. (1) By administering psychiatric instruments multiple times during and around the ketamine infusion, we saw that iEEG patients self-reported increases in dissociation during ketamine (Clinician-Administered Dissociative States Scale, CADSS, $p < 0.001$, N=17, paired t-test) which showed substantial variation in the exact combinations of symptoms. Synchronized intracranial recordings during the entire ketamine infusion identified large scale changes in aperiodic and periodic spectral power that lasted for tens of minutes, including the emergence of band-limited low frequency oscillations. (2) On a faster timescale, we administered an assay consisting of puffs of air delivered to the cornea by a clinical tonometer, capturing how the fast timescale emergence of emotional states was altered by the ketamine infusion. Millisecond-level synchronized neural recordings and transient pharmacological intervention revealed general insights into the multiphasic emergence of emotional state from transient sensory stimuli. The initial study was completed with sufficient power to meet first-stage goals of the study, opening the door to next-stage discovery.

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Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.05/UU9

Topic: J.04. Physiological Methods

Support: NIH U19NS118284

Title: Digital infrastructure for intracortical clinical neuroscience

Authors: *L. YAMADA[1,2,3,4], C. I. RODRIGUEZ[2,5,8], V. BUCH[2,4], K. DEISSEROTH[2,6,1,5], P. NUYUJUKIAN[1,4,3,2,7];
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Abstract: Systems neuroscience has been transformed over the last twenty years by high-temporal resolution multichannel neuroelectrophysiology tightly synchronized to behavior. This approach has been at the core of fundamental new insights in animal studies and a slowly growing number of human studies. Unfortunately, the barrier to maximizing impact of neuroelectrophysiology for clinical and basic discovery in neuroscience remains high, due, in part, to the administrative and technical complexities associated with acquiring data from the hospital. Here we describe full implementation[1] of digital infrastructure that minimizes the burden of clinical neuroscience research in a hospital setting. We previously interfaced directly with the hospital network and placed dedicated research systems in hospital server rooms to acquire neural data streams with minimal clinical interruption[2,3]. As part of the Stanford Human Neural Circuitry Program, we deployed a dedicated research network at both adult and pediatric

hospitals at Stanford, with a minimum of 50 Gbps single-mode fiber per patient room and a 200 Gbps fiber uplink to an on-campus, PHI-compatible, server colocation facility. This network yielded round-trip latencies of less than 1 ms, compatible with realtime computation and brain-machine interface research. Neuroelectrophysiology and behavior is synchronized with sub-microsecond precision using PTP and streamed to on-premises or cloud storage. This infrastructure supports the flexible acquisition of large-scale human participant data[1,2,4,5].

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[2]Yamada, et al., PLOS ONE, 2024
[3]Vesuna*, Kauvar*, et al., Nature, 2020
[4]Qing, et al., J Clin Neurophysiology, 2025
[5]Yamada, et al., IEEE TBME, in press

Disclosures: L. Yamada: None. **C.I. Rodriguez:** A. Employment/Salary (full or part-time): The American Journal of Psychiatry, Neuropsychopharmacology. 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.; Biohaven. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); American Psychiatric Association Publishing. F. Consulting Fees (e.g., advisory boards); Biohaven, Osmind, Biogen. **V. Buch:** None. **K. Deisseroth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics, Cargo Therapeutics. F. Consulting Fees (e.g., advisory boards); Allen Institute, Modulight, RedTree. **P. Nuyujukian:** None.

Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.06/UU10

Topic: J.04. Physiological Methods

Title: miniOEG - a miniaturized macroscope for flexible and robust brain activity interrogation during naturalistic behavior

Authors: *A. D. WHITE[1], Y. WANG[4], J. KOCHALKA[2], M. LIU[1], B. ESHAGHI GHARAGOZ[1], M. K. LO[1], S. QUIRIN[3], K. DEISSEROTH[5];
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Abstract: Here we present the miniOEG - a miniaturized macroscope for optoencephalography (OEG) with a 10x10mm field of view that weighs less than 5g and can record and manipulate cell-type specific neural activity across the dorsal cortex of a freely moving mouse. The new

scope has the sensitivity to resolve single trial neural activity, the spatial resolution to capture sub-regional structures, and the spectral resolution to record in multiple colors. The miniOEG capabilities are further enhanced via a second, independent optical path capable of point-and-shoot optogenetic control. Two-color imaging and simultaneous optogenetic stimulation are achievable at frame rates exceeding 40Hz with 256x256 pixel resolution. To validate the imaging capabilities of the miniOEG, we demonstrate retinotopic mapping in visual cortex as well as pan-cortical functional connectivity mapping in freely behaving animals (CaMKIIalpha-Cre mice expressing GCaMP8m, N = 4). We demonstrate the optogenetic stimulation capabilities of the miniOEG with spatially resolved (100um illumination precision) random access stimulation of mice expressing GCaMP8m in addition to the potent, red-shifted excitatory opsin rsChRmine (N = 4). The ability thereby enabled, to simultaneously record and control activity across cortex in a cell-type- and spatiotemporally specific manner in freely behaving animals, opens the door to unbiased exploration of the endogenous and causal brainwide neural foundations of naturalistic behaviors.

Disclosures: **A.D. White:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The authors filed a provisional patent on this device. **Y. Wang:** None. **J. Kochalka:** None. **M. Liu:** None. **B. Eshaghi Gharagoz:** None. **M.K. Lo:** None. **S. Quirin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The authors filed a provisional patent on this device. **K. Deisseroth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics, Cargo Therapeutics, Provisional Patent on this device. F. Consulting Fees (e.g., advisory boards); Allen Institute, Modulight, RedTree.

Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.07/UU11

Topic: J.04. Physiological Methods

Support: HHMI

Title: Methods for Collection, Imaging, and Molecular Profiling of Human Brain Tissue Residue on Explanted Intracranial Electrodes

Authors: ***S. VESUNA**[1,2], C. KADUR[1,3], J. POWELL[1,3], A. CHIBUKHCHYAN[1,3], B. REID[4,1], E. CHOI[1,4], I. KAUVAR[1,3,5], T. LIU[1,3], L. M. PROLO[9], H. PHILLIPS[6], J. M. HENDERSON[10], C. I. RODRIGUEZ[2,1,11], P. NUYUJUKIAN[3,1,4,7,8], V. BUCH[4,1], K. DEISSEROTH[1,12,2,3]; [1]Human Neural Circuitry (HNC) Program, [2]Dept. of Psychiatry and Behavioral Sci., [3]Dept. of Bioengineering, [4]Dept. of Neurosurg., [5]Sch. of Educ., Stanford, Stanford, CA; [6]Stanford, Palo Alto, CA; [7]Dept. of Electrical Engin., [8]Wu Tsai Neurosci. Program, Stanford, Stanford, CA;

[9]Stanford Univ. Sch. Med., Menlo Park, CA, ; [10]Stanford Univ., Stanford, CA, ; [11]Veteran Affairs Palo Alto Hlth. Care Syst, Palo Alto, CA; [12]Howard Hughes Med. Inst., Chevy Chase, MD

Abstract: Understanding the molecular basis of human brain function likely requires linking gene expression to neuronal activity and mental states within living subjects—a capability that has remained elusive. Current approaches, such as post-mortem studies, cannot correlate molecular maps with same-subject electrical recordings and may not faithfully represent live molecular profiles. Similarly, although surgical resections yield live brain tissue, tissue is typically limited to a single diseased region, precluding within-subject comparisons across anatomical sites or between disparate healthy and pathological areas. We address these limitations by recovering brain tissue residue adhered to previously implanted intracranial electrodes, yielding brain samples from cortex, hippocampus, amygdala, basal ganglia and thalamus from individual living humans. From 12 adult and pediatric subjects, we collected, visualized and sequenced tens of thousands of cortical and subcortical human brain cells across dozens of electrode segments (32 imaged and 140 sequenced electrode segments)**.** Using confocal microscopy, we observed tens of thousands of DAPI-stained nuclei adhered to the electrode and could map each visualized cell to a precise anatomical location in a subject's brain. Quantitative analysis of multiple participants confirmed a uniform cell density from tip to superficial segment (deep vs. superficial, $p = 0.17$), suggesting spatially resolved cellular capture. For molecular profiling, we designed a dissociation and capture protocol optimized for depth-electrode tissue residue, developing a novel ultra-rapid enzymatic digestion and split-fraction processing method to improve yields and RNA quality. For example, from one subject, single-cell RNA sequencing yielded 47,089 high-quality cells, including 1,714 neurons (enriched for RBFOX3). Astrocytes, oligodendrocytes, microglia, and immune cell-types, among others, were identified. Single subject analyses explored transcriptomic signatures differentiating seizure networks from non-epileptic tissue. This method may enable direct correlation between molecular profiles, electrical brain activity and disease states of living humans. Access to multi-region human brain tissue in one living subject overcomes inherent limitations of post-mortem studies and focal resections and may provide new opportunities for discovery into the molecular foundations of human brain health and disease.

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Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.08/UU12

Topic: J.04. Physiological Methods

Support: Klingenstein-Simons Fellowship
Whitehall Foundation

Title: All-optical physiology resolves inhibitory synaptic plasticity at single-cell resolution during behavior

Authors: *K. SWIFT[1], K. WEN[2], A. Q. KASHAY[2], Y. LI[3], B. DUDOK[4], K. DEISSEROTH[5], L. Z. FAN[2];
[1]MIT, Boston, MA; [2]Brain and Cognitive Sci., MIT, Cambridge, MA; [3]Peking Univ., Beijing, China; [4]Baylor Col. of Med., Houston, TX; [5]Stanford, Stanford, CA

Abstract: Learning has been associated with modifications of synaptic and circuit properties, but the precise changes storing information in mammals have remained largely unclear. We combined genetically targeted voltage imaging with targeted optogenetic activation and silencing of pre- and post-synaptic neurons to study inhibitory synaptic plasticity in the hippocampus during behavior. In mice navigating a virtual-reality environment, optogenetic activation of cholecystokinin-expressing inhibitory neurons elicited time-locked inhibitory postsynaptic potentials (IPSPs) in CA1 pyramidal neurons. Simultaneous optogenetic activation of CA1 pyramidal neurons and optogenetic elicitation of IPSPs revealed that strong postsynaptic depolarization of CA1 neurons can induce a transient suppression of their inhibitory synaptic inputs on a timescale of seconds. These results reveal rapid, activity-dependent inhibitory synaptic plasticity during behavior and define a methodology to resolve synaptic plasticity during learning and memory in behaving mammals.

Disclosures: K. Swift: None. **K. Wen:** None. **A.Q. Kashay:** None. **Y. Li:** None. **B. Dudok:** None. **K. Deisseroth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics, Cargo Therapeutics. F. Consulting Fees (e.g., advisory boards); Allen Institute, Modulight, RedTree. **L.Z. Fan:** None.

Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.09/UU13

Topic: J.04. Physiological Methods

Support: P50DA042012
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R01MH133553
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AE Foundation

Anonymous Donors
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Title: Conserved brain-wide emergence of emotional response from sensory experience in humans and mice

Authors: I. KAUVAR[1], E. B. RICHMAN[1], ***T. X. LIU**[1], C. LI[2], S. VESUNA[1], A. CHIBUKHCHYAN[1], L. YAMADA[1], A. FOGARTY[3], E. SOLOMON[1], E. CHOI[1], L. MORTAZAVI[4], G. CHAU[5], P. MUKUNDA[1], C. RAJA[5], D. GIL-HERNANDEZ[1], K. PATRON[3], X. ZHANG[3], J. BRAWER[6], Z. LUSK[7], D. LYU[7], A. MITRA[1], L. HACK[6], L. LUO[8], L. GROSENICK[12], P. VAN ROESSEL[1], L. M. WILLIAMS[9], B. D. HEIFETS[1], J. M. HENDERSON[10], J. A. MCNAB[11], C. I. RODRIGUEZ[1], V. BUCH[1], P. NUYUJUKIAN[1], K. DEISSEROTH[1];
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Abstract: Emotions shape human behavior and mental health, yet the neural processes by which transient sensory experiences give rise to lasting emotional states remain unclear. To uncover conserved principles across species, we studied the emergence of emotional responses using temporally precise, brain-wide intracranial recordings in humans and mice performing the same task. Brief sequences of air puffs to the eye elicited both rapid reflexive responses, and slower sustained affective responses (the latter marked by negative valence, persistence, generalization, and ketamine sensitivity)—in both species. Using intracranial electroencephalography in humans and single cell/single spike resolution electrophysiology in mice, we identified a conserved biphasic neural response to eyepuff: an initial broadcast of sensory signals across the brain followed by a slower, widespread persistent signal underlying the affective response. Ketamine reduced the persistent neural activity without affecting the initial broadcast ($p < 0.001$ mouse, $p < 0.01$ human, paired t-test, pre vs. infusion), and inhibited the behavioral emotional response. In humans and mice, ketamine accelerated the intrinsic timescale of spontaneous activity and reduced population coupling in networks that had persistent eyepuff responses. Together, our findings identify a tunable, distributed mechanism for emotional state formation via persistent neural activity, offering a systems-level framework for understanding the emergence of adaptive and maladaptive emotional states.

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Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.10/UU14

Topic: J.04. Physiological Methods

Support: NIMH R01MH075957

Title: Resolving and engineering cation-π interaction in K^+-selective channelrhodopsins

Authors: ***Y. JO**[1], J. J. NOH[1], P. Y. WANG[1], S. TAJIMA[2], A. DRINNENBERG[1], C. LI[1], M. INOUE[1], E. F. X. BYRNE[1], S.-S. JANG[1], J. SHI[1], L. Z. FAN[1], S. QUIRIN[1], J. R. HUGUENARD[1], Y. KIM[1], H. E. KATO[2], K. DEISSEROTH[1];
[1]Stanford Univ., Stanford, CA; [2]Univ. of Tokyo, Tokyo, Japan

Abstract: YoungJu Jo, Joseph J. Noh, Peter Y. Wang, Seiwa Nakamura, Seiya Tajima, Antonia Drinnenberg, Chelsea Li, Masatoshi Inoue, Masaki Tsujimura, Eamon F. X. Byrne, Thanh-Nga C. Shenoy, Sung-Soo Jang, Ki Eun Pyo, Nadya Andini, Jenny Shi, Kishandra A. Patron, Joseph M. Paggi, Masahiro Fukuda, Yuma Ito, Masahiro Sugiura, Kota Katayama, Yuji Furutani, Hisako Ikeda, Charu Ramakrishnan, Linlin Z. Fan, Sean Quirin, Hiroshi Ishikita, John R. Huguenard, Hideki Kandori, Ron O. Dror, Yoon Seok Kim, Hideaki E. Kato, Karl Deisseroth K^+ selectivity in ion channels is generally conferred by a four-fold-symmetric filter in which dehydrated K^+ ions interact with backbone carbonyls. K^+-selective channelrhodopsins (KCRs), however, lack tetrameric symmetry and the associated sequence motifs, implying a distinct molecular strategy. Building on recent structural insights that cation-π interaction might substitute for the canonical filter in KCRs, we combined high-resolution cryo-EM, extensive MM, QM and QM/MM simulations, structure-guided mutagenesis, in vitro and in vivo electrophysiology, and single-cell resolution optics to investigate and build upon this possibility. Our data show that KCRs employ a sterically constrained dehydration pathway that positions a key aromatic residue for a cation-π contact, creating a geometry that preferentially stabilizes K^+ over Na^+ without the need for tetrameric symmetry and enhances the intrinsic K+ selectivity of aromatic cation-π interactions. Manipulating the interactions near the residue responsible for the cation-π interaction can tune selectivity in both directions, either strengthening or abolishing K^+/Na^+ discrimination, thereby confirming the central role of the cation-π motif. Exploiting this mechanism, we engineered KCR variants that enable: (i) ultra-efficient transcranial inhibition and excitation of deep brain circuits in behaving mammals; (ii) cellular-resolution holographic optical silencing in the intact mouse cortex during visual processing; and (iii) simultaneous red-light voltage imaging and blue-shifted KCR-mediated inhibition for all-optical interrogation of membrane voltage in neuronal networks. These results establish the cation-π interaction as a fundamentally distinct paradigm for K^+ selectivity in ion channels, demonstrate its unexpected effectiveness within partially dehydrated pores, and provide a versatile toolkit that expands the reach and precision of optogenetics across biological systems, including for neuroscience.

Disclosures: Y. Jo: None. **J.J. Noh:** None. **P.Y. Wang:** None. **S. Tajima:** None. **A. Drinnenberg:** None. **C. Li:** None. **M. Inoue:** None. **E.F.X. Byrne:** None. **S. Jang:** None. **J.**

Shi: None. **L.Z. Fan:** None. **S. Quirin:** None. **J.R. Huguenard:** None. **Y. Kim:** None. **H.E. Kato:** None. **K. Deisseroth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock: Maplight, Stellaromics, Cargo Therapeutics. F. Consulting Fees (e.g., advisory boards); Advisory Boards: Allen Institute, Modulight, RedTree.

Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.11/UU15

Topic: J.04. Physiological Methods

Support: R01AG063418
T32 AG0047126
K99AG07687901
T32 AG000266 10
K99AG07849901

Title: A functional genetic screen of neuron-derived peptides identifies Neuromedin U as a regulator of vertebrate aging.

Authors: *R. NATH[1], C. BEDBROOK[2], K. DEISSEROTH[3], A. BRUNET[1];
[1]Genet., [2]Stanford Univ., Stanford, CA; [3]Bioengineering, Stanford, Stanford, CA

Abstract: Aging causes systemic decline and leads to an increased probability of disease. Identifying new strategies to promote healthy aging is essential to counter age-related decrepitude and diseases. Emerging evidence has revealed an exciting role for peptides in the systemic regulation of aging. However, the long timescale and complexity of vertebrate aging have made the discovery of key longevity peptides challenging. Here we used a naturally short-lived vertebrate, the African killifish, to conduct the largest screen of vertebrate longevity to date. We focused on 22 human-conserved neuropeptide-encoding genes, as these genes are known to have a systemic effect on health by regulating key physiological processes, such as sleep, metabolism, and stress. Notably, we discovered six neuropeptide genes that, when mutated, modified lifespan, highlighting the power of the killifish for screening vertebrate lifespan and suggesting that neuropeptides are an important class of vertebrate longevity factors. We focused on Neuromedin U mutants because mutation of this gene resulted in the largest lifespan extension. We discovered that Neuromedin U mutants were behaviorally youthful and exhibited changes to growth, metabolism, and inflammation pathways all of which may coordinate its impact on lifespan.

Disclosures: R. Nath: None. **C. Bedbrook:** None. **K. Deisseroth:** A. Employment/Salary (full or part-time): Human Neural Circuitry (HNC) Program, HHMI, Stanford Dept of Bioengineering, Stanford Dept. of Psychiatry. E. Ownership Interest (stock, stock options,

royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Cargo Therapeutics, Stellaromics. F. Consulting Fees (e.g., advisory boards); Allen Institute, Modulight, RedTree. **A. Brunet:** F. Consulting Fees (e.g., advisory boards); Calico.

Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.12/UU16

Topic: J.04. Physiological Methods

Support: R01AG063418
Helen Hay Whitney Postdoctoral Fellowship
T32 AG000266
K99AG07849901
T32 AG0047126
K99AG07687901

Title: Life-long behavioral monitoring reveals dynamics that forecast lifespan and discrete transitions defining an architecture of aging

Authors: *C. BEDBROOK[1], R. NATH[2], L. ZHANG[3], S. LINDERMAN[4], A. BRUNET[2], K. DEISSEROTH[5];
[1]Bioengineering, [2]Genet., [3]Electrical Engin., [4]Dept. of Statistics and Wu Tsai Neurosciences Inst., Stanford Univ., Stanford, CA; [5]Bioengineering, Stanford, Stanford, CA

Abstract: Mapping the behavioral pattern of individual vertebrate animals across the lifespan is technologically highly challenging, but if achieved, could provide an unprecedented and unbiased view into fundamental processes underlying the progression of aging. Here we address this challenge by creating and applying the first platform for high-resolution continuous longitudinal recording and behavioral tracking of a vertebrate animal across its natural lifespan from adolescence to death--here, of the African turquoise killifish. We first observed that individual animals do not all progress through natural aging in the same way but, rather follow distinct aging trajectories. The behaviors of short-lived animals differed markedly from those of long-lived animals, even in youth; indeed, classification models accurately forecast an individual animal's future lifespan, given only the individual's behavior at a young age. Moreover, despite this predictive individual variability, we unexpectedly found that animals progress through adulthood in an orderly sequence of stable and stereotyped behavioral stages defined by abrupt transitions in behavior. Together these findings, identifying both conserved and variable features of natural aging derived from a quantitative and unbiased perspective of organismal behavior over the course of adult life, define a novel staged structure of the architecture of vertebrate aging, with important ramifications for the fundamental understanding of aging and for identifying interventions targeted to specific life stages.

Disclosures: C. Bedbrook: None. **R. Nath:** None. **L. Zhang:** None. **S. Linderman:** None. **A. Brunet:** F. Consulting Fees (e.g., advisory boards); Calico. **K. Deisseroth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics, Cargo Therapeutics. F. Consulting Fees (e.g., advisory boards); Allen Institute, Modulight, RedTree.

Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.13/UU17

Topic: J.08. Methods to Modulate Neural Activity

Title: Guidelines for Non-human Primate Chemogenetics

Authors: *S. TREMBLAY[1], M. A. ELDRIDGE[2], A. GALVAN[3], T. MINAMIMOTO[4]; [1]Univ. Laval / CERVO, Quebec, QC, Canada; [2]Lab. of Neuropsychology, Newcastle Univ., Ponteland, United Kingdom; [3]Emory Natl. Primate Res. Ctr. and Dept. of Neurology, Sch. of M, Emory Univ., Decatur, GA; [4]Functional Brain Imaging, Natl. Inst. Quantum Scinece and Technol., Chiba, Japan

Abstract: Chemogenetics is a powerful method to control the activity of cells by targeting specific populations with a designer receptor activated by a designer drug. The use of chemogenetics in neuroscience has rapidly expanded in small animal models, and more research groups are now attempting experiments in non-human primates (NHP) with hopes for therapeutic use in humans. To speed up translational applications to patients and facilitate future basic science experiments with the technology, we have created a database listing all attempts, successful and unsuccessful, published and unpublished, of using chemogenetics in the primate brain. We received data from 39 laboratories in 7 countries who provided detailed methods and outcomes on more than 800 experiments, 500 of them never published before. We examine the success of those approaches as a function of viral vector, gene cassettes, brain regions, and 42 other experimental parameters. With this multi-center effort, we hope to provide guidelines for the research community using chemogenetics in primates and speed up the translation of this cell-type-specific neuromodulation technology for clinical applications in neurology and psychiatry.

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Poster

PSTR476: Application of Advanced Physiological Techniques to Examine Neural Networks

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.14/UU18

Topic: I.08. Learning and Memory

Title: Thalamo-prefrontal circuitry dynamically evolves during learning

Authors: *I. ELKINBARD[1], S. SADEGHZADEH[2], V. TSAI[3], T. HO[2], K. DEISSEROTH[2], V. BUCH[4];
[1]Stanford Univ., Belmont, CA; [3]Undergraduate Neurosci. Program, [4]Neurosurg., [2]Stanford Univ., Stanford, CA

Abstract: Learning is an adaptive process which requires precise coordination among multiple brain regions over time. Thalamo-prefrontal circuitry is thought to be important for multiple domains of cognitive control and executive function. In this study, we explored the circuit dynamics of mediodorsal thalamic projections to the dorsomedial prefrontal cortex in six mice, and how circuit activity evolves over the course of learning a temporal expectancy task. We targeted a genetically-encoded Ca^{2+} indicator to the mediodorsal-prefrontal (MD-dmPFC) projection and used multi-fiber photometry to record synaptic dmPFC activity and somatic MD activity. Across all trials, we observed a relative shift of circuit activity from the intra-trial (anticipatory) period to the pre-trial (preparatory) period over the course of learning ($p<0.001$) . Further, during training, anticipatory synaptic dmPFC activity profile differentiated subsequent reaction time (RT, $p<0.02$), while somatic MD activity correlated with RT during the lick reward phase ($p<0.001$). However, after 13 sessions of training, somatic MD activity shifted earlier to mirror the activation profile of synaptic dmPFC. In fastest performing trials (RT < 100ms), preparatory synaptic dmPFC activity only during late experimental sessions specifically preceded the most optimal trials (RT < 35ms, $p<0.001$). Overall, these results suggest that thalamo-prefrontal circuitry evolves over the course of learning, with earlier circuit activation over time leading to earlier discrimination of upcoming performance. This temporal shift may provide evidence of circuit mechanisms of adaptive learning, enabling more efficient processing of cognitive stimuli and behavioral execution.

Disclosures: I. Elkinbard: None. **S. Sadeghzadeh:** None. **V. Tsai:** None. **T. Ho:** None. **K. Deisseroth:** A. Employment/Salary (full or part-time): Human Neural Circuitry (HNC) Program, HHMI, Stanford Dept of Bioengineering, Stanford Dept. of Psychiatry.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics, Cargo Therapeutics. F. Consulting Fees (e.g., advisory boards); Allen Institute, Modulight, RedTree. **V. Buch:** A. Employment/Salary (full or part-time): Human Neural Circuitry (HNC) Program, Wu Tsai Neurosciences Institute, Stanford Dept of Neurosurgery.

Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.01/UU19

Topic: J.07. Data Analysis and Statistics

Support: NIMH Grant U24 MH130919
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NIMH Grant UM1 MH130981
NIMH Grant U24 MH130918
Allen Institute
NIMH Grant R24 MH114788

Title: An operational framework for rapid, open-access sharing of BICAN human omics data.

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Abstract: The past decade has seen major advances in the scale and granularity of transcriptomic and epigenomic sequencing methods, including unprecedented expansion of single cell assays. Coupled with significant BRAIN Initiative investment in cell census projects, these developments have produced high value datasets with the potential to fuel rapid increases in knowledge through data integration and reuse. Open access, low-barrier data sharing can help to realize this potential; however, ethical, legal and social implications (ELSI) of sharing human sequence-level data poses challenges for responsible and compliant data sharing. The regulatory landscape continues to evolve in recent year, and the lack of a clear roadmap to navigate regulations, and lack of consent templates and user-friendly licensing framework that aligns with these policies and their privacy provisions has greatly hindered the broader adoption of open-access genomic data sharing by researchers and data repositories since the appearance of the NIH Genomic Data Sharing (GDS) policy and the EU's Genomic Data Protection Regulation.We present consortium-wide solutions developed in the BRAIN Initiative Cell Atlas Network (BICAN) to enable the open and rapid data sharing while ensuring compliance. First, we developed a spectrum of data sharing policies, and designed a data ecosystem that can accommodate both controlled access and open access data. This ecosystem reduces regulatory burden by separation of concerns across different components, and includes centralized receipt and verification of members' Institutional Certification forms as part of a pathway for rapid release of data to the community.Second, we developed a standardized license (BICAN-BY-NR) that supports open-access human genomic data sharing requiring attribution ("BY", attribution) while explicitly restricting re-identification ("NR", No Re-identification). We also describe consent requirements needed for applying this license to sequence-level human data. Key considerations included clear terms that prohibit reidentification of donors, compliance with international and state-level privacy laws, and the importance of fostering a culture of ethical data use among researchers.This effort is both timely and essential: single-cell transcriptomic data are vital for linking experiments to defined cell types and cross-study analysis, and the

growth of AI technologies and expansion and validation of knowledge graphs will require easier sharing of key datasets. Our framework provides a compliant, scalable path for data sharing while safeguarding privacy, and enhancing the downstream reuse of BICAN data.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Title: Allen Institute Taxonomy (AIT): a new standard for cell type taxonomies

Authors: *J. A. MILLER[1], N. J. JOHANSEN[1], I. KAPEN[1], T. S. MOLLENKOPF[1], L. NG[1], E. BIEDERSTEDT[2], P. RAY[1], X.-P. LIU[1], S. DANIEL[1], C. LEE[1], R. SANCHEZ[1], C. VAN VELTHOVEN[1], M. J. HAWRYLYCZ[1], Z. YAO[1], T. BAKKEN[1], B. TASIC[1], H. ZENG[1], E. S. LEIN[1];
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Abstract: Over the past decade, the Allen Institute, members of the BRAIN Initiative Cell Census/Atlas Network (BICCN/BICAN) and the broader community have published numerous studies classifying and characterizing mammalian brain cell types. The collective taxonomy work describes cell types across species, ages, and disease states and includes comprehensive whole mouse and draft human brain. These efforts utilized a range of experimental techniques, data modalities, and computational approaches, stored in various formats with inconsistent metadata, preventing development of broadly applicable tools for data access, analysis, and visualization.
To address these challenges, we developed the Allen Institute Taxonomy (AIT) standard for cell type taxonomies and associated R and python libraries for their implementation ('scrattch.taxonomy'). AIT utilizes an H5AD file to encapsulate essential taxonomy components along with a formalized schema and controlled vocabulary for data and metadata, facilitating downstream analysis, mapping, and cell type annotation. The AIT format extends common schema in the single cell omics field including CELLxGENE and Human Cell Atlas standards by incorporating additional metadata and statistics for custom mapping, analysis, and visualization. Additionally, the AIT format is designed to flexibly accommodate taxonomy 'modes'

representing subsets of cell types (e.g., all neuronal types, all cells from a specific brain region) or genes (e.g., spatial transcriptomics panel).
We demonstrate AIT's utility on recently published macaque basal ganglia cell types. We show how patch-seq cells can be mapped to an AIT file via scrattch.mapping, how AIT files can be imported into the Cell Annotation Platform for community annotation, and how AIT data can be visualized and explored using custom R shiny applications. Finally, we have converted over a dozen brain cell type taxonomies, including novel cross-species basal ganglia classifications, to the AIT format and made them freely available to promote community usage. The AIT standard, associated code, and taxonomies are available on GitHub (https://github.com/AllenInstitute/AllenInstituteTaxonomy/).

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Title: Managing Metadata Standards in a Large Consortium

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Abstract: The BRAIN Initiative Cell Atlas Network (BICAN) is a collaborative effort to generate comprehensive reference data and tools for understanding cell types in the human,

primate, and mouse brain. To facilitate this, BICAN has developed a structured metadata standards governance process to address harmonization across a distributed data ecosystem, and to align to the principles of FAIR (Findable, Accessible, Interoperable, Reusable). This process emphasizes a federated model that balances democratic participation and consensus-building with the need for technically detailed and well-documented standards. Three case studies representing the development and review of metadata standards are presented here. First, the development of a library minimal metadata model describing essential characteristics for a sequencing library sample was created to be broadly useful for single cell profiling from a variety of transcriptomic and epigenomic experiments. A second case study required the alignment of donor metadata across different species, from mouse to primate and human. The final case study represents the development of a taxonomy and cell annotation standard. Some of the key challenges included: reconciling redundant information across groups, agreeing on a standard versioning schema, documenting transparent decision-making and progress, and improving interoperability while maintaining metadata fidelity. Although there were difficulties in achieving consensus, we also realized successes in standard development and implementation. We synthesize these insights, reinforcing the importance of collaborative efforts in advancing scientific standards and fostering a more cohesive research environment. Such findings offer critical insights and practical guidance that can significantly enhance collaboration frameworks for data standardization practices across diverse biomedical data consortia.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Topic: J.07. Data Analysis and Statistics

Support: NIH UM1MH130981
NIH U01AG076791

Title: Ccf-map: a resource for accessing unified mouse, primate, and human brain atlases and ontology

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Abstract: 3D anatomical atlases provide a common coordinate space for mapping spatial data from multiple sources and modalities within the same species. These atlases and their regional parcellations permit analysis of biological signals in 3D and enable data integration through image registration. Although atlases are powerful data assets, community access and usage has been limited by a lack of supporting computational tools for querying and using atlases for downstream analyses. To address this need, we present the Common Coordinate Framework and Multi-species Atlas Primer (CCF-MAP), a resource for programmatic access to marmoset, macaque, and human atlases developed by the Human and Mammalian Brain Atlas (HMBA) consortium, as well as the CCFv3 mouse brain atlas from the Allen Institute. CCF-MAP is a repository of publicly accessible MRI templates, associated parcellations of basal ganglia structures, and related metadata. These atlases can be viewed interactively in 3D using only an internet browser. We have also included Jupyter notebook tutorials for querying voxel data and downloading region masks and volumes. Because these atlases use a common, unified taxonomy and nomenclature, CCF-MAP also shows examples of querying the same structure across multiple species, enabling cross-species comparison at a structure level. We invite researchers at all levels to access the data and tutorials at https://github.com/AllenInstitute/CCF-MAP

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Poster

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Topic: J.07. Data Analysis and Statistics

Support: U24MH130968

Title: WARP Optimus STARsolo is a bioinformatics workflow for cloud-scale single-cell and single-nucleus gene expression, combined with multiple molecular modalities to produce multi-omic pipelines

Authors: *R. S. COX[1], F. KHAJOUEI[1], A. AWDEH[1], J. WAY[1], E. KIERNAN[2], N. MIRABITO[1];
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Abstract: Bioinformatic pipelines for analysis need to scale and utilize cloud computing resources efficiently. Warp Analysis Research Pipelines (WARP) provides scalable pipelines which can combine data modalities to form multi-omic pipelines. WARP Optimus STARsolo is a single-cell RNASeq alignment pipeline. It combines the best in class performance of the STAR aligner, the simultaneous computation of the solo metrics, with additional optimizations added in the Optimus STARsolo pipeline to provide high scalability and low cost.

We have validated Optimus STARSolo, compared to the 10X Cell Ranger pipeline, and show best-in-class performance which can be scaled on the cloud. Optimus STARsolo provides the standardized solution needed by the BICAN consortium and NeMo project. The consortium required unified processing of single-cell RNA-seq as the central modality for unifying ~20 individual efforts. Optimus STARsolo is that unified pipeline, that can scale to input sizes of greater than 100 GB. Optimus STARsolo has been used for standardized processing of over 60 million single-cells by the BRAIN Initiative® Cell Atlas Network (BICAN), including several multi-omic assays like ATAC-seq. This includes references constructed for multiple species and optimizations gained from standardization.
Multi-omic studies leverage multiple data modalities, such as single-cell gene expression and single-cell Assay for Transposase-Accessible Chromatin (ATAC) to provide a comprehensive picture of cell state. Optimus STARsolo has been combined with other modalities to produce best in class multi-omic workflows. Its modular design allows for the creation of entirely novel multimodal analyses as required. Multiomics empowers new analytic methods, including label (Cell type) alignment and transfer between modalites.
Optimus STARsolo is published in WARP, along with validated scientific tests, methods, and documentation. The WARP repository provides an authoritative source of the Optimus STARsolo pipeline, the pipelines for additional modalities, and the multi-omic pipelines. This includes plumbing and scientific tests of all published pipelines, and extension documentation and methods.

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Poster

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Topic: J.07. Data Analysis and Statistics

Support: R24MH114788
UM1DA052244
U24MH130968

Title: The Neuroscience Multi-Omic Archive (NeMO): A public resource for single cell transcriptomic and epigenomic data from the mammalian brain

Authors: *J. RECEVEUR[1], S. A. AMENT[2], R. ADKINS[1], R. CARTER[1], A. CHATTERJEE[1], M. G. GIGLIO[1], B. HERB[1], T. HODGES[1], O. IFEONU[1], D. LESPERANCE[1], S. NADENDLA[1], D. OLLEY[1], J. ORVIS[1], M. SCHOR[1], R. P. HERTZANO[3], A. MAHURKAR[1], O. WHITE[1];
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Abstract: Scalable technologies to sequence the transcriptomes and epigenomes of single cells are transforming our understanding of cell types and cell states. Large consortia projects and individual research groups are applying these technologies at unprecedented scale in the mammalian brain but there is a critical need for harmonization and tools for interfacing with these data objects. The Neuroscience Multi-Omic Archive (NeMO) serves as the primary sequence data repository for the BRAIN Initiative, SCORCH consortium, and a number of other high-profile efforts exploring the mammalian brain. To date, NeMO hosts over two petabytes of sequencing data from 25 species and 55 different techniques, with over six petabytes of data downloads. Data available at NeMO includes raw data from human and model organisms, as well as summary data processed uniformly through consensus pipelines (for BRAIN Initiative and SCORCH consortia derived data). Archive tools include a searchable web portal, cloud-computing, and API interfaces for large-scale data access and processing, and an interactive analysis platform, NeMO Analytics. NeMO Archive continues to expand with new data and features, and serves as a critical public resource for the neuroscience community.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Topic: J.07. Data Analysis and Statistics

Support: UM1MH130981

Title: Towards a single-cell whole brain atlas across mammalian species

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Abstract: Building a whole brain atlas across mammalian species is essential for understanding brain organization, function, and evolution. However, incomplete data collection and inadequate analytical methods have limited these efforts. Here, we present a beta version of a human whole brain atlas, generated from single-cell transcriptome data totaling over 4 million nuclei, including 1 million newly generated by our team and 3 million from published datasets by Siletti et al. Additionally, we have created a consensus mouse whole brain atlas by integrating two published

studies using scRNA-seq and snRNA-seq respectively, totaling 7.5 million cells. Through cross-species integration with consensus mouse whole brain atlas, we identified homologous classes and subclasses. The construction of this atlas was made possible by developing scalable methods for analyzing large, heterogenous single cell datasets. To address donor-specific effects, we developed an algorithm that identifies gene modules that account for most donor-related variation across majority of cell types, and computes per-cell scores to be used as covariates in downstream analyses, enhancing batch correction compared to using only donor covariates. We also optimized our pipeline for recursive hierarchical clustering using distributed computing, achieving a 24-fold speedup and enabling clustering of millions of cells into thousands of clusters in hours. To overcome limitations in cross-species integration, where current state-of-the-art methods have failed, we developed a scalable graph neural network framework that aligns similar cells across human and mouse while preserving cell-type resolution within each species. Overall, our work establishes a robust and scalable framework for constructing whole brain taxonomies across species.

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Poster

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Support: NIH Grant 5U24NS120057
NIH Grant 5R24MH117295

Title: Ai coding agents with custom model context protocols successfully reproduce foundational systems neuroscience discoveries from nwb data on the dandi archive

Authors: *B. DICHTER[1], J. MAGLAND[2], O. RUEBEL[3], S. S. GHOSH[4];
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Abstract: Recent advances in large language models (LLMs) and AI coding agents present new opportunities to democratize scientific discovery, enhance reproducibility, and accelerate data discovery and analysis. However, translating these capabilities into practical research tools remains challenging due to integration barriers with existing neuroscience data infrastructure. We enhanced an LLM coding agent with custom Model Context Protocols (MCPs) to autonomously reproduce foundational systems neuroscience discoveries using open data from the DANDI Archive. We evaluated our approach by reproducing three seminal findings:

orientation tuning in primary visual cortex (Hubel & Wiesel, 1959), directional tuning in primary motor cortex (Georgopoulos et al., 1982), and place fields in hippocampus (O'Keefe & Dostrovsky, 1971). Our framework integrates the Cline coding agent with specialized MCPs for DANDI Archive access, and interactive plot analysis, enabling seamless interaction between AI systems and standardized neurophysiology data in Neurodata Without Borders (NWB) format. The AI agent autonomously searched DANDI datasets, identified appropriate recordings, implemented statistical analyses, and generated publication-quality visualizations demonstrating each phenomenon. Results show that AI coding agents successfully identified neurons with selective responses to orientation, movement direction, and spatial location across multiple datasets. The agent reproduced characteristic tuning curves, selectivity indices, and population-level analyses consistent with original findings. Notably, the agent discovered and reported a timestamp error in one dataset, demonstrating potential for automated quality control. Our framework required minimal human intervention, with agents completing analyses in 30-90 minutes including dataset discovery, code generation, and figure creation. This work establishes a template for AI-assisted scientific discovery that could accelerate research and improve reproducibility across neuroscience by bridging advanced AI capabilities with existing data infrastructure. This approach could advance neuroscience research by reducing the technical barriers to sophisticated data analysis and dramatically accelerating data search and code generation, though more work is needed to ensure scientific rigor is maintained.

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Poster

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Title: Information Quantification in Feature- Selected Spike Waveforms

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Abstract: Clusterless neural decoding methods tend to outperform traditional spike-sorted methods, but the sources of this improvement remain unclear. To address this question, we developed a set of information-theoretic metrics to quantify the information individual spikes contain about a signal, considered either in isolation or accounting for all prior spiking activity. Applying these metrics to hippocampal recordings from rats performing memory-guided spatial

navigation tasks, we found that the same spikes provided significantly more information in clusterless models compared to spike-sorted models. Additionally, low-amplitude spikes excluded during spike sorting conveyed incremental information comparable to high-amplitude spikes, suggesting that they provide substantial value in aggregate, when retained.To compare the information extracted by each model, we measured the reduction in entropy and absolute error for individual spikes, defined as the decrease in uncertainty or estimation error due to observing that spike. This analysis was performed across seven datasets from two animals. When spikes were evaluated in isolation, 83% resulted in greater entropy reduction in the clusterless model compared to the spike-sorted model. When prior spiking history was taken into account, the reduction in absolute error was, on average, 70% higher in the clusterless model. Furthermore, the spikes excluded during spike sorting contributed a substantial portion of the total information in the clusterless model, accounting for up to 40%, highlighting their importance in population-level decoding.These metrics also allowed us to assess the contribution of different spike waveform features to clusterless decoding. We evaluated several categories of waveform features, including principal component scores, geometric attributes (amplitude, width, peak-to-trough, slope) and nonlinear transformations such as UMAP and t-SNE, to determine their information content and decoding performance. Preliminary analyses suggest that waveform features vary in both the amount of information they carry and their impact on decoding accuracy. These findings challenge the assumption that low-amplitude or otherwise unsortable spikes are merely noise. Instead, they show that these signals can carry distinct and measurable information, especially when paired with appropriate feature representations. This work highlights the potential of clusterless models, when combined with systematic feature selection, not just as an alternative, but as a more complete framework for decoding neural activity.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Support: Simons Foundation (SFARI) Fellows-to-Faculty Award
Burroughs Wellcome Fund/Revson Foundation

Title: Universal reproducibility laws for high-dimensional neuroimaging and genomic data

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Abstract: Reproducibility is a cornerstone of scientific research, yet it remains a significant challenge when working with high-dimensional datasets typical of neuroimaging studies. Such datasets often feature more variables than observations, a regime known as the Large Dimensional Limit (LDL). While the LDL is central to fields ranging from neuroimaging to genomics, its impact on reproducibility and statistical power is poorly understood. This knowledge gap has led to inconsistencies in high-profile brain-wide association studies and neuroimaging genomic studies, highlighting the urgent need for a theoretical framework.
We empirically and theoretically demonstrate that reproducibility in LDL problems adheres to "Universal Reproducibility Laws" (URLs), which precisely quantify the sample size required to ensure robust findings for given signal strengths and dimensionality. Building on Random Matrix Theory (RMT) and high-dimensional geometry, our framework identifies critical "reproducibility phase transitions," providing tools for prospective sample size determination and power analyses. We validate these URLs using human resting state functional (rsf)MRI, genomic, and behavioral data from the Adolescent Brain Cognitive Development (ABCD) and the Parkinson's Progression Markers Initiative (PPMI) datasets, and perform robust cross-validation across 13.876 million model fits.
In brain-wide association studies (BWAS) and gene-to-brain-wide association studies (GBWAS), we find that reproducible associations require far fewer samples than previously suggested when relating rsfMRI to neuropsychiatric behavioral scales. For cognitive abilities, robust reproducibility ($p<0.01$) is achieved with as few as 22 subjects using Support Vector Regression (SVR) or 16 with Regularized Canonical Correlation Analysis (RCCA). For psychopathology measures, 550 (SVR) and 230 (RCCA) subjects suffice, with diminishing returns observed beyond a few hundred samples. This “reproducibility phase transition” aligns with the theoretical RMT predictions, showing rapid initial gains followed by logarithmic improvements in reproducibility as sample size increases.
Our findings demonstrate that thousands of participants are not always necessary for BWAS and GBWAS reproducibility, offering a more attainable path forward for studies in precision psychiatry and neuroscience. By mathematically linking multivariate neuroimaging analyses to statistical physics, we present a unified framework for reproducible machine learning in high-dimensional biomedical datasets.

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Poster

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Title: Bossdb: advancing neuroscience with a robust ecosystem for storing, accessing, and analyzing high-resolution images, annotations, and connectivity data

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Abstract: The NIH BRAIN Initiative Informatics Program was created to establish data archives, define consensus data standards, and develop computational tools for analysis and visualization, all to support the various data communities within the neuroscience research domain. As a part of this, the Brain Observatory Storage Service and Database (BossDB) data archive and ecosystem was developed to support the storage, access, and analysis for high-resolution neuroimaging datasets, particularly those derived from Electron Microscopy (EM) and X-ray Micro/Nanotomography. In adherence to Findable, Accessible, Interoperable, and Reusable (FAIR) practices, BossDB data is accessible through multiple scalable interfaces, and tools are openly available to promote secondary analysis, foster collaborative science, and enable comparative analyses across expanding datasets from various species and modalities. Herein we present on the BossDB integration with community frameworks and tools such as Neuroglancer for 2D/3D data visualization, “NeuVue” for proofreading and annotation, “NeuPrint” for connectomic analysis, “DotMotif” for annotation and graph querying, and the “Connectome Annotation Versioning Engine” (CAVE) platform that supports segmentation proofreading, links annotations to spatial coordinates, and aligns them with corresponding segments, effectively mirroring how annotations relate to metadata. Additional recent developments include improved integration with syGlass for immersive 3D visualization, deployment of an LLM-based BossDB AI Assistant to enhance user interaction, and new tools such as “BossyPaints” for intuitive region annotation and training for BossDB-integrated automated segmentation workflows. BossDB is also advancing spatial tracking capabilities, expanding graph-based analysis, and updating its metadata interface to streamline data management workflows. Ongoing efforts include work on data processing pipelines and planned integration with PyReconstruct for large-scale structural reconstructions.Through these development and community tool integration efforts, BossDB aims to support neuroanatomical and connectomic research at multiple parts of the data and research pipeline, from image processing and annotation to the detailed analysis of connectome networks.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.12/VV8

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant U01NS137250
NIH Grant U01NS132158
NIH Grant U24NS139927
NIH Grant R24MH114785

Title: Neuvue: a scalable and customizable framework for electron microscopy proofreading

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Abstract: NeuVue is a web-based, task-management framework purpose-built for large-scale proofreading of electron microscopy (EM) datasets. Originally developed to support the curation of the Minnie65 connectome for the IARPA MICrONS program, NeuVue has since evolved into a *flexible, modular platform* that now supports multiple community datasets and is hosted as a BossDB service. It has become foundational to several BRAIN CONNECTS initiatives, including *CONNECTS Proof*, *CONNECTS Intelligent Imaging*, and will be integral to the *CONNECTS Data Coordinating Center* for data validation and quality assurance. As NeuVue's adoption expanded, we sought out and implemented new enhancements to the framework. In particular, users identified the need for better support for distributed, community-driven proofreading with minimal setup overhead; the need for new configurable tools that could flexibly adapt to different research pipelines; and we needed deeper integration with automated analysis services and rich biological annotations. These needs shaped this next phase of NeuVue's development, resulting in new capabilities that now extend NeuVue far beyond its original scope. Specifically, (i) public task queues can now be self-managed by users, reducing administrative load; (ii) custom proofreader groups with task-chaining now support complex decision fusion workflows; (iii) our interface is now configurable with support for multiple visualization backends—including three Neuroglancer versions (spelunker, mainline, and legacy) and third-party tools like BossyPaints for manual ground truth annotation; (iv) a plugin system allows external services to operate within tasks, such as on-demand NEURD runs for identifying segmentation errors and generating targeted correction tasks; finally (v) integration with CAVE (Connectome Annotation Versioning Engine) enables users to interact directly with rich annotations like synapses, nuclei, and cell type predictions within the proofreading environment. These features open the door to high-value workflows previously unsupported: validating automated error detection and correction, aligning functional and structural datasets for multimodal studies, and using NeuVue as a digital lab notebook to track hypotheses across visualized circuit motifs. With over 150,000 edits across two major volumetric datasets and more than 8,000 hours logged by 60+ proofreaders, NeuVue continues to be a critical platform for reproducible, scalable proofreading. Its new capabilities are essential to emerging use cases and

central to the BRAIN CONNECTS mission of building accurate, synapse-level maps of brain connectivity.

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Poster

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Topic: J.07. Data Analysis and Statistics

Support: NIH Grant 1U01NS132158

Title: Benchmarking SmartEM High-Throughput Imaging Strategies Through Repeated Imaging of a Human Cortex Tissue Sample

Authors: *C. A. BISHOP[1], H. MARTINEZ[2], I. S. CHANDOK[3], D. XENES[2], Y. WU[4], J. MATELSKY[2], E. C. JOHNSON[2], D. R. BERGER[5], N. SHAVIT[6], Y. MEIROVITCH[4], J. W. LICHTMAN[4], A. D. SAMUEL[3], B. A. WESTER[2];
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Abstract: High-throughput connectomics, essential for constructing synapse-level wiring diagrams of neural tissue, remains limited to a few institutions due to the cost of generating and processing high-resolution image volumes. SmartEM addresses this by accelerating image acquisition in affordable single-beam scanning electron microscopes. This method integrates machine learning into real-time data collection, allowing the microscope to intelligently allocate imaging dwell time. The microscope first performs a fast scan of all pixels, followed by a slower rescan of subregions that require a higher signal for accurate reconstruction. This SmartEM pipeline results in datasets acquired at a 7-fold speedup without sacrificing reconstructability. To validate this method, we imaged four volumes of the same 50*50*3 μm^3 region of human cortex tissue (a subvolume of the published H01 dataset) using SmartEM and control approaches. Controls include data acquired with homogeneous dwell times, while SmartEM involves imaging at a combination of fast and slow dwell times, resulting in an effective dwell time. These four image collections include: ● Low-fidelity or "fast" volume: homogeneous dwell time of 100 ns/pixel ● SmartEM volume: effective dwell time of 150 ns/pixel ● "Time control" volume: homogeneous dwell time equal to SmartEM's effective dwell time ● High-fidelity or "slow" volume: homogeneous 800 ns/pixel. We evaluate how these imaging strategies affect downstream analysis quality. For example, we verify that SmartEM's accelerated imaging maintains 3D segmentation and wiring diagram accuracy. To enable direct comparisons across imaging conditions, we perform cloud-based alignment to register all four volumes into a shared

coordinate frame. This registration facilitates rigorous, spatially resolved evaluation of downstream tasks (e.g., membrane detection, segmentation, synapse identification, circuit reconstruction). By controlling for anatomical variability, we isolate the impact of acquisition strategies on data quality, offering insights into tradeoffs between imaging throughput and analytical fidelity. Given that we can register four volumes into a shared coordinate system, we can now conduct systematic transfer learning experiments in which models trained on one imaging condition are evaluated on anatomically matched regions in the others (e.g., assess how pre-trained models (e.g., FFN) transfer to SmartEM hybrid data). These approaches and new datasets will enable the community to explore the relationship between imaging quality, downstream reconstruction outcomes, and model generalization across image acquisition regimes.

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Poster

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Program #/Poster #: PSTR477.14/VV10

Topic: J.07. Data Analysis and Statistics

Support: BRAIN CONNECTS: Toward a Statistical and Molecular Framework for Structural Connectomics

Title: Scalable Metrics for Connectome Quality Assessment

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Abstract: Connectomes are increasing in size, from the Drosophila Hemibrain to the MICrONS cubic millimeter and the human H01. Generating a connectome relies on multiple process steps, including automated machine segmentation, which generate data that can introduce various errors in the final morphological and neural circuit reconstruction. Proofreading - whether manual or automatic - remains essential to ensure a high-quality connectome. Furthermore, assessing the quality of a connectome is a critical step for scientific discovery so that downstream users are aware of the status of the connectome, including the confidence in the validity of its synaptic connectivity.In large and heterogeneous connectomic volumes, the number of fully proofread neurons is often limited. This motivates the need for methods that can evaluate connectome quality independently of available ground truth. Such methods can leverage

biological priors, labeled connectivity errors, and connectivity patterns across a large volume.We present a new pipeline and a set of metrics to assess the quality of fully or partially proofread connectomes, with the goal of informing ongoing proofreading activities and downstream analyses. Our quality measures operate at both the neuron and volume levels, using available metadata and connectivity structure. We introduce a framework which specifies minimal metadata needed to assess the quality of connectomes, including synaptic connectivity to identify merge errors and orphan segments, as well as cell-type annotations to detect issues such as unclassified neurons or non-neuronal cells. We demonstrate the method on the MICrONS cubic millimeter connectome, with emphasis on a fully proofread cortical column spanning all layers of the mouse visual cortex. Finally, we relate our metrics to existing definitions of connectome completeness in the Drosophila hemibrain and propose new definitions for MICrONS-scale datasets.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Program #/Poster #: PSTR477.15/VV11

Topic: J.07. Data Analysis and Statistics

Support: RF1MH132653 - cloudSLEAP

Title: Lablink: a cloud-based platform for reproducible and accessible scientific software training

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Abstract: The increasing complexity of computational tools in neuroscience poses barriers to access, reproducibility, and training. This constraint is exacerbated by the increasingly prevalent use of deep learning in scientific software, requiring specialized hardware such as graphics processing units (GPUs) and complicated software dependencies.To address these challenges, we developed LabLink, a general-purpose cloud infrastructure for delivering standardized, compute-enabled virtual machine environments tailored for scientific software—accessible directly through a web browser. LabLink enables researchers to explore, train, and run scientific tools without requiring local installation or high-performance hardware.LabLink consists of three modular components. The LabLink Allocator is a lightweight Flask-based service that automates virtual machine provisioning, assignment, and lifecycle management using a PostgreSQL backend and Terraform orchestration. It exposes a user-friendly web interface and RESTful API for managing resources, and is packaged as a Docker image with continuous integration support.The LabLink client base image provides a flexible, Linux-based environment with

NVIDIA GPU compatibility and is designed to support a wide range of research applications. It includes essential tooling such as Miniforge, Node Version Manager (nvm), and uv for fast and reproducible environment management. This base image ensures researchers have the building blocks needed to install and run domain-specific software with minimal friction.Each client VM also runs the LabLink client pip package (lablink-client-service), which launches a lightweight subscriber process on boot to connect with the allocator server. This subscription enables real-time message handling for session management and simplifies orchestration across distributed user environments.We demonstrate LabLink with SLEAP, an open-source pose estimation toolkit widely used in neuroscience. LabLink has facilitated GPU-powered, installation-free training sessions for hundreds of users, empowering researchers of all backgrounds to adopt advanced computational tools. Its modular, extensible architecture offers a reusable blueprint for deploying training-ready research environments across disciplines.

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Poster

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Program #/Poster #: PSTR477.16/VV12

Topic: J.07. Data Analysis and Statistics

Support: RF1MH132653 - cloudSLEAP

Title: Dreem: a transformer-based framework for multiple object tracking

Authors: *M. SHAIKH[1], T. D. PEREIRA[2], E. AZIM[4], U. MANOR[6], A. PRASAD[5], A. SHERIDAN[3], C. SCHIAVON[7];
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Abstract: Understanding the mechanistic basis for neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Charcot-Marie-Tooth disease (CMT) requires characterization of biological movement dynamics across multiple spatial and temporal scales. For example, investigating lysosome motility in neurons derived from patients with CMT can help to target future treatments. Similarly, analyzing the movement of mouse models of ALS can help to identify early signs of disease onset. However, capturing complex dynamics and interactions of animals, cells, and organelles in image sequences remains a challenging task. While detecting these in biological imaging data is now much more accessible in live microscopy (e.g., using CellPose) and in behavioral videos (e.g., using SLEAP), reliably linking these detections over time—i.e., multiple object tracking (MOT)—remains a major challenge, especially in settings with sparse visual cues and complex, variable imaging conditions. Current MOT models from the computer vision community, largely developed for domains like

pedestrian tracking, are limited by their reliance on local spatiotemporal information and convolutional neural networks (CNNs) that lack inductive biases suitable for biological data.Here we present DREEM (DREEM Relates Every Entity's Motion), a transformer-based MOT framework that directly learns temporal associations between instances across frames to address these challenges. DREEM uses attention mechanisms on features containing visual and spatiotemporal positional information to effectively combine these signals. We demonstrate that DREEM achieves state-of-the-art results on both animal and microscopy videos, with strong generalization to varying instance densities and imaging modalities.To promote accessibility and reproducibility, we release pretrained models for both microscopy and animal tracking tasks, along with all code and thorough performance evaluations using widely known metrics. By offering a generalizable MOT framework tailored for biological data, DREEM supports neuroscience research at multiple scales—from behavior to cellular dynamics—enabling better analysis of neural function and dysfunction.

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Poster

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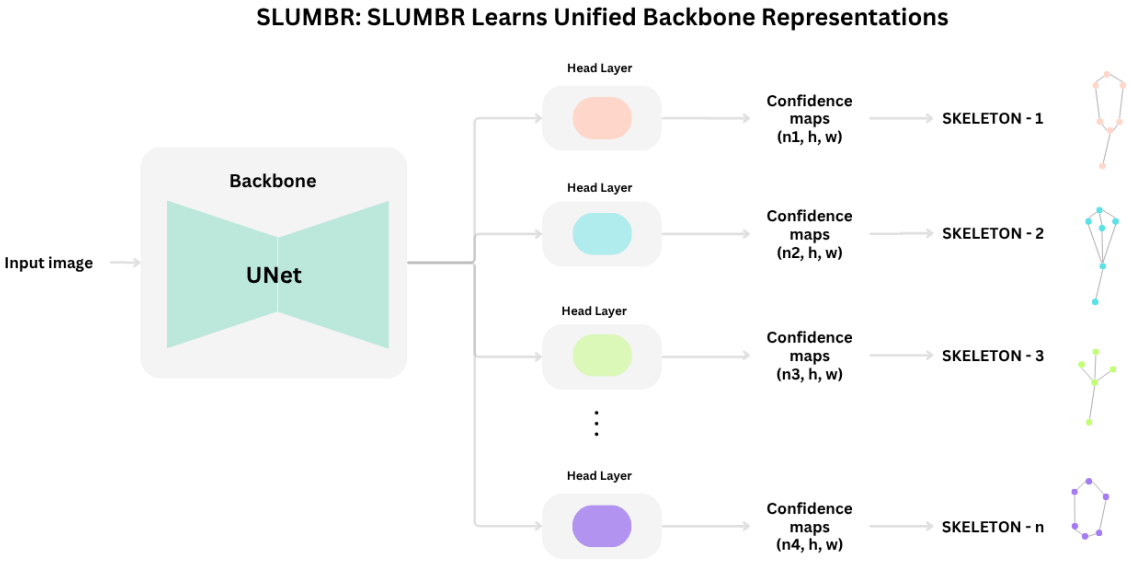
Title: Slumbr - Slumbr Learns Unified Backbone Representations

Authors: *D. MURALI[1], L. MAREE[2], C. R. LEE[3], R. L. MIRANDA[3], C. JIA[7], A. C. BASTUBA[4], N. NONO[1], S. N. OLINE[8], S. AFSHAR[9], K. M. TYE[5], A. L. FALKNER[10], T. D. PEREIRA[6];
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Abstract: Quantifying animal movements is key to understanding how the brain produces behavior and has advanced significantly with deep learning tools like SLEAP (Pereira et al., 2022). However, accurate pose prediction often requires large manually labeled datasets and varies across studies due to annotation biases. A promising solution is a foundation model trained on diverse datasets, enabling it to learn general representations and reducing the need for retraining, even under moderate domain shifts. Such a model can be used zero-shot or fine-tuned, depending on image-domain similarity.We present a foundation model for mice, trained on 13 diverse datasets comprising ~160,000 instances across 99,000 annotated frames, capturing

variation in resolution, zoom, brightness, and color. To learn shared representations across datasets with differing skeleton formats and annotation styles, we use a multi-head architecture inspired by prior human pose estimation work (Sárándi et al., 2023). Each dataset has a dedicated output head; the backbone is shared and trained using gradient accumulation, receiving updates from all datasets, while heads are updated with dataset-specific gradients.Training on diverse datasets allows the model to learn a shared feature space that generalizes zero-shot to unseen datasets and species. We observed that the shared backbone produces feature maps resembling segmentation masks, which each head refines into keypoint predictions tailored to its skeleton. These findings support the potential of shared representation learning to enable scalable, generalizable models for behavioral analysis. The model will be released in a major SLEAP update for enhanced multi-animal tracking.





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Poster

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NIH R24DA064430

Title: Ecosystem for multi-modal brain-behavior experimentation and research (EMBER): Towards a living resource for neurophysiological and behavioral data storage, harmonization, dissemination, and analysis

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Abstract: Neuroscience research has historically been limited by highly controlled environments and siloed research practices. The NIH BRAIN Initiative's Brain Behavior Quantification and Synchronization (BBQS) program offers an opportunity to overcome this challenge by supporting multi-modal, multi-scale approaches to behavioral neuroscience. Empowered by novel sensing technologies, advances in artificial intelligence and machine learning, and the availability of computing power, the neuroscience community is closer than ever to identifying neural bases of behavior in complex environments. An integral part of the BBQS mission is the creation and maintenance of a system that will allow storage, standardization, and dissemination of diverse datasets across human and non-human species, data modalities (e.g., behavioral, neural, physiological, and environmental), experimental paradigms, and scientific questions. Here, we introduce the Ecosystem for Multi-modal Brain-behavior Experimentation and Research (EMBER) which is the data archive for multi-modal neurophysiological and behavioral data, supporting the BBQS program. The architecture of EMBER is founded on two primary bases: (a) addressing ethical, legal, and social implications (ELSI) for storing and sharing human and animal subjects' data; and (b) adhering to findable, accessible, interoperable, and reusable (FAIR) data principles. As such, EMBER has three primary objectives: (1) institute a scalable cloud infrastructure that combines services such as EMBER-DANDI, an instance of the existing Distributed Archives for Neurophysiology Data Integration (DANDI) archive, and EMBERvault, a secure, HIPAA compliant resource for sensitive human data (e.g., PHI/PII), with flexible

metadata structures that enable data provenance, replication, and querying; (2) implement data synchronization and harmonization by leveraging data standards (e.g., NWB, BIDS, Psych-DS, and HED) that reduce barriers to reuse and analysis of complex, temporally dynamic brain-behavior datasets; and (3) integrate analysis tools and pipelines via the EMBER portal to enable broad community contributions and access. Community-driven development will be central to EMBER's success, creating an evolving ecosystem that enables not only today's neuroscientists but also future generations to make novel discoveries. EMBER will continue to work in close collaboration with the companion BBQS Data Coordination and Artificial Intelligence Center (DCAIC) to closely engage with and provide valued resources for the research community. This work is part of the broader BBQS EMBER effort, which is showcased at Booth #3830.

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Poster

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NIH #1R24MH117295 DANDI: Distributed Archives for Neurophysiology Data Integration
NIH #2R24MH117179-06 OpenNeuro: An open archive for analysis and sharing of BRAIN Initiative data
NIH #1R24MH136632-01 Ecosystem for Multi-modal Brain-behavior Experimentation and Research (EMBER)
NIH #1RF1MH132747-01 Psych-DS: A FAIR data standard for behavioral datasets
NIH #3OT2OD030541 K-CORE: Curation and Knowledge Management for SPARC
NIH #U24NS120057 Advancing Standardization of Neurophysiology Data Through Dissemination of NWB

Title: The Ecosystem of Standards in Neuroscience: Which Ones Are For You?

Authors: *Y. O. HALCHENKO[1], C. BAKER[1], J. BOLINE[2], K. BOUCHARD[3], A. P. DAVISON[4], S. E. DEVRIES[5], B. DICHTER[6], S. S. GHOSH[7], T. GILLESPIE[8], J. GRETHE

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Abstract: The neuroscience community has witnessed a proliferation of data standards aimed at enhancing reproducibility, data sharing, and collaboration. However, this abundance creates challenges for researchers navigating which standards to adopt. This presentation provides an overview of the current ecosystem of neuroscience data standards, their interrelationships, and practical implementation guidance.
We will survey established data standards for (i) storing and transmitting data, such as DICOM for neuroimaging, NWB for neurophysiological recordings, and OME-NGFF/-Zarr for microscopy images, (ii) for managing entire study datasets, such as BIDS, (iii) modality specific additional annotation of data, such as HED, and (iv) metadata model for integration and searchability in database systems, such as openMINDS and NIDM. We will also overview related tooling interface standards, such as BIDS-Apps and Boutiques. For each standard, we will outline scope, primary data domains, implementation requirements, community adoption, extension mechanisms, and integration with other standards, analysis pipelines, and platforms.This presentation aims to demystify the neuroscience standards landscape, empowering researchers to make informed choices about data management practices that enhance scientific reproducibility and collaboration. The presentation will map relationships between these standards and major data repositories, including DANDI, EMBER, NEMAR, OpenNeuro, SPARC, EBRAINS, BRAINLIFE, GIN, and others. We will highlight how these repositories and organizations like INCF promote, extend and enforce use of standards, while discussing their critical importance to ongoing initiatives such as the Brain Behavioral Quantification and Synchronization (BBQS) and BRAIN Connectivity Across Scales (BRAIN

CONNECTS). We will conclude with practical decision-making guidance for researchers to help identify which standards best suit specific research needs. Case studies will demonstrate how laboratories have successfully implemented combinations of standards to enhance their research workflows and facilitate data sharing. Find many of us in the cluster of exhibit booths #3824-3833 and 3924.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.20/VV16

Topic: J.07. Data Analysis and Statistics

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Title: Integration and development of AI/ML and analytical tools for the Data Ecosystem for the Brain-Behavior Research Community

Authors: *R. HINGORANI[1], G. BEZOLD[1], N. GUITTARI[1], N. THOMAS[1], W. COON[1], M. OGG[1], L. DIAZ[1], N. E. TREGONING[1], R. T. HIDER, Jr.[1], E. C. JOHNSON[1], C. BAKER[2], K. BOUCHARD[3], B. DICHTER[5], R. LY[4], O. RUEBEL[3], B. WOSSENSEGED[6], Y. O. HALCHENKO[2], S. S. GHOSH[7], T. D. PEREIRA[8], H. YI[1], B. A. WESTER[1];
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Abstract: For the past several years, there have emerged a set of highly capable analytical tools for quantifying organismal behavior, including for humans and non-human animals (e.g., pose estimation; behavioral segmentation; speech analysis; facial analysis). Supported by a

combination of advances in sensing technology and artificial intelligence/machine learning (AI/ML) approaches, these emerging methods are expected to help elucidate the neural bases of complex behaviors in naturalistic environments. To date, however, these AI/ML and analytical tools cannot be easily deployed and compared across multiple datasets, as they are designed for specific use cases, hosted in separate repositories, with idiosyncratic installation steps, while adhering to disparate data standards. Recently, the NIH BRAIN Initiative has launched the Brain Behavior Quantification and Synchronization (BBQS) program, of which ambitious mission includes creating a Data Ecosystem for analytical tools and behavioral neuroscience datasets that can be easily utilized by a wide range of researchers. A crucial component of this programmatic push is the Ecosystem for Multi-modal Brain-behavior Experimentation and Research (EMBER), the official Data Archive for the NIH BBQS program. Through EMBER, we have taken initial steps to integrate and standardize community-developed and custom analytical tools into a common platform. Here, we present two major achievements: (1) a standardized, cloud-based approach to store and access training and inference data for Social LEAP Estimates Animal Poses (SLEAP), an open-source deep-learning framework for multi-animal pose tracking (Pereira et al., 2022), enabling easier reproducibility and data sharing; and (2) novel foundation models for extracting features from speech recorded in ecologically valid settings and from electrophysiological recordings for personalized, data-driven sleep profiles. Going forward, we will broaden our efforts to encompass a wider range of analytical tools paramount to not only the BBQS-funded research activities but also the broader community. This will create a dynamic, Data Ecosystem in which data and analytical tools can be collocated to enable rapid exploration and accelerate neuroscience discoveries. This work is part of the broader BBQS EMBER effort, which is showcased at Booth #3830.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

Location: SDCC Halls B-H

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Program #/Poster #: PSTR477.21/Web Only

Topic: J.07. Data Analysis and Statistics

Title: Enabling Neurophysiology Reanalysis with LLM Tools for the DANDI Archive

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Abstract: The growing availability of open neurophysiology data can greatly accelerate discovery, improve reproducibility, and enable new analyses beyond original experiments. The DANDI Archive hosts over 350 standardized NWB-format datasets spanning various modalities, including electrophysiology, calcium imaging, fiber photometry, and behavioral data. However, many researchers struggle to reuse these resources due to unfamiliarity with NWB and difficulty finding relevant datasets.

To address these challenges, we developed an AI-powered system that leverages large language models (LLMs) in conjunction with autonomous tools for data inspection, visualization, and documentation generation. Our system aims to reduce the cognitive and technical overhead associated with accessing and reanalyzing public neurophysiology datasets, particularly for researchers who are not already deeply familiar with the NWB ecosystem or the DANDI Archive.

The system consists of two primary components: (1) an interactive chat-based assistant for answering dataset-specific questions in real time, and (2) an agent that explores datasets, generates visualizations, and produces introductory Jupyter notebooks tailored to each dandiset. These notebooks serve as structured starting points for further analysis, including code examples for data access, metadata inspection, and visualization.

A key innovation of our approach to generating notebooks is the use of a two-phase pipeline. In the first phase, an LLM agent systematically examines a dandiset's structure with some human supervision. This includes generating and executing Python scripts to inspect NWB file contents and producing initial visualizations. In the second phase, a separate LLM uses the results of this exploration to write an introductory Python notebook that includes relevant explanations and runnable code blocks. Importantly, the notebook generator is capable of catching and correcting its own errors during execution.

We applied this system to 12 recently published dandisets, producing notebooks with a total of 40 plots. Upon inspection, only 2 of these plots had significant problems, i.e., missing data or bad formatting. The other AI-generated plots and tutorials appeared to be sufficient and valid for helping users to get started working with the dandiset. In future work, we plan to have each notebook reviewed by human evaluators and assessed for scientific relevance, correctness, clarity, and usability. Once the exploration phase is further optimized we plan to apply this procedure to all dandisets on the archive.

Disclosures: J. Magland: None. **B. Dichter:** A. Employment/Salary (full or part-time): CatalystNeuro. **R. Ly:** None. **O. Ruebel:** None.

Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.22/VV17

Topic: J.07. Data Analysis and Statistics

Support: NIH #1RF1MH132747-01 Psych-DS: A FAIR data standard for behavioral datasets

Title: Psych-DS: A fair data standard for behavioral datasets

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Abstract: Behavioral data is central to biomedical research, including both measures taken in concert with imaging and other techniques (e.g. recording both brain activation and button-press responses in an fMRI scan), and those performed independently (e.g. comparing activations in a reading task to a standard literacy instrument.)
Compared to neurophysiology and brain imaging data, experimental behavioral data is also small, with dataset sizes in the megabytes rather than terabytes. The key roadblock is not size but variability: many studies are not designed for automated processing, and those that are lack common standards of format, organization, or documentation.
Psych-DS is a community-developed data standard for studies in the social/behavioral sciences that is supported by the BRAIN initiative, and currently available as both CLI and a fully client-side browser tool. The standard is designed for the needs of researchers who may be comfortable in a variety of programming languages, or who have not worked with automated analytic pipelines. It relies on standard open-source file formats, and can be implemented by hand for simple cases. Critically, it uses a single JSON-LD metadata file which will validate against the schema.org Dataset type, meaning that Psych-DS datasets come equipped for indexing (e.g. Google Scholar), inclusion of unique identifiers (ORCID, DOI), and other linked data integration.
While Psych-DS is designed to be simple enough for small datasets and implementable by hand, it is also designed to be "BIDS-aware." Compatible Psych-DS datasets can be converted to the participant-level and session-level TSV files in a BIDS architecture. BIDS directories can also be exported to a Psych-DS compliant directory containing only the behavioral response data and metadata. Allowing behavioral experimental data to be easily extracted from and merged with related neurophysiological and neuroimaging data can provide both increased flexibility and reduced complexity of analytic processing pipelines suited to each type of data.
The lack of consensus around how seemingly simple behavioral data are organized and documented limits the integration of behavioral research data into neuroscience infrastructures. Implementation and adoption of the Psych-DS standard will provide a machine-readable format for diverse research contexts, and support further efforts in standardization and reproducibility.

Disclosures: M. Kline Struhl: None.

Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Program #/Poster #: PSTR477.23/VV18

Topic: J.07. Data Analysis and Statistics

Support: Schmidt Futures Foundation SF 857
National Human Genome Research Institute 1RM1HG011543
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Institute for the Biology of Stem Cells
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Title: Spikecanvas: a modular cloud interface for HD-MEA data processing and electrophysiology feature analysis

Authors: *J. GENG[1,2], K. VOITIUK[1,2], D. PARKS[3,2], A. ROBBINS[1,2], H. SCHWEIGER[4,2], S. HERNANDEZ[1,2], J. GONZALEZ FERRER[3,2], A. SPAETH[1,2], J. SEVETSON[4,2], T. SHARF[3,2], S. SALAMA[4,2], D. HAUSSLER[3,2], M. A. MOSTAJO RADJI[2], M. TEODORESCU[1,2];
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Abstract: Cloud computing has become essential for high-throughput neural data processing because it provides ample resources to analyse massive amounts of data. High-density microelectrode arrays (HD-MEAs) capture thousands of neuronal spikes simultaneously, preserving rich information about the in vitro functional neural networks. Rapidly processing this data poses challenges to typical workstation hardware and orchestrating cloud resources often requires specialized DevOps expertise. To address these challenges, we created SpikeCanvas, a web-based graphical interface that allows users to compose containerised algorithms as “blocks” to build scalable, cloud-based processing pipelines. A one-click wizard packages GitHub repositories into Docker images and registers them as reusable blocks. As a job runs, the browser updates resource usage and live job status. SpikeCanvas supports the Neurodata Without Borders (NWB) file format and has already processed terabytes of recordings from HD-MEAs with thousand of channels. This pipeline ships with built-in blocks for spike sorting and electrophysiology feature-extraction modules, such as local field potential and functional connectivity analysis. To demonstrate SpikeCanvas’s capabilities, we show the processing of 160 longitudinal recordings of cortical organoids. This experiment was performed using MaxWell’s MaxOne HD-MEA, and the activity of cortical organoids was sampled every hour for seven days. Single-unit data were generated using SpikeCanvas’s spike sorting and autocuration functions. As a result, we tracked neuronal units over seven days while simultaneously providing visualizations of their locations on the HD-MEA and their firing rate trajectories over time. As an open-source and modular pipeline, SpikeCanvas combines cloud scalability and container-level reproducibility while lowering the barrier to advanced neuronal data analysis.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Program #/Poster #: PSTR477.24/VV19

Topic: J.07. Data Analysis and Statistics

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Title: Quantitative mapping of mesoscopic structural connectivity at the single axon level using deep learning and high-resolution light sheet fluorescence microscopy

Authors: *A. ATTARPOUR[1,3,4], M. RAFFIEE[6,7], T. XU[1,3], J. OSMANN[3], S. PATEL[3], G. YU[3], A. CROW[6,7], B. ESHAGHI GHARAGOZ[6,7], M. W. ROZAK[1,3], I. AUBERT[5,2], J. MCLAURIN[5,2], K. DEISSEROTH[6,7], B. STEFANOVIC[3,1,4], M. GOUBRAN[1,3,4];
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Abstract: Understanding alterations to brain networks in neurodegeneration necessitates a comprehensive investigation of 3D structural neuronal connectivity. Advances in light sheet fluorescence microscopy (LSFM) and tissue clearing have enabled high-fidelity whole-brain connectivity imaging in intact tissue. However, current computational pipelines lack the generalizability required to accurately map individual single axons and analyze their group-wise connectivity quantitatively.We developed MAPL3 (Mapping Axonal Projections in Light sheet fluorescence microscopy in 3D), an end-to-end pipeline for brain-wide axonal mapping and connectivity analysis across populations. By integrating convolutional neural networks and vision transformers, MAPL3 employs an innovative deep learning model architecture to capture fine-grained local features within each image patch and long-range contextual information between 3D sub-volumes. This model was pre-trained using self-supervised learning with an image reconstruction task on an exceptionally large dataset of 22,000 unlabeled 3D sub-volumes to enhance model robustness and address the difficulty of producing manual annotations. This was followed by model fine-tuning on large LSFM data of AAV-based virus tracing (1000 3D sub-volumes) with labels, using an advanced hybrid loss function tailored to address substantial class imbalance. We evaluated our model against state-of-the-art (SOTA) algorithms, D-LMBmap and TrailMap, on the test and an unseen (out-of-distribution) dataset (from a different microscope and resolution). To highlight its utility, we apply MAPL3 to chart axonal projections originating from the right orbitofrontal cortex (OFC; labeled with AAV8-CaMKIIa-eYFP-NRN; N=4) in comparison to SOTA pipelines.MAPL3 outperformed SOTA methods across all evaluation metrics, achieving significantly higher segmentation accuracy (an average improvement in Dice of 0.30 vs. D-LMBmap, and 0.50 vs. TrailMap; $p < 0.0001$). On the unseen

dataset, MAPL3 achieved significantly higher recall (0.82 ± 0.12) than both D-LMBmap (0.20 ± 0.30) and TrailMap (0.58 ± 0.20), highlighting its superior generalizability in detecting axonal projections in new experimental protocols ($p < 0.0001$). Notably, MAPL3 uncovered long-range and sub-regional projections such as fibers from the right OFC crossing to the contralateral hemisphere or reaching the dorsal raphe nucleus that were missed by existing models.MAPL3 enables generalizable mapping of single axons across tera-voxel whole-brain datasets, unlocking mesoscopic quantification of structural connectivity with unprecedented scale.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

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Program #/Poster #: PSTR477.25/VV20

Topic: J.07. Data Analysis and Statistics

Title: Multiscale Recording and Analysis of Supra- and Sub-threshold Neuronal Activity Using Nanoelectrode Arrays

Authors: *S. SHUKLA[1], C. WALSH[2], S. BANSAL[3], G. CAUWENBERGHS[4], S. CHALASANI[6], Z. JAHED[5];
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Abstract: The laws governing neuronal behavior transcend length scales. Technological advancements in spatiotemporal resolution have revealed that individual neurons utilize subcellular dynamics to process information, modulate excitability, and communicate changes of state to distant neurons within neural networks. In other words, the interrelationship between intracellular signaling cascades and network-level dynamics is becoming increasingly accessible for identifying therapeutic targets in neurological disorders and detecting early biomarkers of neurodegenerative diseases. However, while scalable methods for subcellular chemical and genetic characterization are mainstream for modern neuroengineers, the development of a parallel platform for the orthogonal but crucial phenomenon of sub- and supra-threshold neuronal bioelectricity has trailed behind. Current high throughput neuroelectronic tools such as *in vitro* and implantable microelectrode arrays do not have subcellular resolution, while nanostructured electrode arrays (NEAs) suffer from severe attenuation and distortion, obscuring the neuron's true electrophysiological state. Progress in neuronal NEA platforms has slowed, mainly due to 1) insufficient clarity in understanding the biophysical mechanism behind

neuron/nanomaterial interfaces, and 2) underdeveloped tools for extracting and analyzing multi-dimensional neural data from highly sensitive nanoscale biosensors. In this work, I elucidate universal tenets of neuronal electrical signaling, define the limitations of existing nanoscale biosensors used for neural recording, characterize my own nanoelectrode array capable of recording supra- and sub-threshold electrical and electrochemical events across diverse neuronal populations, and offer more appropriate and scalable analytical methods for future multiscale neuro-technologies. Critically, I developed a multiscale dynamic spike sorter that integrates local field potentials, action potentials, and subthreshold potentials, providing unprecedented insight into the excitability states of single neurons and mapping them to network activity. This novel approach enables the detection of subtle changes in neuronal excitability associated with early stages of neurodegenerative and neurodevelopmental disorders, long before structural changes become apparent. This approach can accelerate the development of versatile neuroelectronic interfaces that lead to improved diagnostics and therapeutic interventions for neurological diseases in the coming decades.

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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

Location: SDCC Halls B-H

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Program #/Poster #: PSTR477.26/VV21

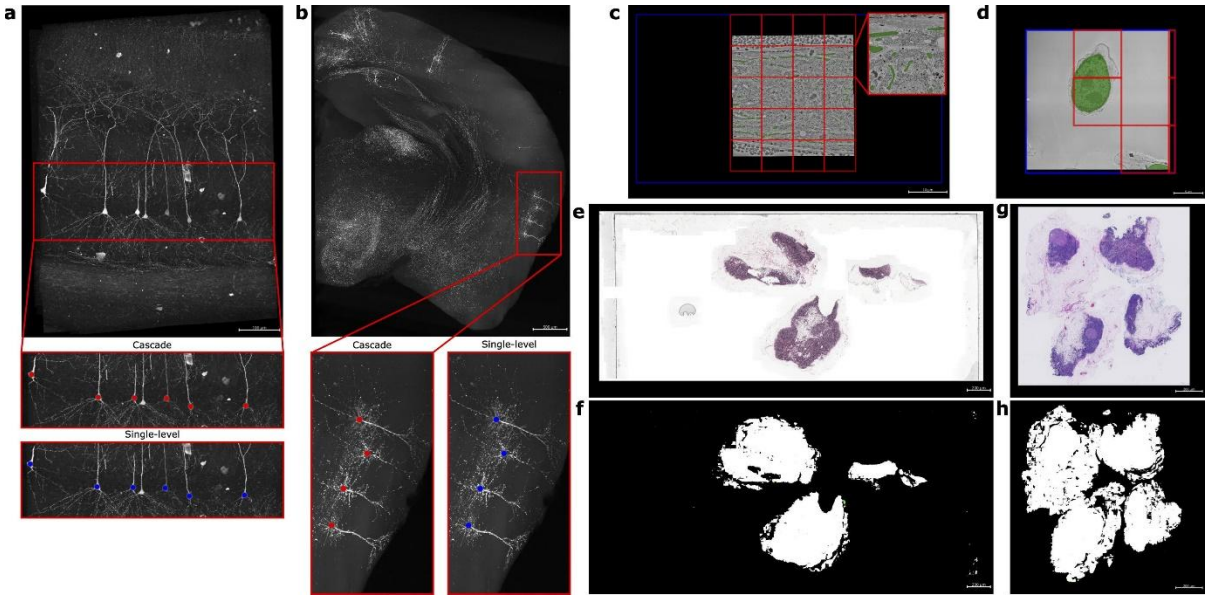
Topic: J.07. Data Analysis and Statistics

Support: MIT-Novo Nordisk Artificial Intelligence Postdoctoral Fellowship

Title: Cascade Detector Analysis and Application to Biomedical Microscopy

Authors: *T. L. ATHEY;
MIT, CAMBRIDGE, MA

Abstract: As both computer vision models and biomedical datasets grow in size, there is an increasing need for efficient inference algorithms. We utilize cascade detectors to efficiently identify sparse objects in multiresolution images. Given an object's prevalence and a set of detectors at different resolutions with known accuracies, we derive the accuracy, and expected number of classifier calls by a cascade detector. These results generalize across number of dimensions and number of cascade levels. Finally, we compare one- and two-level detectors in fluorescent neuron detection, organelle segmentation, and tissue segmentation across various microscopy modalities. We show that the multi-level detector achieves comparable performance in 30-75% less time. The attached image shows the results of our method on a variety of datasets, including fluorescence images of mouse brains, and electron microscopy images of the C. elegans head. Our work is compatible with a variety of computer vision models and data domains.



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Poster

PSTR477: Cellular-Level Tools, Standards, and Analyses

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.27/VV22

Topic: J.07. Data Analysis and Statistics

Title: Optic: rapid and efficient semi-automated analysis toolbox for multi-cellular calcium imaging data

Authors: *N. FUKATSU[1,3], Y. TANISUMI[3], Y. SAITO[2], A. HASHIMOTO[2,3,4], H. WAKE[2,3]; [2]Dept. of Anat. and Mol. Cell Biol., [1]Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan; [3]Div. of Multicellular Circuit Dynamics, Natl. Inst. for Physiological Sci., Okazaki, Japan; [4]Max Planck Inst. for Biol. of Ageing, Cologne, Germany

Abstract: The amount of data generated in neuroscience research continues to grow exponentially. Specifically, calcium imaging data frequently reach gigabyte or even terabyte scales. Although automated analytical tools like Suite2p (Pachitariu et al., 2017) and CaImAn (Giovannucci et al., 2019) efficiently extract regions of interest (ROIs) from imaging data, several downstream analyses still rely on manual intervention, including curating genuine ROIs from noise and tracking identical cells across multiple sessions. To address these challenges, we aimed to develop a semi-automated analytical toolbox. We developed OPTIC (OPtimized Toolbox for Image-based Cellular analysis), comprising three GUI applications: 1) Calcium Imaging ROI Curation, assisting in the verification of true cell ROIs; 2) Calcium Imaging ROI Tracking, facilitating the matching of identical ROIs across multiple imaging sessions; and 3)

Microglia Tracking, enabling tracking and analysis of microglial cells in 2D time-series data. OPTIC implements Elastix-based image registration and automated ROI tracking based on optimal transport theory. Compared to existing ROI tracking applications such as CellReg (Sheintuch et al., 2017) and TrackMate (Ershov et al., 2022), OPTIC demonstrated significant performance improvements. For Calcium Imaging ROI Tracking, OPTIC achieved an F1-score of 0.94, a recall of 0.96, and a precision of 0.92, outperforming CellReg (F1-score: 0.44, recall: 0.46, precision: 0.53) and TrackMate (F1-score: 0.21, recall: 0.19, precision: 0.26). Similarly, for Microglia Tracking, OPTIC attained an F1-score of 0.90, a recall of 0.83, and a precision of 0.99, substantially surpassing CellReg (F1-score: 0.34, recall: 0.29, precision: 0.49) and TrackMate (F1-score: 0.02, recall: 0.01, precision: 0.09).OPTIC significantly improves cell tracking accuracy compared to published tools, enabling previously challenging research approaches, including long-term cellular activity tracking and large-scale comparative analyses. This package is publicly available on GitHub and can be freely installed and used (https://github.com/dhino2000).

Disclosures: N. Fukatsu: None. **Y. Tanisumi:** None. **Y. Saito:** None. **A. Hashimoto:** None. **H. Wake:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

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Program #/Poster #: PSTR478.01/WW1

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant R01EB034143

Title: Multiscale cortical circuit model predicts evoked response to transcranial magnetic stimulation

Authors: *Z. ZHAO[1], A. ABERRA[2], A. OPITZ[1];
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Abstract: Non-invasive brain stimulation techniques like transcranial magnetic stimulation (TMS) offer promising avenues for modulating brain activity, but the neural circuits activated during TMS are still poorly understood. Detailed neuronal morphology and E-field coupling are essential for modeling TMS effects, highlighting limitations of previous point-neuron approaches. We present a novel multi-scale computational cortical circuit model to investigate TMS effects within the primary motor cortex (M1) at both single-cell and population levels. Our model comprises approximately 8,000 multicompartmental biophysically realistic pyramidal neurons and 2,000 inhibitory interneuron models, interconnected by over 10 million excitatory and inhibitory synaptic connections. These neurons are arranged in cortical layers based on the M1 cytoarchitecture. We integrated this model into a finite element method (FEM) head model to couple realistic TMS-induced electric fields with the neuron population. Background and

thalamic inputs were implemented to generate ongoing intrinsic activity. We measured early and later responses to TMS and compared the model predictions with *in vivo* recordings. Our model demonstrates that L5 pyramidal neurons are directly activated by single-pulse TMS at the lowest intensity compared to other cell types. The cortical column model reproduces a number of experimentally known responses, including early excitation lasting ~30 ms followed by >100 ms inhibition of firing rates below baseline. Both the early excitation and the duration of the following inhibition increased with stimulation intensity. Model local field potentials (LFPs) replicate the dose-dependent N50 component of TMS-evoked potentials observed in non-human primate recordings. These findings have important implications for optimizing TMS protocols in both research and clinical applications, potentially leading to more effective therapeutic interventions for neurological and psychiatric disorders.

Disclosures: Z. Zhao: None. **A. Aberra:** None. **A. Opitz:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.02/WW2

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant 1RF1DA055665

Title: Biologically Constrained Nelder-Mead Optimization of Large-Scale Mechanistic Model of Rat Hippocampal CA1 Area

Authors: *C. XU[1], G. J. YU[3], X. ZHANG[1], D. SONG[2,1], L. NIEDERMEIER[4];
[1]Alfred E. Mann Dept. of Biomed. Engin., [2]Dept. of Neurolog. Surgery, USC, Los Angeles, CA; [3]Psychiatry and Behavioral Sci., Duke Univ., Durham, NC; [4]Stafa, Zurich, Sweden

Abstract: Large-scale mechanistic models of spiking neural networks (SNNs) provide a powerful framework for investigating hippocampal dynamics. However, real-time optimization of such models is challenging due to their high-dimensional parameter space, large memory footprint, and computational demands. We present a biologically constrained optimization strategy using the Nelder-Mead (NM) heuristic algorithm, implemented in CARLsim6—a GPU-accelerated platform for simulating Izhikevich SNNs.Our rat hippocampal CA1 model includes 8 neuron types, 64,916 neurons, and 40 anatomically constrained connection types. The optimization goal is to match the mean firing rates of each neuron type to values reported in the literature. Synaptic weights across connections were the free parameters. Optimization was performed using CARLsim6's built-in scaleWeights function, which allows real-time weight adjustment without reconfiguring the network.The objective function was defined as the average percentage error between simulated and target firing rates. Since NM requires n+1 initialization sets for n parameters (41 in our case), we developed a two-step biologically informed initialization strategy. First, each synaptic weight was tuned based on literature-reported

postsynaptic potential amplitudes and half-height widths. Second, 40 additional initialization sets were generated by applying ±35% symmetric log-domain perturbations, with log-uniform sampling to ensure balanced exploration.This biologically constrained initialization significantly improved convergence: the average error decreased from over 7900% to ~78% after 600 iterations. In contrast, random initialization across a broader range (0.1×-10×) led to poor convergence, with final errors stabilizing around 146%.These findings highlight the importance of incorporating biological constraints into heuristic optimization for large-scale SNN modeling.

Disclosures: C. Xu: None. **G.J. Yu:** None. **X. Zhang:** None. **D. Song:** None. **L. Niedermeier:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.03/WW3

Topic: J.06. Computation, Modeling, and Simulation

Support: DOD NDSEG Fellowship

Title: Constraint-based modeling of the drosophila connectome reveals genetic determinants of synaptic connectivity

Authors: *B. MOHAMMED, M. RUBINOV;
Biomed. Engin., Vanderbilt Univ., Nashville, TN

Abstract: Recent advances in mapping the Drosophila connectome have enabled brain-wide analyses of neural circuitry at single-synapse resolution. With over 130,000 neurons and 54 million synapses, the Drosophila connectome offers a unique opportunity to study an entire adult brain at single-cell resolution (Dorkenwald et al., 2023). At the same time, advancements in sequencing technology enabled single-cell transcriptomics data of an entire adult Drosophila with over 580,000 cells sequenced (Li et al., 2022). Despite this wealth of data, the genetic and molecular determinants underlying synapse formation and the overall architecture of brain connectivity remain poorly understood. Here, we present an integrative pipeline combining single-cell transcriptomic data from the Fly Cell Atlas with the Flywire connectome to investigate genetic drivers of structural connectivity. Using differential gene expression analysis, we compared neuron clusters with and without synaptic connections, filtering from ~18,000 genes to identify those significantly associated with connectivity. We then computed gene co-expression metrics to quantify gene-gene interactions for each neuron cluster pairing. To investigate how these genetic factors relate to network structure, we employed constraint-based modeling (Rubinov, 2016) to generate null connectome samples preserving varying degrees of neuron cluster connectivity. By fitting a non-negative linear model to predict these null samples from gene co-expression data, we assessed the influence of gene interactions on constraints governing neuron cluster connectivity.Our pipeline revealed 110 genes ($p < 0.001$) strongly

associated with synaptic connectivity, many previously implicated in synapse formation. Analysis of null models showed that as the number of neuron clusters' degree constraints decreased, model performance became consistently less than the empirical connectome's performance ($p < 0.001$ when only 1 node is constrained). This relationship suggests that gene co-expression patterns among the filtered genes is associated with the number of connections for each neuron cluster, highlighting their role as determinants of structural connectivity. Our findings provide novel insights into the genetic factors shaping brain structural connectivity and a mathematical approach to demonstrate that constraint-based network modeling effectively uncovers the complex interplay between gene expression and neural circuit architecture in the Drosophila brain.

Disclosures: B. Mohammed: None. **M. Rubinov:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.04/WW4

Topic: J.06. Computation, Modeling, and Simulation

Support: Wallace Coulter Foundation
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Natural Sciences and Engineering Research Council of Canada (NSERC)
Provincial Endowed Academic Chair in Autism
Canada Foundation for Innovation (CFI)
Western University BrainsCAN award grant
NIEH T32ESO33955

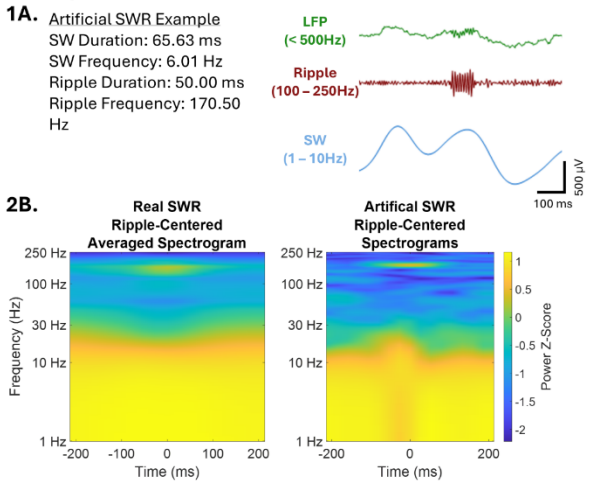
Title: Modeling Sharp-Wave Ripples in the Primate Hippocampus: From Wavelet-Based Synthesis to Biophysically Realistic Microcircuits

Authors: *C. OTERO[1], D. B. PIZA[3], J. C. MARTINEZ-TRUJILLO[4], J. J. RIERA[2]; [2]Biomed. Engin., [1]Florida Intl. Univ., Miami, FL; [4]Dept. of Physiol. and Pharmacol. and Psychiatry, [3]Western Univ., London, ON, Canada

Abstract: Sharp wave-ripples (SWRs) are synchronous local field potential (LFP) signatures within hippocampus (HPC) implicated in memory processes. While well-characterized in rodents, few computational models capture the distinct neuroanatomy of the primate HPC, where cell morphology differ significantly. Moreover, most existing models do not integrate SWR simulations with real primate neural data, limiting our understanding of how primate-specific circuitry governs SWR dynamics. Here, we present a dual approach: (1) a wavelet-based artificial SWR generator informed by the statistical properties of real SWRs recorded from marmosets (Fig. 1A), and (2) a biophysically realistic CA1 columnar model constructed using the Allen Institute's Brain Modeling Toolkit (Fig. 2A). To generate synthetic SWRs, we

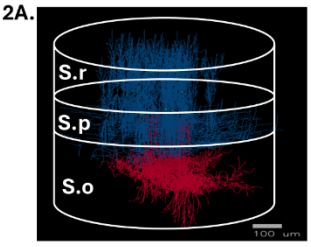
independently modeled wavelets to compose both the sharp wave and ripple components respectively. These wavelets were then combined with a Wiener process to represent the LFP signature of a SWR. The duration and frequency of each component were sampled from empirically fitted distributions derived from thousands of real marmoset SWR events. This enabled realistic composition of synthetic SWRs with biologically grounded variability. For the biophysical model, we created a primate-specific CA1 microcircuit aligned to the hippocampal mantle, incorporating 25 pyramidal cells and 5 parvalbumin-positive basket cells. Using BMTK, we simulated extracellular signals from this network to reproduce the key electrical features of SWRs under a point-source approximation. Comparison between 6000 real and 6000 artificial SWRs using ripple-centered spectrograms reveals strong similarity ($r = 0.958$, $p < 1e\text{-}16$) (Fig. 1B). Electrode recordings from the biophysical model reproduce spectral features of SWR-filtered activity (Fig.2B). Together, these models offer a computational foundation to study the composition and neural circuitry of SWRs in primates, advancing our understanding of hippocampal memory processes.

Fig. 1. Wavelet-Based Artificial SWR Generator



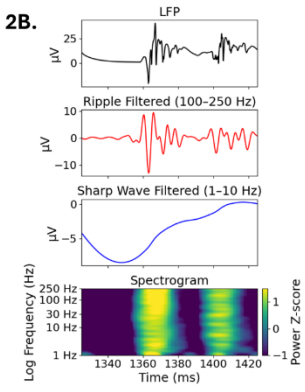
1A. Example of an artificial SWR generated using the wavelet-based synthesis method. Features shown on the left, filtered EEG signals on the right. Scale bar applies to all traces. **2B.** Average ripple-centered spectrograms of 6000 real recorded SWRs from marmoset hippocampus vs 6000 Artificial generated SWRs using wavelet-based synthesis. There was a strong positive correlation between the flattened signal of the real and artificial SWR averaged spectrograms (Pearson, $r = 0.958$, $p < 1 \times 10^{-16}$).

Fig. 2. Biophysical Realistic CA1 SWR columnar model



Number of cells:
25 CA1 Pyramidal Cells
5 Parvalbumin Basket Cells
Connections:

Synapse	From	To
AMPA	PC	PVBC Soma
AMPA	PC	PC apical (≥100 µm)
GABA	PVBC	PC soma
GABA	PVBC	PVBC soma
AMPA	Model Input	PC apical (≥200 µm)



2A. Visual representation of columnar structure with the number of each cell and synapse connections table on the right. **2B.** Electrophysiological signals in a 100ms window derived using a point-source approximation method from a representative electrode placed in center of the network. The top trace shows the LFP, the middle shows the ripple filtered signal, and the bottom trace shows the sharp wave-filtered signal.

Disclosures: C. Otero: None. **D.B. Piza:** None. **J.C. Martinez-Trujillo:** None. **J.J. Riera:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.05/WW5

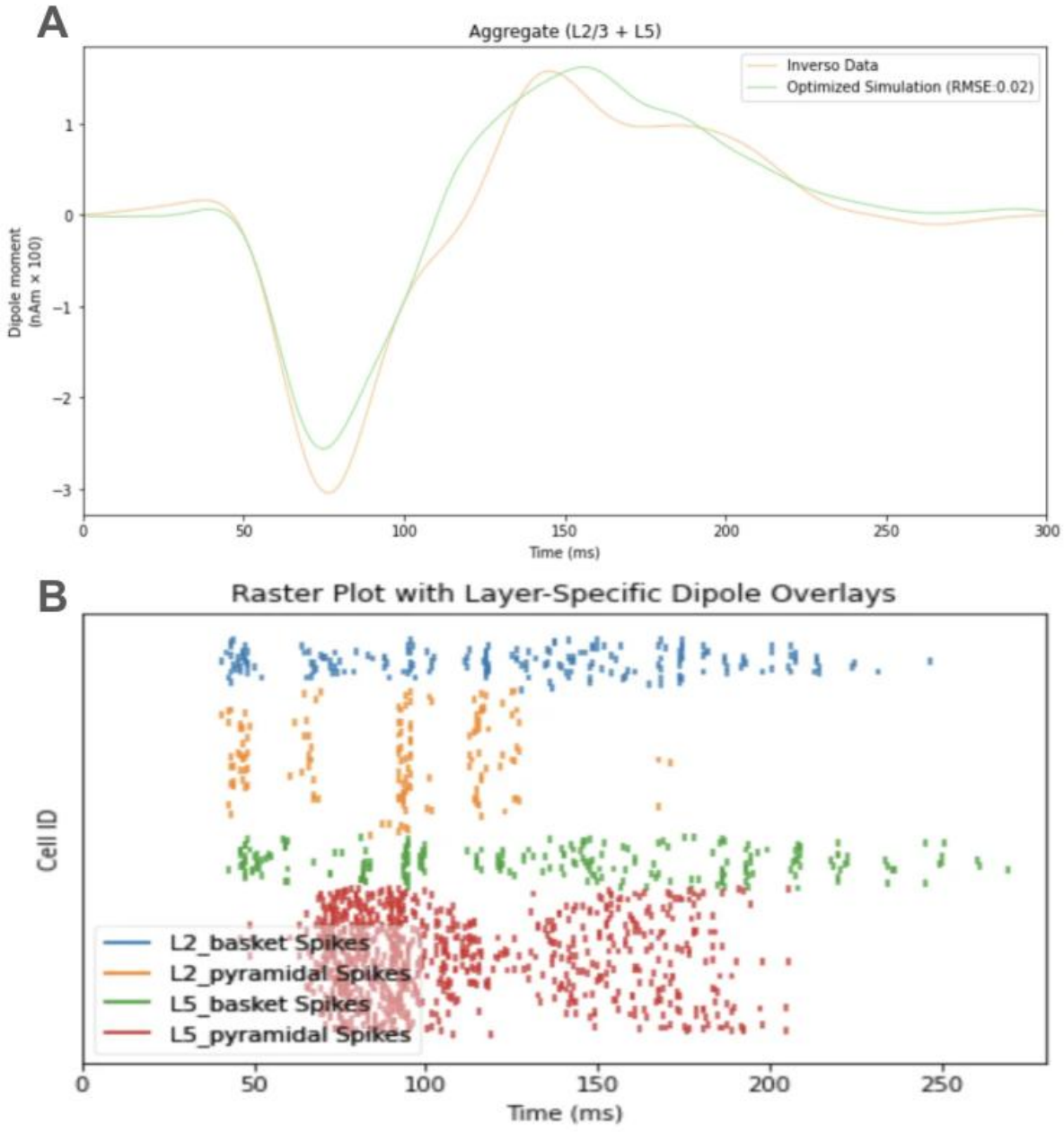
Topic: J.06. Computation, Modeling, and Simulation

Support: NINDS-U24 GR5272173

Title: Biophysical neural modeling with the Human Neocortical Neurosolver to uncover multiscale thalamocortical dynamics in visually-evoked potentials

Authors: *E. KAPLAN[1,2], S. R. JONES[2];
[1]Cognitive Sci., UCSD, San Diego, CA; [2]Dept. of Neurosci., Brown Univ., Providence, RI

Abstract: Event-related potentials (ERPs) recorded from primary visual cortex (V1) after stimulus presentation represent early visual processing. Despite extensive research on V1 ERPs, the precise cellular and circuit origins of specific ERP components measured with electroencephalography (EEG) in humans remain elusive. Identifying these neural mechanisms is crucial for linking macroscopic electrophysiological signals to the underlying cortical microcircuits of V1, which are fundamental to visual perception. This investigation utilized the Human Neocortical Neurosolver's (HNN) biophysical model of a canonical neocortical circuit, with layer specific drive from exogenous thalamic and cortical areas, to simulate the cellular and circuit mechanisms underpinning source localized V1 ERPs generated by the presentation of a dartboard stimulus in healthy subjects. A unique feature of HNN is that simulated current source input can be directly compared to source localized signals in the same units of measure (nAm), enabling interactive examination of model parameters that can account for recorded data. We demonstrate that a specific sequence of exogenous thalamo-cortical and cortical-cortical drives, previously shown to account for somatosensory and auditory ERPs, can produce the V1 ERP (Figure1). Due to HNN's level of biophysical detail, corresponding layer and cell-type spiking, local field potential / current source density, and intracellular processes like dendritic calcium dynamics can all be quantified, providing multiscale targets to constrain and test model-derived predictions. We show that the predicted results are consistent with prior studies using invasive techniques in animal models. These results may suggest a canonical thalamocortical mechanism promoting sensory-perception at the circuit-level in human V1.



Disclosures: E. Kaplan: None. **S.R. Jones:** None.

Poster

PSTR478: Network Models II

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Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.06/WW6

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant 5U24NS129945-03

Title: Human Neocortical Neurosolver (HNN): An open-source software for cellular and circuit-level interpretation of human MEG/EEG

Authors: *S. R. JONES[1], **D. DANIELS**[2], A. E. SOPLATA[7], N. TOLLEY[2], K. DUECKER[3], M. JAS[8], R. THORPE[4], G. T. DANG[5], C. FERNANDEZ PUJOL[6];
[1]Brown Univ., Hingham, MA; [3]Neurosci., [4]Dept. of Neurosci., [5]Ctr. for Computation and Visualization, [2]Brown Univ., Providence, RI; [6]Dept. of Neurosci., Brown Univ., cutler bay, FL; [7]Anesthesia, Critical Care and Pain Med., Blue Brain Project, EPFL, Genève, Switzerland; [8]Radiology, Massachusetts Gen. Hosp., Boston, MA

Abstract: The Human Neocortical Neurosolver (HNN) is a user-friendly neural modeling software designed to provide a cell and microcircuit-level interpretation of macroscale magneto- and electroencephalography (M/EEG) signals (hnn.brown.edu, Neymotin et al. 2020). The foundation of HNN is a biophysically-detailed neocortical model, representing a patch of neocortex receiving thalamic and corticocortical drive. The HNN model was designed to simulate the time course of primary current dipoles and enables direct comparison, in nAm units, to source-localized M/EEG data, along with layer-specific cellular activity. HNN workflows are constructed around simulating commonly measured ERPs and low-frequency oscillations.
HNN is available as a Python package (deemed HNN-Core, Jas et al. 2023) and can be accessed through an interactive and user-friendly graphical user interface (GUI) or through the Python application programming interface (API), which provides additional functionality beyond what is available in the GUI. HNN-Core was created with best practices in open-source software to allow the computational and human neuroscience communities to understand and contribute to its development.
HNN-Core has recently been updated to version 4.0, which includes a newly-redesigned GUI with a clean interface and updated tutorials on simulating ERPs and low-frequency oscillations in the alpha, beta, and gamma bands. Other new features in version 4.0 include the ability to run batches of simulations across multiple parameter sets, the ability to record calcium concentrations at the soma or all section of the neurons, the ability to render the network in 3D with animations, and significant improvements to the API, documentation, and pedagogical exemples.
HNN is available to install with a single command on PyPI (`pip install hnn_core`). We also offer a new set of instructions to install HNN with MPI parallelism using Conda. Parallelism significantly speeds up simulations, and the new Conda installation method notably streamlines the process of setting up parallel simulations on personal computers. HNN is also accessible through computing resources offered by the Neuroscience Gateway (NSG) enabling large simulation workloads.
Overall, HNN is a one-of-a-kind, openly-distributed tool designed for a broad user community to develop and test hypotheses on the multiscale origin of human M/EEG.

Disclosures: S.R. Jones: None. **D. Daniels:** None. **A.E. Soplata:** None. **N. Tolley:** None. **K. Duecker:** None. **M. Jas:** None. **R. Thorpe:** None. **G.T. Dang:** None. **C. Fernandez Pujol:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.07/WW7

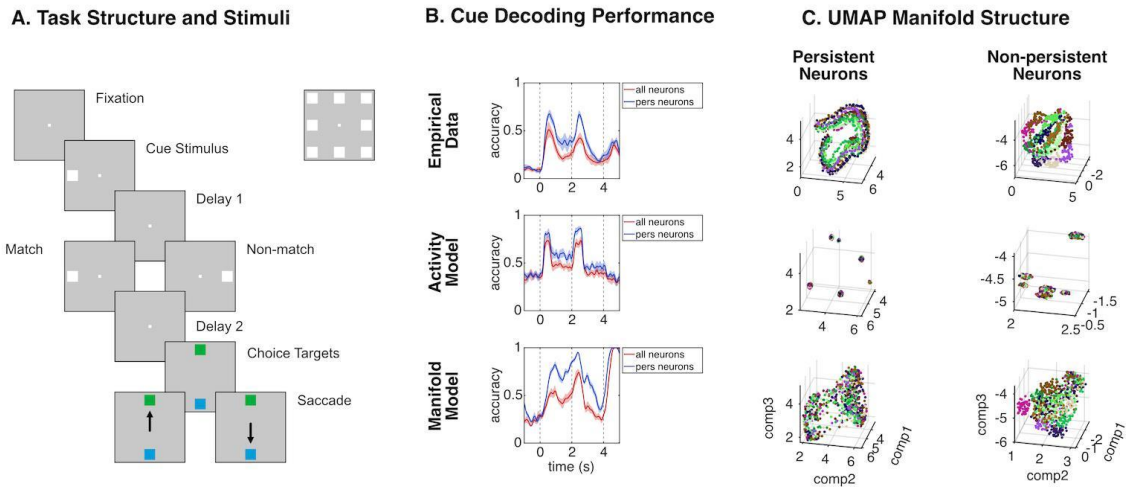
Topic: J.06. Computation, Modeling, and Simulation

Support: NIH R01 EY017077

Title: Statistical importance of persistent activity and temporal covariance for working memory

Authors: *A. ABBASI[1], A. NANDA[1], W. DANG[1], B. SINGH[2], C. CONSTANTINIDIS[1], M. RUBINOV[1];
[1]Biomed. Engin., [2]Vanderbilt Univ., Nashville, TN

Abstract: Working memory is the temporary storage and manipulation of information that supports complex cognition. One theory of working memory attributes this process to persistent activity of neuronal populations in the prefrontal cortex. Another theory attributes it to the "activity silent" reconfiguration of patterns of activity in these populations, that do not alter mean firing rate during cognition. The extent to which these theories make mutually exclusive predictions is unclear. Here, we developed an advanced statistical framework to test these models in population recordings of prefrontal cortex of macaque monkeys performing a spatial working memory task.
We analyzed responses of persistent (n=413) and non-persistent (n=649) prefrontal neurons from tasks centered on eight spatial cues (Fig 1A). We developed models of data with diverse neurobiological constraints. Our first model preserved each neuron's mean activity and norm across task epochs (such as fixation period and cue presentation period), thus constraining covariance between epochs. Our second model preserved the first three temporal principal components of persistent and non-persistent populations per cue for each cue location. We evaluated both models using two metrics: SVM decoding accuracy of cue location over time (Fig 1B), and UMAP manifold structure (Fig 1C).
We found that both models decoded the cue similarly to empirical data, with the "activity" model showing slightly better performance. Notably, we found that decoding based on persistent neurons alone outperformed decoding of the full population activity. Separately, we found that persistent neurons in empirical data formed smooth trajectories, while non-persistent neurons did not. This structure was partly preserved in the "manifold" model but not in the "activity" model, which showed epoch-aligned clustered patterns. Collectively, our results highlight the importance of persistent activity and temporal covariance structure to the decoding performance of working memory.



A. Task Structure and Stimuli. Animals maintained central fixation during each trial. After fixation offset, they saccaded to a green target if two stimuli matched or to a blue target if they differed. The task involved spatial location matching, with eight cue locations used for analysis (shown in inset).

B. Decoding Accuracy Over Time. SVM performance for the spatial task relative to cue onset, using persistent and non-persistent neuron populations (n = 200; 10-fold cross-validation). Shaded areas show standard deviation over 10 repetitions. Analyses were performed on: empirical data (top); the activity model that preserves the sum of activity of persistent and non-persistent neurons within each epoch for each of the eight cues (middle); and the manifold model that preserves the first three temporal principal components of persistent and non-persistent neurons for each of the eight cues (bottom).

C. Low-Dimensional Manifold Structure. For each cue, neuronal activity was concatenated across time for each neuron, and UMAP was applied separately to persistent and non-persistent populations to reduce dimensionality to three. The resulting 3D trajectories reflect temporal evolution across trials, with colors indicating individual trials. Left column shows manifolds for persistent neurons, right for non-persistent. Rows correspond to empirical data (top), the activity model (middle), and the manifold model (bottom).

Disclosures: A. Abbasi: None. **A. Nanda:** None. **W. Dang:** None. **B. Singh:** None. **C. Constantinidis:** None. **M. Rubinov:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.08/WW8

Topic: J.06. Computation, Modeling, and Simulation

Support: NIMH T32: MH126388
NINDS U24: 1U24NS129945-01A1
NIMH CONTE: P50MH109429
Carney Institute for Brain Science (Brown University)

Title: Computational Neural Modeling with the Human Neocortical Neurosolver (HNN) Reveals Local Neural Circuit Dynamics Driven by Transcranial Magnetic Stimulation (TMS) Pulses

Authors: J. GAO[1], *D. D. SLIVA[2], S. R. JONES[2];
[2]Dept. of Neurosci., [1]Brown Univ., Providence, RI

Abstract: Transcranial Magnetic Stimulation (TMS) is a non-invasive brain stimulation method that is FDA-approved for multiple mental health disorders, including Major Depressive and Obsessive Compulsive Disorders. However, patient responses to standard TMS protocols are highly variable, largely stemming from a lack of understanding of how TMS drives complex interactions of cells at the neural circuit level, and how these dynamic interactions relate to behavioral outcomes. We developed an open-source neural modeling software called the Human Neocortical Neurosolver (HNN) that can uniquely address this challenge. HNN is a biophysically principled neocortical column model designed to simulate the primary currents underlying electroencephalography (EEG) signals with cellular and circuit-level details. HNN's construction enables one-to-one comparison between simulated primary current signals and source localized EEG in equal units (nAm), together with multi-scale interpretation.
To study the impact of TMS on local neural dynamics, we collected EEG concurrently with single and paired (100 msec inter-pulse-intervals) TMS pulses to the primary somatosensory cortex (SI; 100% active motor threshold, 100 trials). For a single subject with high-quality data, the source waveform from a localized region of interest within SI was estimated. HNN simulation of the source waveform predicts TMS drives an initial transient burst of inhibitory cell spiking, followed by a more prolonged and complex pattern of inhibitory and excitatory activity, producing a simulated waveform in close agreement to recorded data. Further, a prominent peak (~100 msec) corresponded with a large increase in intracellular dendritic calcium concentration of layer 5 pyramidal neurons.
To test the model predictions, we simulated the arrival of a second TMS pulse at a 100ms latency using the exact same model parameters as the first pulse. Subsequent comparison between the predicted and empirical waveforms showed remarkable similarity, supporting our generative model predictions. These results suggest that multiscale model predictions provide useful insights to interpret and potentially improve responses to TMS stimulation protocols.

Disclosures: J. Gao: None. **D.D. Sliva:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The methods described in this abstract are proprietary and currently being evaluated for patentability. **S.R. Jones:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The methods described in this abstract are proprietary and currently being evaluated for patentability.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.09/WW9

Topic: J.06. Computation, Modeling, and Simulation

Support: Labatt Family Network for Research on the Biology of Depression

Title: The effects of reduced somatostatin interneuron inhibition in depression on multilayered human cortical microcircuit activity

Authors: *H. YAO[1,2], E. HAY[1,2];
[1]Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada; [2]Univ. of Toronto, Toronto, ON, Canada

Abstract: Major depressive disorder (depression) is associated with reduced cortical inhibition from somatostatin-expressing (SST) interneurons, as indicated by decreased SST expression in human post-mortem studies. We previously showed in simulations of human cortical layer 2/3 that reduced SST interneuron inhibition would increase baseline cortical activity (noise) to significantly reduce the signal-to-noise ratio in signal processing and contribute to cognitive deficits observed in depression. However, as SST interneuron proportion and connectivity vary across cortical layers, it is unclear how reduced SST interneuron inhibition in depression differentially affects activity in other cortical layers and the propagation of signals across layers. In this study, we generated detailed models of human cortical multilayer microcircuits that encompass layers 2/3, 4 and 5. Our models were constrained with human cellular, synaptic, neuron proportion, and connectivity data, and reproduced baseline firing rates across cell types and oscillatory dynamics as seen in human resting-state electroencephalogram (EEG). By systematically reducing SST inhibition within and across layers, we quantified the layer-specific contributions to circuit-level dysfunction and altered EEG power spectral density during resting state. Our study characterizes the effect of reduced inhibition in depression on cortical activity and signal processing across layers.

Disclosures: H. Yao: None. **E. Hay:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.10/WW10

Topic: J.06. Computation, Modeling, and Simulation

Support: MJFF-020020

Title: Early Detection of Freezing of Gait episodes in Parkinson's disease using a Deep Learning Approach

Authors: *P. J. CANTLAY[1], K. OWEN[2], C. FELIX[2], J. L. ALBERTS[1,2], A. ROSENFELDT[1], A. BAZYK[1], M. MILLER KOOP[1];
[1]Biomed. Engin., [2]Neurolog. Inst., Cleveland Clin., Cleveland, OH

Abstract: Freezing of Gait (FOG) in patients with Parkinson's Disease (PwPD) increases with disease progression, often causing adverse outcomes such as falls, injuries, and hospitalizations. FOG remains partially refractive to traditional interventions; however, adaptive deep brain

stimulation (aDBS) paradigms offer promise to treat lower extremity dysfunction. Accurate prediction of FOG is a crucial precursor to aDBS treatment efficacy. Emerging local field potential (LFP) data suggest heterogeneity of Subthalamic nucleus (STN) neural activity relating to the environmental context provoking the FOG event. The aim of this project was to identify the unique neural signature of FOG across patients and environments and predict FOG events prior to their onset. STN LFP data were collected from 5 PwPD implanted with the Medtronic Percept DBS platform. Participants performed the Cleveland Clinic-Virtual Home Environment, walking on an omnidirectional treadmill through a virtual reality environment, inducing FOG through physical, anxiety-provoking, and cognitive dual-task modules. Raw time-series LFP data with numerous custom power and duration metrics per PwPD per module were modeled using Cox proportional hazards to quantify signal strength over time and determine feature importance in pre-freeze windows. These insights were leveraged in a Deep Neural Network to predict FOG across participants and modules. The model achieved strong performance, particularly the dual-task module with an average F1 score (an accepted measure of class-imbalanced model accuracy; range 0-1; higher values represent greater accuracy) of 0.69 across trials, accurately predicting a dual-task-evoked FOG event ~2 seconds prior to the clinician labelled FOG. Over 60% (18/29) of freezes across all modules were detected by the model at or before clinical onset. The model also succeeded in properly classifying periods of up to 60 seconds without a FOG event. Across 8 trials with low or no FOG, the model achieved over 90% accuracy. The model's early detection capability highlights the potential for real-time aDBS intervention, while its extended detection range suggests that pre-freeze and post-freeze periods share a similar, though more subtle, neural signature with FOG episodes. Results from the model are encouraging, however, performance is predicted to improve with additional high-quality data. Advancement of real-time FOG detection is critical for effective aDBS intervention in PwPD.

Disclosures: P.J. Cantlay: None. **K. Owen:** None. **C. Felix:** None. **J.L. Alberts:** None. **A. Rosenfeldt:** None. **A. Bazyk:** None. **M. Miller Koop:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.11/WW11

Topic: J.06. Computation, Modeling, and Simulation

Support: ERC Grant 101069192

Title: Predicting Structure-Function Relationships in Cortex via Artificial Neural Networks

Authors: *M. R. KEATON[1], M. OBERLAENDER[2];
[1]Max Planck Inst. for Neurobio. of Behavior, Bonn, Germany; [2]Integrative Neurophysiol., Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: The coupling of information streams is a hallmark feature of cortical function, and it is believed that network architecture is key to this. Neuroanatomical studies have shown that the specificity of projections of particular cell types both to and from the cortex facilitate the formation of characterizable networks. However, determining the impact these structures have on how incoming information streams are coupled and processed is not well understood and remains challenging to observe. Here, we propose a computational approach to studying this by informing artificial neural network models with increasing detail from neuroanatomical reconstructions of the cortex. We demonstrate that by training such cortically-inspired networks on a battery of machine learning tasks, we obtain concrete predictions on how network architecture and wiring specificity therein could facilitate function. We explore such structure-function relationships with respect to biologically-relevant tasks like generalization and show how these networks compare to other possible architectures. Our approach provides promising results and empirically testable predictions which we hope will shed new light on how interareal connectivity patterns facilitate the coupling of information streams.

Disclosures: M.R. Keaton: A. Employment/Salary (full or part-time): Max Planck Institute for Neurobiology of Behavior. **M. Oberlaender:** A. Employment/Salary (full or part-time): Max Planck Institute for Neurobiology of Behavior, Vrije Universiteit Amsterdam.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.12/WW12

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH award R01 NS135850-02

Title: Vector-based navigation inspired by directional place cells

Authors: *H. ESPINO[1], J. L. KRICHMAR[2];
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Abstract: We introduce a navigation algorithm inspired by directional sensitivity observed in CA1 place cells of the rat hippocampus. These cells exhibit directional polarization characterized by vector fields converging to specific locations in the environment, known as ConSinks. By sampling from a population of such cells at varying orientations, an optimal vector of travel towards a goal can be determined. Our proposed algorithm aims to emulate this mechanism for learning goal-directed navigation tasks. We employ a novel learning rule that integrates environmental reward signals with an eligibility trace to determine the update eligibility of a cell's directional sensitivity. Compared to state-of-the-art Reinforcement Learning algorithms, our approach demonstrates superior performance and speed in learning to navigate towards goals in obstacle-filled environments. Additionally, we observe analogous behavior in our algorithm to

experimental evidence, where the mean ConSink location dynamically shifts toward a new goal shortly after it is introduced.

Disclosures: H. Espino: None. **J.L. Krichmar:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.13/Web Only

Topic: J.06. Computation, Modeling, and Simulation

Support: The European Union's Horizon Europe research and innovation programme under Grant Agreement No 101192194
(IITP) grant funded by the Korean government (MSIT) (No. RS-2024-00435652)

Title: Neuromodulation inspired semantic communication networks, a bioinspired approach to ultra-lightweight edge intelligence

Authors: *Y. KYUNG, S.-L. KIM;
Yonsei Univ., Seoul, Korea, Republic of

Abstract: Visual detection of looming stimuli is essential for escape behaviors across diverse species. In insects such as locusts and Drosophila, specialized interneurons—like the Lobula Giant Movement Detector (LGMD)—exhibit selective firing to approaching objects, reliably triggering rapid evasive maneuvers. These neurons effectively transform complex visual scenes into sparse, behaviorally salient spike trains that quickly guide motor outputs.Inspired by these well-characterized neural circuits, we developed a neuromorphic communication system integrating three core biological principles: LGMD-inspired looming detection, reward-based spike-timing-dependent plasticity (R-STDP), and manifold compression. The LGMD-inspired module faithfully captures key electrophysiological properties observed in locust LGMD neurons, notably integrating excitatory and delayed inhibitory inputs to produce robust spike bursts signaling object approach—mirroring responses documented in Drosophila looming-sensitive neurons.The R-STDP mechanism emulates neuromodulatory reinforcement observed in invertebrate sensory circuits, modulating synaptic efficacy based on task-specific feedback. Through reinforcement-driven plasticity, our system selectively enhances responses to biologically significant looming stimuli while suppressing irrelevant visual input. This biological plasticity model ensures efficient tuning of neural responses to environmental relevance.Furthermore, we implemented a manifold embedding technique inspired by dimensionality-reducing strategies employed by insect sensory neuropils. This embedding efficiently compresses spike data into behaviorally relevant, low-dimensional semantic representations, focusing exclusively on critical parameters such as object size and expansion rate, thus minimizing communication bandwidth while retaining behavioral precision.In

simulated predator-prey scenarios, our neuromorphic framework accurately anticipates collision events and communicates only salient looming signals rather than raw visual data. This biologically inspired approach significantly reduces the bandwidth required for timely evasive decisions, demonstrating the feasibility of implementing efficient, adaptive semantic transmission systems grounded firmly in principles from invertebrate neurophysiology.

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

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.14/WW13

Topic: J.06. Computation, Modeling, and Simulation

Title: Weakly supervised learning for 3D pathology image analysis and cancer prognosis prediction

Authors: *Y. HE, S. ZHAO;
Natl. Biomed. Imaging Center, The Col. of Future Technology, Peking Univ., Beijing, China

Abstract: Three-dimensional (3D) histopathological image analysis has emerged as a pivotal frontier in digital pathology and cancer prognosis due to its ability to overcome the limitations of traditional 2D slice-based analysis, such as sampling bias and incomplete structural representation. Here, we present a novel weakly supervised learning framework designed specifically for automated analysis and prognosis prediction from large-volume 3D pathological images. To address imaging artifacts and staining inconsistencies, we developed a preprocessing pipeline combining HED color space perturbation with 3D morphological filtering, significantly improving structural integrity preservation.
Given computational constraints, we introduced an efficient 2.5D feature extraction strategy using a lightweight MobileNetV4 backbone, effectively balancing rich spatial representation with training feasibility. Furthermore, we innovatively constructed HistoVolNet, a specialized architecture integrating multi-scale feature fusion and non-local attention mechanisms, enhancing the model's ability to capture spatial heterogeneity and inter-layer dependencies in tumor tissues.
Employing a multiple instance learning paradigm, our model leverages only patient-level prognosis labels, circumventing the need for pixel-level annotations. Extensive validation was performed on two distinct datasets: a synthetic 3D dataset, where our approach achieved a classification accuracy of 95.4% and an F1 score of 0.951, demonstrating strong structural discriminability; and a real-world OTLS prostate cancer dataset, where it significantly outperformed conventional 2D (AUC 0.745) and baseline 3D CNN methods (AUC 0.842), achieving an AUC of 0.874 for five-year recurrence prediction. Kaplan-Meier survival analysis further confirmed the model's efficacy in patient stratification (Log-rank $p < 0.01$).
In summary, our proposed framework systematically integrates weak supervision, efficient 3D

feature modeling, and robust clinical prognosis prediction, significantly reducing annotation dependency while enhancing predictive accuracy and robustness. This scalable AI-driven approach holds substantial potential for personalized cancer prognosis and clinical decision support.

Disclosures: Y. He: None. **S. Zhao:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.15/WW14

Topic: J.06. Computation, Modeling, and Simulation

Title: Dynamics of Cortico-Subcortical Interactions in Functional Brain Networks

Authors: A. YAVARI[1], J. FASKOWITZ[2], R. BETZEL[3], *F. ZAMANI ESFAHLANI[1];
[1]Univ. of Oklahoma, Norman, OK; [2]Psychological and Brain Sci., NIH, BETHESDA, MD;
[3]Dept. of Psychological and Brain Sci., Univ. of Minnesota, Minneapolis, MN

Abstract: The human brain is a dynamic network of functionally connected regions. Resting-state fMRI studies suggest that brief, high-amplitude co-fluctuations in cortical activity, called events, play key roles in shaping time averaged functional connectivity (FC) patterns (Esfahlani et al. 2020). However, most previous studies of events have focused on cerebral cortex, leaving subcortical events underexplored. In this study, we use resting-state fMRI data from 914 participants included in the Human Connectome Project (Elam et al., 2021) to investigate the relationship between cortical and subcortical co-fluctuation patterns using edge time series analysis (Esfahlani et al. 2020, Faskowitz et al. 2020).We first examined the cross-correlation between the overall cortical and subcortical co-fluctuation patterns, quantified using the root mean square (RMS) of their respective edge time series. Our results show significant coupling between cortical and subcortical RMS time series (mean peak $r = 0.374 \pm 0.129$, $p < 0.001$, 95% CI = [0.369, 0.386]), with the median peak occurring at zero lag (IQR: -1.0-0.0 s). We next examined the role of cortical events in shaping cortico-subcortical temporal coupling using a lagged regression analysis where subcortical RMS was predicted from time-shifted cortical RMS signals. To specifically evaluate the contribution of cortical events in predicting subcortical activity, we compared their performance (i.e., regression coefficients) to non-event intervals from cortical RMS with comparable mean and standard deviation. Our results show that cortical events significantly outperformed non-event segments in predicting subcortical activity ($p<0.001$).Finally, we applied k-means clustering to characterize the temporal organization of cortico-subcortical interactions by defining neural states that combine RMS cross-correlation patterns and their temporal derivatives. We identified three recurring brain states across subjects: “Stable State” (79.4% ± 10.9%, mean RMS = 0.4501); “High-Amplitude State” (13.0% ± 5.3%, mean RMS = 0.6581) comprising most of cortical events (71.9% ± 17.3%); and “Diffuse State” (7.6% ± 5.4%, mean RMS= 0.5388). Overall, our findings suggest that cortical events play an

important role in shaping large-scale cortical-subcortical interaction, providing new insight into the temporal architecture of brain network dynamics.

Disclosures: A. Yavari: None. **J. Faskowitz:** None. **R. Betzel:** None. **F. Zamani Esfahlani:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

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Program #/Poster #: PSTR478.16/WW15

Topic: J.06. Computation, Modeling, and Simulation

Support: UB SPARC Award
UB Research and Creative Activities for Undergraduate Students Program

Title: Building brain networks from tractography: end-to-end vs. pass-through construction

Authors: *E. KILCOYNE[1], T. WU[1], J. HARTZ[2], E. CASTRO[3], S. E. MULDOON[4]; [1]Univ. at Buffalo, SUNY, Buffalo, NY; [2]SUNY Univ. at Buffalo, Buffalo, NY; [3]SUNY Buffalo, Buffalo, NY; [4]Dept. of Mathematics, State Univ. of New York, Univ. at Buffalo, Buffalo, NY

Abstract: White matter tracts serve as a scaffolding that allows information transfer between brain regions, and mapping their patterns of connectivity also can contribute to a better understanding of brin function and dysfunction. To build brain networks, one generally maps a pre-determined atlas composed of multiple brain regions onto the brain. The brain regions outlined in the atlas are network nodes and the number or density of tracts connecting brain regions are the edges of the network. Many studies that examine brain structure determine the number of connecting tracts between two regions by counting the number of tracts that start in one region of interest (ROI) and end in the other ROI (end-to-end method). However, only end-to-end counting may filter out critical information, as often the tracts pass through multiple brain regions as they travel between two ROI. Another, less commonly used method for creating brain networks, is thus to count a connection between two ROI if a tract passes through each region, independently of where it starts/ends (pass-through method). Here, we compare and contrast properties of brain networks built from the same tractography data using both methods to build the network. We find differences in standard network measures, such as the degree distribution and clustering coefficient, depending on if end-to-end or passthrough networks are created. Further, we simulate lesions within the brain and show that pass-through networks are more sensitive to detecting spatial disturbances in tracts that could reflect pathological changes. These differences in overall brain network structure highlight how the choice of method can change research findings and lead to new strategies for detection and intervention of pathological changes in brain structure.

Disclosures: E. Kilcoyne: None. **T. Wu:** None. **J. Hartz:** None. **E. Castro:** None. **S.E. Muldoon:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

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Program #/Poster #: PSTR478.17/WW16

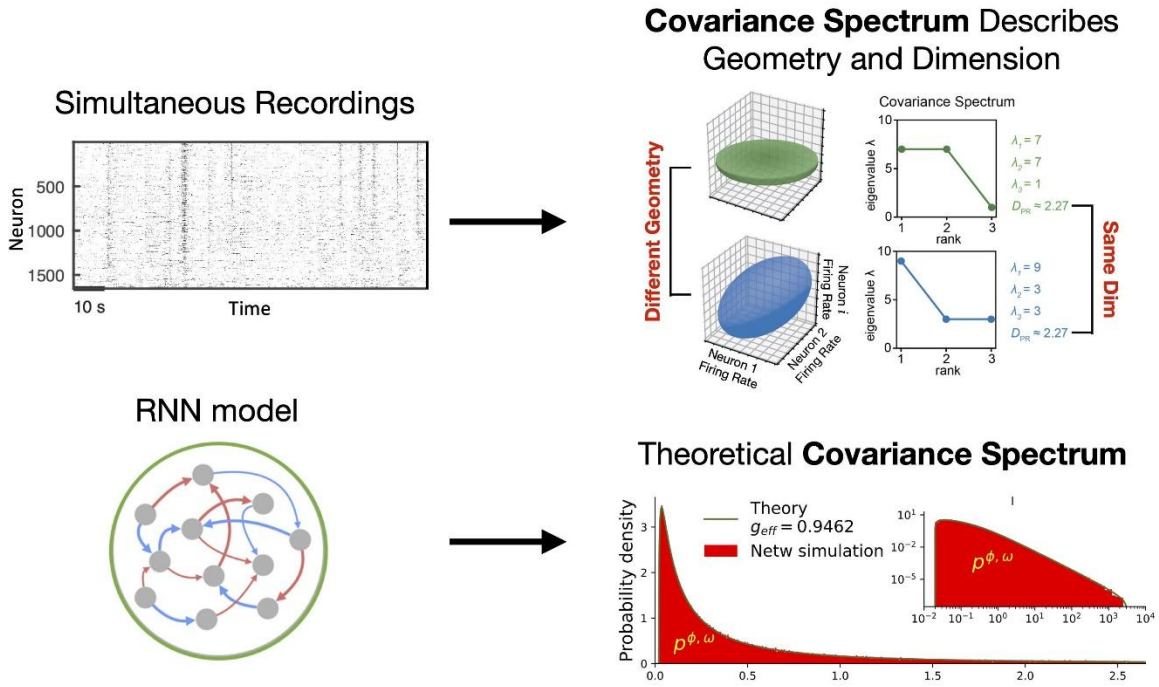
Topic: J.06. Computation, Modeling, and Simulation

Support: Hong Kong RGC ECS Grant 26303921

Title: Geometry of Nonlinear Neuron Population Dynamics Shaped by Recurrent Interactions

Authors: X. SHEN[1], ***Y. HU**[2];
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Abstract: Advances in simultaneous recordings of large numbers of neurons have driven significant interest in structures of neural population activity such as dimensionality. A key question is how these dynamic features arise mechanistically and their relationship to circuit connectivity. In previous work (Hu & Sompolinsky 2022), we proposed to use the covariance eigenvalue distribution, or spectrum, which can be analytically derived in random recurrent networks, as a robust measure for describe the shape of neural population activity beyond the dimension. Applications of the theoretical spectrum have broadly found accurate matching to experimental data across brain areas providing mechanistic insights into the observed low dimensional population dynamics (Morales et al. 2023; Calvo et al., 2024). However, the empirical success highlights a gap in theory where the neural network model used to derive the spectrum was minimal with linear neurons. In this work, we aim to close this gap by studying the covariance spectrum in nonlinear networks and broader dynamical regimes including chaos. Surprisingly, we found that the spectrum can be precisely understood by equations analogous to the linear theory while using an effective connectivity parameter reflecting the nonlinear neurons. Across the dynamical regimes, we found this effective connectivity goes through an increasing and then decreasing trend with the turning point near the edge of chaos. These results further our understanding of nonlinear neural population dynamics and provide additional theoretical support for applying the covariance spectrum in biological circuits.



Disclosures: X. Shen: None. **Y. Hu:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

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Topic: J.06. Computation, Modeling, and Simulation

Support: NSERC RGPIN-2020-06342 (MT)
NSERC-Alberta Innovates Supplements 232403195 (MT)
Alberta Graduate Excellence Scholarship (AGES)

Title: Exploring Deep Belief Nets as a model for the neocortex in hippocampal-neocortical interactions

Authors: *J. LIANG[1], A. SINGH[2], M. TATSUNO[3];
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Abstract: The standard model of systems consolidation proposes that new explicit memories are initially encoded in the hippocampus, but over time, they are gradually transferred to the neocortex and become less dependent on the hippocampus. Experimental evidence shows that

memory reactivation during sleep in the hippocampus and the neocortex is essential for this memory transfer to occur. Neural network modeling provides a valuable tool for better understanding the consolidation mechanisms. Beginning with an effort to model the hippocampal-cortical interaction using the Boltzmann machine (Kali and Dayan, 2004), a recent study combining the Modern Hopfield Nets (MHN) as a model for the hippocampus and the Variational Autoencoder (VAE) as a model for the neocortex offered important insights into the systems consolidation and was able to reproduce various experimental observations (Spens and Burgess, 2024). However, their model does not explicitly incorporate the sleep state, which is crucial for memory consolidation in the animal's brain. Here, we investigated the possibility of using Deep Belief Nets (DBN) to model the neocortex because it allows learning through both wake and sleep stages. As the first step, we evaluated whether the DBN would exhibit the properties seen in Spens' study, such as prototypical distortion in the regenerated output. Analyses using the grayscale MNIST datasets revealed that the images sampled in the DBN's regenerated output displayed significantly smaller intra-class variance than the original input images ($p<0.001$ for all digits, Wilcoxon signed rank test + Bonferroni correction), suggesting that the same effect was also present in the DBN. However, the prototypical distortion disappeared when the binarized MNIST images were used. We also evaluated how the latent space representations might change when the network was presented with continuously morphing input images. We found that the latent space representations showed an initial steep change followed by a gradual morphing, indicating a potential pattern separation feature in the DBN's latest space. These results provide valuable insights into the development of a full model combining MHN and DBN for hippocampal-cortical interaction through the wake and sleep phases.

Disclosures: J. Liang: None. **A. Singh:** None. **M. Tatsuno:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.19/XX1

Topic: J.06. Computation, Modeling, and Simulation

Title: Enhanced Cortical Network Reorganization During Thinking Following Meditation: A Causal EEG Connectivity Analysis

Authors: *S. MADATANAPALLI[1], R. BISWAS[2], P. CHINNAM RAGHU[1];
[1]Independent Researcher, San Francisco, CA; [2]Neurol., Univ. of California, San Francisco, San Francisco, CA

Abstract: Meditation has been shown to enhance cognitive performance, yet the neural mechanisms underlying its effects on active thinking remain poorly understood. This study examines how meditation modulates functional connectivity between brain regions during cognitive tasks, compared to breathing exercises and neutral thinking. While traditional

approaches for functional connectivity are based on associations, we obtained causal functional connectivity using the recently developed Causal Inference in Time Series (CITS) algorithm. To assess brain dynamics, we used publicly available 64 channels EEG data recorded from 98 healthy individuals performing randomized alternating blocks of meditation and thinking. We found that meditation induced significantly increased connectivity among frontal (anterior, central, temporal), parietal, and occipital cortices compared to neutral and post-breathing thinking. Specifically, meditation enhanced causal connectivity from left anterior frontal to left frontal, left parietal-occipital to left frontal-central and bilateral frontal regions, which are interactions implicated in executive control, attention, and visuospatial integration. These connections were absent during other conditions. Conversely, connections prevalent during neutral thinking or post-breathing thinking, such as left central to left temporal, right central to left frontal, and right central-parietal, right central pathways, were reduced or suppressed following meditation, suggesting inhibition of sensorimotor loops and self-referential processing. Together, these connectivity changes suggest a functional reorganization associated with a more efficient and goal-directed cognitive state following meditation. Our findings offer preliminary mechanistic insights into the cognitive effects of meditation, highlighting its potential to modulate large-scale cortical network dynamics during active thought.

Disclosures: S. Madatanapalli: None. **R. Biswas:** None. **P. Chinnam Raghu:** None.

Poster

PSTR478: Network Models II

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.20/XX2

Topic: J.06. Computation, Modeling, and Simulation

Support: NEI R01EY023261

Title: The Role of the Dorsal Attention Network in Emerging Convergent Eye Movements

Authors: *F. HAJEBRAHIMI[1], S. GOHEL[2], T. ALVAREZ[1];
[1]New Jersey Inst. of Technol., Newark, NJ; [2]Rutgers Univ., Newark, NJ

Abstract: Recent neuroimaging research emphasizes the importance of network-based models in studying specific brain regions associated with distinct functions. Resting-state functional connectivity emerges as a crucial indicator, revealing how different brain structures interact and shape responses to tasks across the entire brain. In this study, we employed a predictive model to compute the cortical contributions to local brain activations linked to binocular convergent eye movements by analyzing the propagation of functional brain activations across resting-state connectivity networks throughout the entire cortex. Our findings confirmed the involvement of the dorsal attention networks (DAN) in both hemispheres, in addition to the visual networks, in propagating functional activations through resting-state networks during convergent eye movements. The findings highlight the interplay between visual networks and DAN in

facilitating convergent eye movements, suggesting a complex relationship between attentional systems and binocular control of eye movements. This interplay may help clarify why individuals with attention deficits often face challenges with oculomotor function and near-vision tasks, while those with binocular dysfunctions might experience attentional problems due to compromised convergence oculomotor coordination.

Disclosures: F. Hajebrahimi: None. **S. Gohel:** None. **T. Alvarez:** None.

Poster

PSTR479: Magnetic Stimulation Development and Applications

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.01/XX3

Topic: J.08. Methods to Modulate Neural Activity

Support: NIDCD R01DC004290
NIMH R01MH132074-01

Title: Transcranial magnetic stimulation to the dorsolateral prefrontal cortex modulates single neuron activity in humans

Authors: *C. W. DICKEY[1], H. KAWASAKI[3], A. E. RHONE[3], P. E. GANDER[6], N. T. TRAPP[4], A. D. BOES[5], C. J. KELLER[1,7,2], J. I. BERGER[3];
[1]Psychiatry, [2]Wu Tsai Neurosciences Inst., Stanford, Palo Alto, CA; [3]Neurosurg., [4]Psychiatry, [5]Pediatrics, Neurol. & Psychiatry, Univ. of Iowa, Iowa City, IA; [6]Iowa Neurosci. Inst., Iowa City, IA, ; [7]Veterans Affairs Palo Alto Healthcare System, and the Sierra Pacific Mental Illness, Research, Education, and Clin. Ctr. (MIRECC), Palo Alto, CA

Abstract: Transcranial magnetic stimulation (TMS) to the dorsolateral prefrontal cortex (DLPFC) is an effective treatment for many patients with medication-resistant depression. However, variability in clinical outcomes may be linked to an incomplete understanding of how TMS induces plasticity in distributed cortico-limbic circuits. In particular, it remains unclear how TMS influences the activity of single neurons, including in deep brain regions implicated in mood disorders. Leveraging a unique opportunity to record from intracranial microelectrodes in patients with epilepsy, we investigated the direct effects of single-pulse TMS to the left DLPFC. Across 4 patients, we isolated 166 single units from a broad set of cortical and subcortical regions spanning limbic and associative networks. To analyze these data, we developed new methods to correct and account for stimulation artifacts in these sensitive recordings. Our data reveal that TMS elicits time-locked changes in the spike rates of single units (~30%) in a subset of deep cortical and subcortical structures, including the putamen and thalamus, in both ipsilateral and contralateral hemispheres. We found multiple single unit response characteristics across regions, often with facilitation of spiking at short latencies lasting up to approximately 300 ms after stimulation, with some units exhibiting subsequent spike rate suppressions. Single unit response phenotypes share similar characteristics as those reported in animal models. Spike

rate modulations were linked to broader network activity changes, including modulations in multi-unit activity and local field potentials. Our findings provide the first direct evidence in humans that TMS to the DLPFC engages deep brain circuits at the single neuron level, providing a basis by which TMS may induce widespread plasticity underlying its therapeutic effects in psychiatric disorders.

Disclosures: C.W. Dickey: None. **H. Kawasaki:** None. **A.E. Rhone:** None. **P.E. Gander:** None. **N.T. Trapp:** None. **A.D. Boes:** None. **C.J. Keller:** None. **J.I. Berger:** None.

Poster

PSTR479: Magnetic Stimulation Development and Applications

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.02/XX4

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant R01AG068317

Title: Network-targeted theta burst stimulation for memory improvement in mild cognitive impairment

Authors: *W. JIANG[1], E. POPESCU[3], J. BAHAM[3], B. GUZMAN[3], R. MUSTAPHA[3], A. AGGARWAL[3], M. SEEBER[3], L. ERCOLI[4], A. LEUCHTER[3], N. A. SUTHANA[2]; [1]Neurosurg., [2]Neurosurg. and Biomed. Engin., Duke Univ., Durham, NC; [3]Psychiatry, [4]Psychology, UCLA, Los Angeles, CA

Abstract: Mild cognitive impairment (MCI) represents a critical transitional stage between normal aging and dementia, making early intervention essential for preserving cognitive function. Network-targeted transcranial magnetic stimulation (TMS) has emerged as a promising, non-invasive method for memory enhancement; however, its effect sizes and underlying neural mechanisms remain unclear. In this double-blind, sham-controlled study, we combined functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and behavioral memory assessments to investigate the effects of TMS in individuals with MCI. Over three weeks, participants received 15 sessions of daily intermittent theta burst stimulation (iTBS) or sham stimulation, targeting a region within the left lateral posterior parietal cortex (LPPC) functionally connected to the left hippocampus as determined by resting-state fMRI. Behavioral data from object recognition, face-name association, and verbal memory tasks were collected at baseline, after the 1st, 5th, 10th, and 15th sessions, and at 72-hour and 2-month follow-ups. Blinded analyses revealed a significant main effect of time on object recognition performance ($n = 31$; one-way repeated-measures ANOVA, $F(1,30) = 145.16$, $p < 0.05$). Post-hoc analyses indicated significant improvements from baseline at all post-treatment timepoints except the 5th session (paired t-test, $p < 0.05$, Bonferroni-corrected). Although face-name association and verbal memory tasks did not show statistically significant improvements, positive trends were observed. Resting-state fMRI analyses demonstrated significantly increased functional

connectivity between the left hippocampus and right anterior and dorsolateral prefrontal cortices following treatment (n = 18; paired *t*-test, $Z > 2.3$, $p < 0.05$, cluster-corrected). These frontal regions are associated with cognitive control, planning, and working memory, suggesting potential enhancement in the top-down regulation of memory networks. EEG analyses did not show significant changes in brain oscillations post-treatment (n = 24; paired *t*-tests, $p > 0.05$). However, exploratory trends indicated increased theta (4-8 Hz) power in the cingulate gyrus and increased alpha1 (8-10 Hz) power in the precuneus. These preliminary results suggest that network-targeted iTBS may modulate large-scale cognitive networks and support memory function in individuals with MCI. Definitive conclusions regarding the specificity and robustness of these effects will be determined after unblinding. As participant recruitment is ongoing, current analyses remain blinded to treatment assignments.

Disclosures: W. Jiang: None. **E. Popescu:** None. **J. Baham:** None. **B. Guzman:** None. **R. Mustapha:** None. **A. Aggarwal:** None. **M. Seeber:** None. **L. Ercoli:** None. **A. Leuchter:** None. **N.A. Suthana:** None.

Poster

PSTR479: Magnetic Stimulation Development and Applications

Location: SDCC Halls B-H

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Program #/Poster #: PSTR479.04/XX6

Topic: J.08. Methods to Modulate Neural Activity

Support: Simons Foundation Shenoy Undergraduate Research Fellowship in Neuroscience
National Institutes of Health (NIH) Grant 5R01MH129367-02
National Institutes of Health (NIH) Grant MH124004
National Institutes of Health (NIH) Grant P50MH106435
Shared Instrumentation Grant S10OD020039

Title: Variability in the electric field intensity received in the lateral prefrontal cortex in transcranial magnetic stimulation

Authors: *J. ZHUO[1], A. BILLOT[4], W. SUN[2], K. RODRIGUES[2], R. L. BUCKNER[3], M. ELDAIEF[5];
[1]Harvard Univ., East Elmhurst, NY; [3]Psychology and Ctr. for Brain Sci., [2]Harvard Univ., Cambridge, MA; [5]Neurol. and Psychiatry, [4]Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation technique that treats major depressive disorder (MDD) by targeting the lateral prefrontal cortex (LPFC). However, clinical outcomes may vary, potentially due to anatomical differences that influence induced electric field (E-field) distributions. Most clinical protocols rely on a TMS dosing method based on the excitability of the motor cortex but this does not account for variability in skull curvature, scalp-to-cortex distance, or cortical folding, factors influencing

cortical E-field intensity. This study aimed to evaluate E-field intensity variability in the LPFC across individuals and scalp positions and assess whether regions anticorrelated with the subgenual anterior cingulate cortex (sgACC) coincide with areas of maximal E-field strength. E-field simulations were conducted on structural MRI data from 11 participants (ages 18-34), 6 with MDD and 5 controls. T1-weighted structural MRI scans were collected, and the resting motor threshold (MT) was measured for each participant by stimulating the primary motor cortex and recording the minimal stimulator output (%MSO) required to elicit ≥ 3/6 motor-evoked potentials. A left LPFC search space was projected to each individual native space, and ~300 scalp coordinates were projected above the cortical search space. E-field simulations were run at each scalp coordinate at a 45-degree angle using each participant's MT dose with the SimNIBS v.4.0. toolbox. For each scalp coordinate, the average E-field intensity received by the cortex was computed across the top 25 vertices of the E-field map. These maximal E-field values were used to construct individual-specific E-field intensity maps. Each participant's TMS coil position, personalized to optimally target the LPFC region most anticorrelated to the sgACC, was then compared to the E-field intensity received. Simulation results revealed substantial inter-individual variability in both the spatial distribution and the magnitude of the maximal E-field intensity received by the LPFC, despite consistent MT-based dosing. Neighboring TMS coil positions yielded markedly different E-field strengths. Importantly, while the sgACC-anticorrelated LPFC target often aligned with high-intensity regions, it did not consistently align with the absolute E-field maximum, suggesting that current TMS protocols may induce variable stimulation strength. These findings support a new hypothesis that the clinical effectiveness of sgACC anticorrelated TMS targeting may stem from both targeting the correct functional region and inducing enhanced E-field intensity in most individuals.

Disclosures: J. Zhuo: None. **A. Billot:** None. **W. Sun:** None. **K. Rodrigues:** None. **R.L. Buckner:** None. **M. Eldaief:** None.

Poster

PSTR479: Magnetic Stimulation Development and Applications

Location: SDCC Halls B-H

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Program #/Poster #: PSTR479.05/XX7

Topic: J.08. Methods to Modulate Neural Activity

Support: NIMH Grant R01MH113700
Neuronetics provided equipment support

Title: Examining anhedonia as a predictor of response with transcranial magnetic stimulation treatment of major depressive disorder in adolescents

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Abstract: Transcranial magnetic stimulation (TMS) is a promising, noninvasive neuromodulation treatment for adolescents diagnosed with major depressive disorder (MDD). In 2024 the FDA cleared TMS as an adjunctive treatment of MDD in patients ages 15-21 years, however previous research only shows modest clinical effects in this age group. Here, we describe an exploratory, double-blind, randomized trial aimed at examining anhedonia as a predictor of repetitive TMS (rTMS) treatment response for MDD in adolescents. The study included 41 participants aged 12-18 years (60.98% female, 82.92% White), with a Children's Depressed Rating Scale- Revised (CDRS-R) ≥40. Participants were randomly assigned to either a 1 Hz or 10 Hz daily rTMS application for 30 days (5 days/week, 6 weeks). Anhedonia was assessed using related items from the CDRS-R and Beck Depression Inventory-II. Treatment outcome was measured using the Clinical Global Impressions-Improvement (CGI-I) scale. Logistic regression was used to estimate the likelihood of CGI-I treatment response at week 6 from the change in anhedonia scores (baseline to week 6), and a linear mixed model of repeated measures was used to assess changes in anhedonia across the TMS groups over the 6-week study duration. Adjusted least squares for anhedonia showed significant improvement in anhedonia across both TMS groups (1 Hz, $p<0.0001$, $d=0.8536$; 10 Hz, $p<0.0001$, $d=0.9032$), but overall least squares TMS treatment group means show no significant TMS group effects for 1 Hz vs. 10 Hz [5.121 (SE=0.450) vs. 5.894 (SE=0.486), p=0.2559]. Logistic regression revealed a significant inverse relationship between anhedonia symptom changes and CGI-I response for both 1Hz (δ= -1.1017, SE=0.5003, $p=0.0277$) and 10 Hz (δ= -0.8581, SE=0.3371, $p=0.0109$) groups, but no significant interaction between TMS treatment group and change in anhedonia symptoms on CGI-I response (p = 0.3204). Overall, TMS stimulus frequency (1 Hz vs. 10 Hz) did not have specific effects on the change in anhedonia scores or CGI-I response. Future studies should further investigate anhedonia and other potential moderators of TMS outcomes to inform precision treatment in adolescents.

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Poster

PSTR479: Magnetic Stimulation Development and Applications

Location: SDCC Halls B-H

Time: Wednesday, November 19, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.06/XX8

Topic: J.08. Methods to Modulate Neural Activity

Support: Defense Advanced Research Projects Agency (HR00112320032).

Title: Neural Activation and Pattern Decoding in TMS-fMRI: Comparing Block and Event-Related Designs

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Abstract: Concurrent transcranial magnetic stimulation and functional MRI (TMS-fMRI) enables causal mapping of brain networks by perturbing cortical regions while measuring distributed hemodynamic responses. However, the temporal structure of stimulation—block versus event-related—can affect signal strength, spatial specificity, and inter-subject consistency. Optimizing this design choice is essential for enhancing experimental sensitivity and guiding translational protocols. This within-subject study compared block and event-related stimulation at the left and right dorsolateral prefrontal cortex (L-DLPFC, R-DLPFC) and pre-supplementary motor area (pre-SMA) in 28 healthy adults. fMRI data were acquired on a 3T scanner and preprocessed with slice-timing correction, motion correction, spatial normalization, nuisance regression, and filtering. TMS targets were localized using standard anatomical coordinates. First-level contrasts were computed for each condition using a general linear model (GLM), followed by group-level one-sample and paired *t*-tests. One-sample voxelwise *t*-tests revealed robust event-related activation: pre-SMA (mean $t = 3.60$, max $t = 9.74$; >122,000 voxels, FDR-corrected), R-DLPFC ($t = 3.27$), L-DLPFC ($t = 3.03$). Paired voxelwise *t*-tests (DLPFC only) showed stronger activation in R-DLPFC for event-related TMS ($t(26) = 4.30$, $p = 0.0002$); L-DLPFC showed no significant difference ($t(27) = 1.05$, $p = 0.302$). ROI analyses (Harvard-Oxford masks and 6mm spheres) confirmed greater event activation: pre-SMA ($t = 5.21$, $p < 0.0001$), L-DLPFC ($t = 2.38$, $p = 0.0247$), R-DLPFC ($t = 2.48$, $p = 0.0200$). To classify stimulation condition, logistic regression, SVM, and random forest classifiers were trained on (1) mean ROI *t*-values and (2) PCA-reduced voxelwise maps (~115k features). Accuracy ranged from 67-71%, evaluated via stratified 5-fold cross-validation and 1,000-iteration permutation testing ($p < 0.05$). ROI models showed higher recall for block trials, while voxelwise classifiers were more sensitive to event-related patterns. These findings demonstrate that event-related stimulation produces stronger and more spatially extensive activation across all targeted regions, supporting its utility for flexible, multi-site engagement in TMS-fMRI studies. In contrast, block designs yielded more stable activation patterns across individuals. This design-dependent trade-off between response magnitude and consistency provides practical guidance for selecting stimulation protocols aligned with specific cognitive, mechanistic, or translational goals.

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Poster

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Program #/Poster #: PSTR479.07/XX9

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant 1R01NS117405-01

Title: Short-latency responses to transcranial magnetic stimulation in awake non-human primate brain

Authors: *N. GOSWAMI[1,2], M. CLINTON[3], R. KOTHARE[2], S. M. GOETZ[3], B. WANG[3], W. M. GRILL[2], A. V. PETERCHEV[3], M. A. SOMMER[2];
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Abstract: Transcranial magnetic stimulation (TMS) is a non-invasive form of neuromodulation used for both clinical and research purposes. While the macroscopic effects of TMS have been observed in humans, its effects on individual neurons and local networks are not well understood. In this study, we report TMS-evoked single neuron activity and local field potentials (LFPs) in primary motor cortex (M1), somatosensory cortex (S1), and parietal cortex across two nonhuman primate (NHP) subjects, with a focus on responses within the first 10 ms of the TMS pulse. Leveraging our novel electrophysiology system that allows for simultaneous neural recordings and TMS stimulation at the same site (Mueller et al., 2014), we can recover low-latency neural signals within 0.5 ms of the start of the TMS pulse. These include high frequency oscillations at ~600 - 1000 Hz approximately 1-7 ms after the TMS pulse, whose amplitude and frequency are dose-dependent. These oscillations were observed in areas M1 and S1, but not in parietal cortex, suggesting that TMS recruits large populations of neurons to synchronously fire in these brain regions. Additionally, these oscillations were not observed in the sham configuration. Single neurons also exhibited TMS-evoked responses in the form of low latency excitation followed by a rebound. Some neurons in areas M1 and S1 fired synchronously with the peaks of the high frequency oscillations in the active TMS configuration, but not in sham. These results demonstrate the differences in local, electrophysiological responses to TMS across distinct regions of primate cerebral cortex.

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Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: Direction Générale de l'Armement
Fondation des Gueules Cassées

Title: Assessing Motor Evoked Potentials induced by TMS in awake and anesthetized rats

Authors: *J. THOMASSON[1], R. TROUBAT[3], B. POLY[2], M. OGIER[2], W. EL-HAGE[4], A. DUFFAUD[2], D. CLAVERIE[2];
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Abstract: Transcranial Magnetic Stimulation (TMS) is a non-invasive technique that uses magnetic fields to modulate neuronal activity. Most preclinical studies employ this technique under anesthesia, primarily to facilitate targeting and ensure reproducibility. However, understanding how anesthetics influence TMS-induced motor evoked potentials (MEPs) is crucial for preclinical neuromodulation research. This study investigated the feasibility of performing TMS in awake but restrained rats. We compared MEP responses across three physiological states: wakefulness, isoflurane anesthesia, and ketamine-medetomidine anesthesia. Biphasic TMS pulses were delivered at intensities ranging from 10% (0.27 Tesla) to 70% (1.87 Tesla) of the maximum stimulator output. Electromyographic (EMG) signals were recorded from the forelimb muscles under each condition: awake with physical restraint, anesthetized with 2% isoflurane, and anesthetized with ketamine (75 $mg.kg^{-1}$) combined with medetomidine (0.3 $mg.kg^{-1}$). For each intensity level, multiple stimulation trials were performed to determine MEP thresholds and response reliability. In awake animals, MEPs were reliably induced starting at 30% of the stimulator output, with response rates reaching a maximum at 50%, indicating consistent activation of the corticospinal tract. EMG traces displayed the classical post-MEP silent period, consistent with previously reported patterns in rodents and humans. Under isoflurane anesthesia, no MEPs were detected across the full range of stimulation intensities. This absence aligns with the potent inhibitory effects of isoflurane on synaptic transmission, which are known to result from reduced presynaptic calcium entry and disruption of the exocytotic machinery. In the ketamine-medetomidine group, only weak and inconsistent MEPs were recorded, suggesting partial suppression of corticospinal excitability. While ketamine has been reported to potentiate MEP amplitude, medetomidine - a selective α2-adrenergic agonist - may counteract this effect by reducing motor output and muscle tone. Our findings indicate that TMS can be effectively applied in awake, restrained rats to induce reproducible MEPs, making this model suitable for longitudinal studies on cortical excitability and plasticity. In contrast, isoflurane anesthesia abolishes TMS-induced MEPs and is therefore incompatible with such protocols. Although ketamine-medetomidine anesthesia permits limited MEP induction, its suppressive effects restrict its utility. These results support the awake condition as the most reliable state for assessing TMS-induced responses in rodent models.

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Poster

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Program #/Poster #: PSTR479.09/XX11

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH/NINDS (1U24NS113647)

Title: High-frequency subthreshold rTMS alters spatial learning and cognitive flexibility in rats performing the Barnes maze task

Authors: *C. HSU[1], W. JIANG[3], W. CHOI[1], M. MCHUGH[1], M. MESSAY[1], A. LEE[1], J. LIN[1], M. WU[1], D. LEE[2], C. LIU[2], D. SONG[1,2];
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) is emerging as a promising non-invasive neuromodulation technique for treating various neurological and neuropsychiatric disorders with cognitive deficits. While the primary focus of rTMS research has been on human clinical applications, rodent models are essential in elucidating its potential cognitive impacts and underlying mechanisms. To investigate the effects of rTMS on spatial learning and memory in behaving animals, we applied subthreshold rTMS to rats performing a Barnes maze (BM) task. The task consisted of 5 phases including a habituation phase to acclimate the animals to the restraint and environment, an acquisition phase where learning took place, an acquisition probe trial to assess spatial memory retrieval, a reversal learning phase to test cognitive flexibility, and a reversal learning probe trial to evaluate adaptability of the learned responses. Twenty-four male Sprague Dawley rats were randomly divided into rTMS (n=12) and sham groups (n=12). During the acquisition and reversal learning phases, sessions of 5-minute, 10 Hz rTMS or sham stimulation were applied above the medial prefrontal cortex (mPFC) of restrained rats. Two stimulation sessions were conducted per day. Each session was immediately followed by a BM trial. No stimulation was applied during the habituation phase or probe trials. Results showed that the rTMS group required a longer time and made more errors in acquiring the task during the acquisition phase compared to the sham group. However, this trend was inversed during the reversal learning phases, when the rTMS group outperformed the sham group. Moreover, the rTMS group spent significantly more time in the area where the escape box was previously placed compared to the sham group in both probe trials. Our findings reveal that chronic subthreshold 10 Hz rTMS initially disrupted spatial learning in healthy rats during the acquisition phase of the Barnes maze task. It enhanced cognitive flexibility during the reversal learning phase and strengthened spatial episodic memories of previous target locations in the acquisition and reversal learning probe trials. However, the acute effects of rTMS were not evident on spatial learning and memory. These findings could hint at the potential clinical applicability of rTMS in addressing cognitive deficits and guide the optimization of rTMS protocols, maximizing therapeutic benefits while minimizing potential cognitive disruptions.

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Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: W.A. Franke Honors Exploratory Mini-Grant

Title: Enhancing cortical plasticity: investigating transcutaneous auricular vagus nerve stimulation (taVNS) as a primer for intermittent theta burst stimulation (iTBS)

Authors: *C. JEZERC[1], K. LAI[1], G. ARNOLD[1], C. CHEN[1], S. DWIVEDI[1], M. SUNDMAN[2], Y.-H. CHOU[2];
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Abstract: Neural plasticity is an integral function of the brain, denoting its capacity to remain malleable and adapt in response to new information or injury. A growing body of research suggests that transcutaneous auricular vagus nerve stimulation (taVNS) may enhance neural plasticity by upregulating the release of neuromodulators. Notably, taVNS has been proposed as a priming intervention, a mechanism to increase cortical receptivity to subsequent plasticity-inducing therapies. Yet, direct empirical evidence demonstrating taVNS as a primer for non-invasive brain stimulation remains scarce. This study explores the novel combination of taVNS and intermittent theta burst stimulation (iTBS), a form of repetitive transcranial magnetic stimulation (rTMS) known to induce robust and measurable plasticity changes. We hypothesize that preconditioning with taVNS will enhance responsiveness to iTBS, resulting in amplified motor-evoked potential (MEP) changes relative to sham. This study design consisted of single-blinded, crossover randomized controlled trials of the taVNS protocol with healthy adults between 18-27 years old (n = 18; 10 females). Sham taVNS consisted of placing the electrodes at the same stimulation site as active taVNS, but delivering no stimulation. Participants were therefore blinded to the protocol as active taVNS was administered at an intensity just below their perceptual threshold. At a 90% winsorization, our preliminary results indicate an average 32.87% ± 49.1% MEP Change post-iTBS for active taVNS and 8.65% ± 39.10% for sham taVNS. Although active taVNS led to a stronger post-iTBS MEP response ($t = 1.76$, $p = 0.05$), the effect did not reach statistical significance under the Bonferroni-corrected alpha level of 0.025 for a paired t-test. To measure changes in cortical excitability, the resting motor threshold (RMT) was acquired before and after the taVNS protocol. There were minimal changes in cortical excitability with an average of 1.43% ± 5% RMT Change for active taVNS and 0.85% ± 3% for sham taVNS. Data collection is ongoing and future research efforts are required to elucidate the potential of taVNS to enhance the brain's responsiveness to rTMS and other neuromodulatory interventions.
Extra:MEPs (One-tailed: $t = 1.758$, $p = 0.05$) or RMT (Two-tailed: $t = 0.538$, $p = 0.6$)

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Poster

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Topic: J.08. Methods to Modulate Neural Activity

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Title: Depression of sound-driven responses in the mouse auditory cortex induced by continuous and intermittent theta-burst magnetic stimulation to a narrow brain region

Authors: *T. YOSHIKAWA[1], T. TATENO[2];
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Abstract: Repetitive transcranial magnetic stimulation is a brain stimulation technique used to treat several neurological and psychiatric disorders. Among repetitive stimulation patterns, theta-burst stimulation (TBS) — 50-Hz triplet bursts repeated at 5 Hz — has gained interest due to its ability to alter brain activity lasting for 20 minutes following the short stimulation duration of only 40 s, potentially shortening treatment durations. Yet, the mechanisms underlying the rapid effects of TBS remain unclear, requiring further investigation through animal studies. Most studies using rodents have targeted the motor cortex, likely due to its accessibility and well-established protocol. However, previous studies focusing on the auditory cortex (AC), crucial to sound processing, were comparatively rare. Moreover, most of these studies have employed large coils suited for human use, which can stimulate the entire brain of rodents, leaving the specific effects on local brain areas unexplored. In this study, we examined whether TBS could modulate sound-driven activities in the mouse AC. We used a self-made millimeter-sized coil that can locally stimulate the cerebral cortex. Under anesthesia, we inserted a 16-channel silicon probe into the exposed AC. To evaluate the effect of TBS on the AC, we assessed two conditions: (i) continuous TBS (cTBS, TBS continuously delivered for 40 seconds), which is generally known for its inhibitory effects; (ii) intermittent TBS (iTBS, 2-second TBS delivered every 10 seconds for a total of 200 seconds), which typically has facilitatory effects; and (iii) a sham condition with no voltage input (0 V) to the coil. Sound-driven potentials (SDPs) in the AC were measured from 5 min before to 30 min after TBS at 5-min intervals. Comparing SDPs before and after TBS revealed that negative peak amplitudes of SDPs decreased after both cTBS and iTBS compared to the sham condition. Additionally, latencies of negative peaks increased after cTBS compared to the sham condition. The results suggest that cTBS had an inhibitory effect on SDPs, which is consistent with previous research. In the other hand, iTBS also showed

an inhibitory effect on SDPs, opposing from the known facilitatory effect reported by previous research targeting motor cortical regions, requiring further investigation into the underlying mechanisms of this unexpected result. Moreover, these findings may provide insights into TBS effects variance across brain regions, which could contribute to the optimization of TBS-based treatments for hearing disorders.

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Poster

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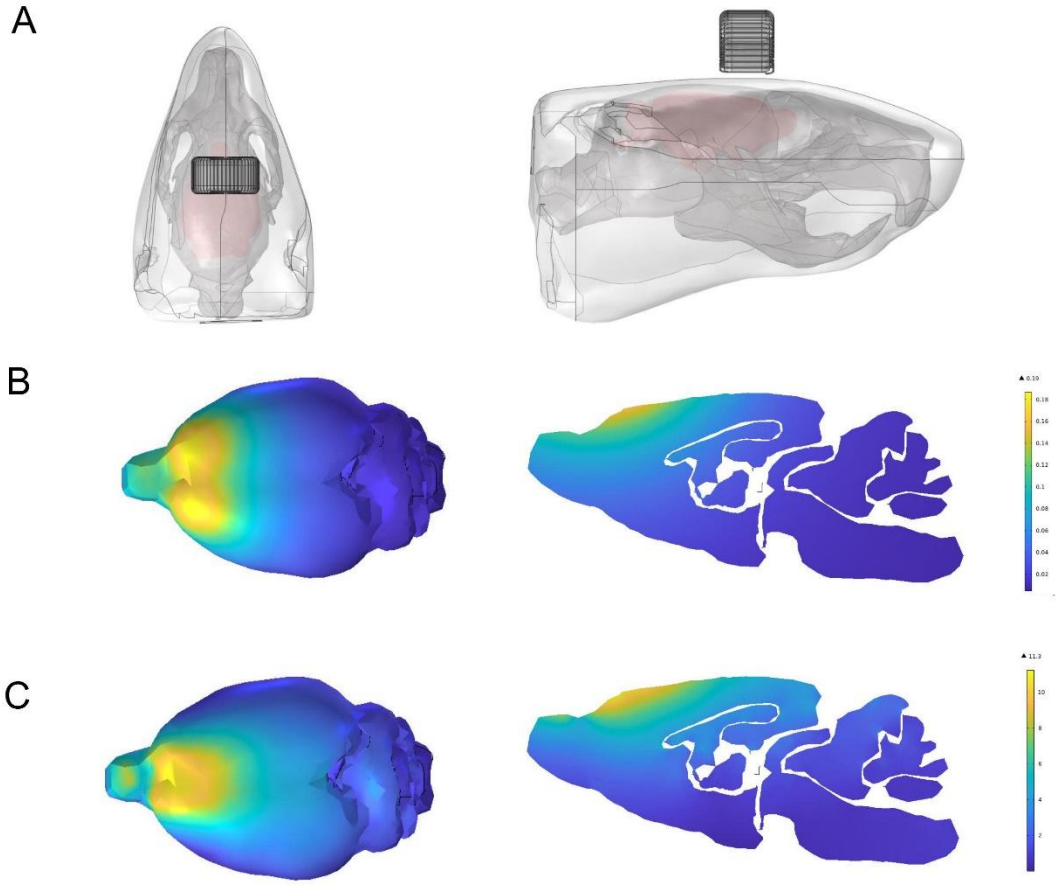
Topic: J.08. Methods to Modulate Neural Activity

Title: Characterizing Electric and Magnetic Fields Induced by a Custom TMS device onto the Rat Brain

Authors: *M. MCHUGH[1], W. JIANG[2], M. TASHLI[3], W. LOHR[3], R. HADIMANI[3], D. SONG[4];
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Abstract: Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation technique that induces electric currents in the brain via time-varying magnetic fields. It has shown promise for treating neurological and neuropsychiatric disorders, including depression, OCD, epilepsy, schizophrenia, and autism. Recent studies using a miniaturized TMS coil in rats suggest its potential for enhancing cognitive flexibility. However, the underlying biophysical mechanisms remain unclear, hindering protocol and coil optimization. To address this, we simulated the electric (E) and magnetic (B) fields induced by the custom coil in a rat brain using finite element modeling.
A 3D anatomical model of the rat head was constructed from high-resolution CT and MRI scans, segmented into five compartments: skin, skull, cerebrospinal fluid (CSF), gray matter, and white matter. The resulting mesh was smoothed and made manifold. Tissue-specific electrical properties were assigned based on standard dielectric databases. A custom TMS coil, previously developed in-house, was incorporated into the simulation domain. Field simulations were performed using COMSOL Multiphysics 6.0.
The simulations revealed peak induced electric fields of 11.3 V/m at the cortical surface, decreasing to 4 V/m at a depth of ~3 mm. The corresponding magnetic field strength peaked at 0.19 T at the surface and attenuated to 0.07 T at the same depth. These spatial field distributions are illustrated in Figure 1, showing (A) coil orientation, (B) magnetic field topography, and (C) sagittal electric field profiles.
These results provide a quantitative baseline for assessing TMS field focality and penetration in

small animal models. This work supports future efforts to optimize stimulation protocols and interpret behavioral and physiological effects in rodent TMS studies.



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Poster

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Support: 1. National Research Foundation of Korea(RS-2023-00220237)
2. Ministry of Trade, Industry and Energy(RS-2024-00422269)
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Title: Direction Selective Microcoil Stimulation of mPFC Pyramidal and PV Neurons for Targeted Modulation of Social Circuits in Mouse

Authors: *M. BANG[1], J. PARK[2], S. PARK[2], Y. SEO[2], H. YOO[2], J. KWON[2], S. LEE[2];
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Abstract: The medial prefrontal cortex (mPFC) plays a crucial role in mouse social behavior, and projections from its infralimbic (IL) and prelimbic (PL) regions to the basolateral amygdala (BLA) have also been shown to be important for social interaction. Activation of parvalbumin-positive (PV) interneurons suppresses pyramidal neurons' activity, which in turn inhibits BLA projections and contributes to social deficits. To modulate specific circuits in this pathway, we applied directionally selective microcoil stimulation to the pyramidal neurons and parvalbumin-positive (PV) interneurons, the dominant interneuron subtype in the mPFC IL and PL regions that support IL/PL-BLA connectivity. Microcoil-based magnetic stimulation induces asymmetric electric fields around the coil perpendicular to the coil current , enabling spatially selective neuronal activation without direct metal-to-tissue contact, thus improving biocompatibility and long-term stability over conventional electrical stimulation. We used a pyramidal neuron-specific transgenic mouse expressing GCaMP6f and injected AAV-RCaMP6f into PV-Cre mice for PV neuron labeling. Coronal Acute brain slices containing mPFC slices were prepared and stimulated with microcoils across varying orientations and parameters. Fluorescent sliceIn vitro calcium imaging was used to assess responses to coil orientations (parallel or perpendicular to cortical layers) and stimulation parameters (70 to 200 mA current intensity, monophasic 1000 Hz1 ms-duration sine pulse). To isolate direct stimulation effects from PV-to-pyramidal synaptic transmission, we added NBQX (10 μM), bicuculline (10 μM), and d-APV (50 μM) to block excitatory and inhibitory synaptic inputs. Pyramidal neurons exhibited clear direction-selective responses, with fluorescence changes phase-locked to stimulation at 70 to 100 mA current intensity under 1000 Hz 40 pulse conditions. PV interneurons, in contrast, responded differently from pyramidal neurons, highlighting cell-type-specific effects of directional magnetic stimulation. These findings demonstrate that microcoil-based stimulation enables precise, selective modulation of neural subtypes within social behavior circuits and could be extended to broader mPFC-subcortical pathways.

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Poster

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Title: Microcoil magnetic stimulation for alleviating Parkinson's symptoms at the deep brain level

Authors: *S. PARK[1], S. LEE[2], Y. SEO[2], M. BANG[2], H. YOO[2], T.-I. KAM[3,2], S. LEE[2];
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Abstract: Deep brain stimulation (DBS) has long used electrical currents to treat drug-resistant neurodegenerative diseases. However, conventional electrical stimulation often leads to broad current spread and reduced long-term efficacy due to fibrous encapsulation layers. As an alternative, magnetic stimulation using microcoils is gaining attention for its potentials to achieve more precise and durable effects. However, the efficacy of microcoil-based stimulation has so far been validated only in brain slice experiments and limited in vivo studies at the cortical level. Therefore, in vivo validation at the deep brain level is essential to assess its therapeutic potential, and this study aims to address that need.We investigated the feasibility of using microcoils to stimulate the subthalamic nucleus (STN), a key deep brain target in Parkinson’s disease. Electric field simulations in Maxwell 3D guided the design of rectangular microcoils, fabricated with laser micromachining and printed circuit board (PCB) manufacturing processes.The in vivo experiment targeted the right subthalamic nucleus (STN) of a Parkinson’s disease mouse model induced by 6-hydroxydopamine (6-OHDA). As a result, the rightward rotational tendency of the PD mouse decreased, and c-Fos imaging confirmed a 30% reduction in neural activity within the STN.These results demonstrate that magnetic stimulation using microcoils is effective not only at a theoretical level but also in deep brain regions, highlighting its potential as a therapeutic approach for neurodegenerative diseases.

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Poster

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Title: Enhancing Spatial Selectivity in Visual Cortex Stimulation Using Multi-Microcoil array

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Abstract: Visual cortical prosthesis (VCP) aims to restore vision by electrically stimulating the primary visual cortex, eliciting artificial visual percepts known as phosphenes. Although numerous clinical and preclinical studies have demonstrated the feasibility of artificial vision through VCPs, the wide spatial spread of electrical stimulation within the cortex results in low visual acuity and also leads to rapid inhibition of visual neural circuits, limiting the duration of visual perception. Moreover, the mechanical property mismatch between electrode materials and brain tissues leads to the formation of glial scars and a decrease in the stimulation effects, posing significant challenges for long-term implantation. Motivated by these limitations, microcoil-based magnetic stimulation has emerged, offering the ability to generate focal, asymmetric induced electric fields and maintain consistent performance regardless of impedance changes in the implantation area. To improve the stimulation resolution of VCPs, we developed a novel coil structure that maximizes the asymmetry of the induced electric field and fabricated a biocompatible, multi-channel modular microcoil array using liquid crystal polymer (LCP) film. The effectiveness of this system was validated through electrophysiological experiments. To investigate whether it is possible to selectively stimulate either pyramidal neurons or inhibitory interneurons arranged orthogonally to each other, we conducted electromagnetic field simulations based on finite element methods and calculated the spatial gradient of the induced electric field for each coil design. We then fabricated various forms of multi-array microcoils using LCP and UV laser processing, followed by insulation testing. Subsequently, we used genetically modified mice that allow cell-type-specific visualization (excitatory pyramidal neurons and inhibitory interneurons) to compare cortical activation patterns across different coil geometries and with conventional electrical stimulation. Consistent with simulation results, magnetic stimulation produced more localized and pyramidal neuron-selective activation than electrical stimulation, and the stimulation efficacy was highest in coil designs utilizing magnetic field constructive interference.

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Poster

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Title: Implantable Microcoil-Based Magnetic Stimulation of the Spinal Cord in Rats

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Abstract: Spinal cord stimulation (SCS) is a key technique in brain-spinal interfaces (BSIs), which aim to restore motor function and relieve pain in patients with paralysis. While traditional SCS uses electrical stimulation, it suffers from low spatial resolution due to the difficulty in controlling the direction of electric fields within tissues. In contrast, magnetic stimulation induces asymmetric electric fields that allow for spatially selective stimulation and is highly biocompatible as it avoids direct contact between the metal and tissue. In this study, we implanted microcoil into the spinal cords of rats to evaluate hindlimb responses elicited by magnetic stimulation. Finite element methods simulations were used to design coils optimized for targeted stimulation, and the fabricated coils were surgically implanted into the T13-L1 segments of anesthetized 12-week-old male Sprague Dawley rats. We investigated the effects of coil orientation and stimulation parameters on hindlimb movements. We investigated the effects of coil orientation and stimulation parameters on hindlimb movements. Stimulation efficiency depended on whether the electrode was implanted perpendicular or parallel to the spinal cord's longitudinal axis. Parallel implantation failed to produce any limb movement, whereas perpendicular implantation evoked toe movement at 1 A and progressive leg muscle contraction at 1.34 A and above. These findings suggest that magnetic stimulation using implanted microcoils can effectively induce limb movement and holds potential for high-resolution neuromodulation.

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